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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

Survival data

All patients were offered an intensive follow-up. Minimum intervals of recall were 3 months during the first 2 years, 6 months from the 3rd to the 5th year and once a year until the 10th year. Clinical examination and sonography of the neck were performed at each scheduled visit, a CT-scan of the head and neck and a chest X-ray were performed in 6-month intervals until the 5th year. Chest X-rays were continued in 12-month intervals until the 10th year. The follow-up was regularly frequented by 158 patients. For determination of the survival status of this survey every patient's chart was analysed. In 64 cases uncertainty remained after this procedure. Survival status was then clarified by the national people register. After this inquiry status of all patients (alive and dead) was determined. Causes of deaths were obtained from autopsy protocols and death certifications.

Statistics

The Kaplan-Meier method was used to estimate the events of interest, including overall survival, disease-specific survival, and local control. For overall survival all patients were included. For disease-specific survival patients who died of other causes but recurrences and metastases were censored. For locoregional control probability patients who died of other causes but locoregional recurrences were censored. The log-rank test was used for comparison of local control and survival curves of different groups. Overall, the significance level was set to $\alpha = 0.05$. The analyses were performed using SPSS for windows, version 11.5.

Results

From March 1990 until December 2000, 222 patients were treated as described above. In January 2003, after a median surveillance time of 72.3 months (24–152 months), 131 (59.0%) patients were still alive and free of disease, and 91 (41.0%) had died. Deaths were not associated with the primary tumour in 33 (14.9%) patients, whereas in 58 (26.1%) patients death was a consequence of the oral SCC, including 12 (5.4%) early postoperative deaths. Forty-six (20.7%) patients died of their primary disease. For detailed distribution of causes of death see Table 3, for detailed distribution of type of recurrence see Table 4. Numbers for incidence and mortality of recurrences were found equal. Regardless whether salvage therapy (surgery or chemotherapy) was performed, all patients who developed recurrences died.

Table 3. Distribution of causes of death (classified)

Causes of death	Frequency	Percent
Oral SCC	46	20.7
Thoracic second cancer	9	4.1
Second cancer in the head/neck region	7	3.2
Other cancer	2	0.9
Postoperative	12	5.4
Other	15	6.8
Alive	131	59.0
Total	222	100.0

Overall 2-year survival probability was 76.2% and overall 5-year survival probability was 62.4% (see survival function in Fig. 1). Disease-specific 2-year survival probability was 78.0% and the disease-specific 5-year survival probability was 70.0% (see survival function in Fig. 2). Two-year local control probability was 87.7%, the 5-year local control probability was 81.0% (see survival function in Fig. 3).

Five-year overall survival and 5-year local control probabilities for different groups of T- and N-classifications and UICC disease stages are listed in Table 5. Whereas no significant survival differences were found between T3 and T4, both differed significantly from T2 (log-rank test; $P = 0.005$). As far as N-classification is concerned, significant differences were found between N0 and N3 (log-rank test; $P = 0.001$). Differences between N0 and N2 were observed, but did not reach the conventional statistical significance level (log-rank test; $P = 0.06$). For groups of UICC disease stages II–IV significant differences were found between stages II and IV (log-rank test; $P = 0.013$) (see Fig. 4 for disease-specific survival functions of stage II and more advanced stages).

Discussion

This survey reports the outcome data of 222 consecutively treated patients, who received multimodal therapy for advanced oral and oropharyngeal cancer from 1990 until 2000. The reported treatment protocol included RT, ChT and surgery, with the intention to maximize tumour control and to minimize unfavourable side effects. RT and ChT were administered concomitantly in a preoperative setting. The concurrent application of RT and ChT is in accordance with recent studies that show synergistic effects[1,2,14,22,27]. The disadvantages of a preoperative setting for RCT, like increased propensity of bleeding during surgery and delayed wound healing, were accepted with the advantages of preoperative RCT in mind.

Table 4. Distribution of type of recurrence

Presence of recurrence	Frequency	Percent
Locoregional recurrence	22	9.9
Pulmonary metastases	3	1.4
Other distant metastases	4	1.8
Locoregional recurrence and pulmonary metastases	9	4.1
Locoregional recurrence and other metastases	2	0.9
Pulmonary and distant metastases	1	0.5
Locoregional recurrence, pulmonary, and distant metastases	5	2.3
No recurrence nor metastases	176	79.3
Total	222	100.0

Table 5. Outcome according to T-, N-, and UICC-stages

Groups of T-, N-, UICC-stages	T2	T3	T4	N0	N1	N2	N3	II	III	IV
5-year overall survival (%)	81.1	52.6	53.3	69.5	57.5	57.6	28.6	84.4	57.8	55.6
5-year local control (%)	90.9	65.7	73.0	87.0	69.6	74.1	35.7	93.0	73.5	73.8

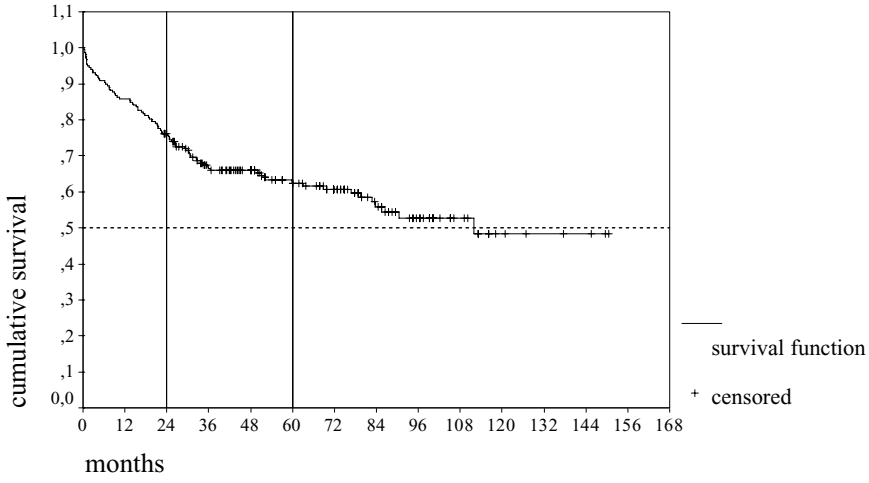

Fig. 1. Function of overall survival.

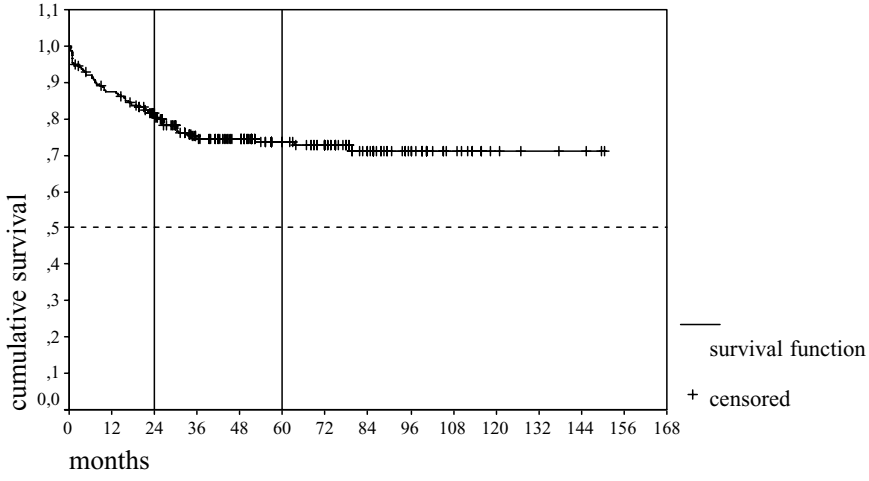

Fig. 2. Function of disease-specific survival.

First, RT is deemed to be more effective in surgically unaffected and well oxygenated tissue[3,9,21]. Second, the reduction of vital tumour volume by RT is believed to reduce the risk of implanted metastases during surgery. For the applied protocol with a radiation focus dosage of 50 Gy and ChT with Mitomycin C and 5-Fluorouracil great efficacy with acceptable toxicity was shown before[6]. Surgery followed essential oncological guidelines: resection was performed according to pretherapeutic tumour-borders with a minimum safety margin of 10 mm following an en bloc-resection technique with an obligatory neck dissection. These criteria can only be fulfilled when reconstruction of defects is possible. Since the introduction of microsurgically revascularized free flaps, even large defects in the lateral pharynx can be reconstructed with good results[19].

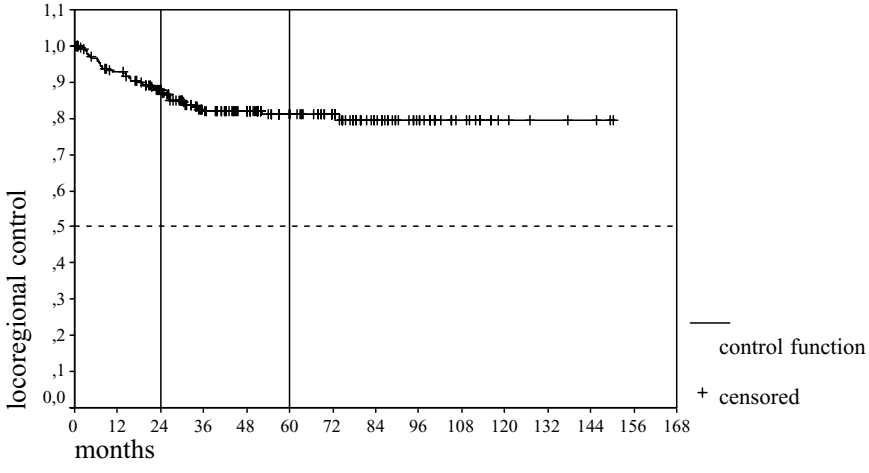

Fig. 3. Function of locoregional control probability.

The outcome data of this survey is in concordance with previously published data of our institution by Glaser et al. in 2001[10]. In our analysis patients with disease stages II–IV were included. For stage II patients, 5-year overall survival and 5-year local control probabilities were 84 and 93%, respectively. These outcome results are favourable compared with data for stage II patients in the DOSAK register as reported by Howaldt et al. in 1999[13]. Combined treatment is deemed to have a higher morbidity than monotherapy with either surgery or radiotherapy alone. Thus a combined treatment regime for stage II patients seems to be controversial. In our opinion there is a difference between T2 N0 tumours with a size just above 2 cm and those just below 4 cm. The latter group is expected to have a much higher risk of occult infiltration of important anatomical structures. In a recent study, Licitra et al.[18] chose 3 cm as crucial tumour size to include T2 N0 patients in a trial with a combined treatment regime. We agree to this opinion. However, a randomized study is needed to prove the prognostic relevance of the primary tumour size in T2 N0 patients. For advanced disease stages III and IV, 5-year overall survival was 58 and 55%, respectively, and local control probability was 74% for both groups. Compared with the data of the meta-analysis of 70 randomized trials by Pignon et al.[22] and with the data of the DÖSAK tumour register as reported by Howaldt et al.[12,13] we see a survival benefit for the reported treatment protocol with preoperative RCT and radical surgery. Other outcome surveys of a similar therapeutic concept (preoperative RCT and radical surgery) reported about smaller cohorts and shorter periods of surveillance. Survival and control probability were found in a similar range with 2-year overall survival probabilities ranging from 63 to 86% and 2-year local control

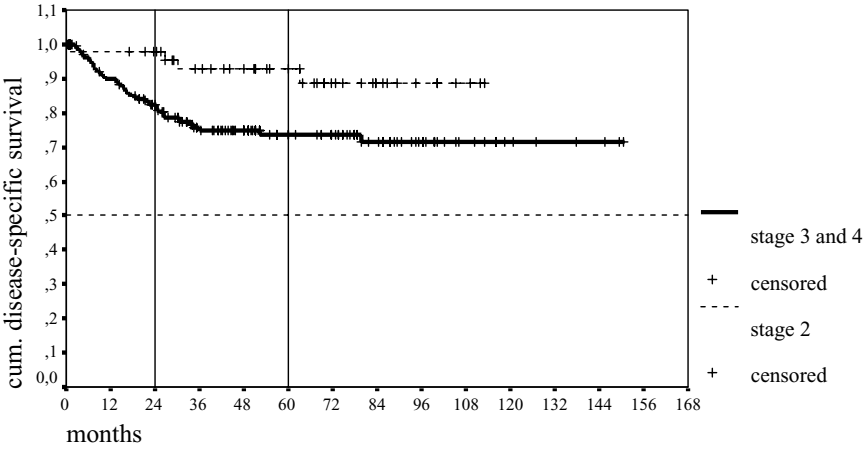

Fig. 4. Function of disease-specific survival for stage II vs. stages III and IV.

probabilities ranging from 68 to 84%[6,7,15,20]. Comparison with outcome data reported after postoperative adjuvant RCT is difficult. In many studies with advanced disease a large proportion of patients are reported having unresectable tumours. If resectable, 2-year overall survival probability is reported ranging from 50 to 65%[2,26]. In unresectable cases, prognosis is significantly worse, as reported by Pradier et al.[23] and Zakotnik et al.[29], with 2-year overall survival probabilities of 23 and 26%, respectively.

Wanebo et al.[25] recently showed that surgical resection is necessary to maximize tumour control in function-preserving, aggressive chemoradiation protocols for advanced SCC of the head and neck. In their investigation among patients with 100% clinical remission-rate after RCT they found complete histological response only in 66% and neck metastases in 22%. A recent study of Del Campo et al.[4] showed that the indication for surgery may be determined diversely. Whether a tumour is regarded resectable or not depends on various factors. For one, resectability obviously depends on the tumour's dimensions. Basic to our treatment-protocol, objective criteria for inoperability were defined by tumour-infiltration of the skull base, the internal carotid artery, and the prevertebral fascia and muscles. Second, the patients' general physical condition may compromise operability. Physical shape scores, like the Karnovsky performance status and WHO score are suitable instruments to assess the patients' operability. Third, resectability depends on the subjective estimation of the surgeon: a surgeon has to be aware of the size of the defect created by the resection and the subsequent necessity to close it. The ability to reconstruct the defect depends on the surgeon's skills as well as on infrastructure like the availability of long-time use of operation facilities and intensive care units. Both are associated with substantial financial expenses that have to be covered by public health services. Thus operability of advanced SCC may be considered differently at different centres.

For the entire collective, 5-year locoregional control probability was 81.0%, but survival probability was significantly lower as demonstrated with a 5-year survival probability of 62.4%. Thus, a significant number of patients died due to reasons caused by their comorbidity[17]. It is widely accepted[17] to obtain data of causes of death and comorbidity from autopsy protocols and death certifications. Among our patients, locoregional recurrences (17.6% of all patients) occurred within the first 36 months after surgery in 93%. Distant metastases were found in 26 patients (11.7%), mostly occurring in cases of existing locoregional recurrence. Distant metastases without locoregional recurrence were only found in 4.1%. A similar low incidence of distant metastases without locoregional recurrence was reported by Kirita et al.[15] who suggest that preoperative chemotherapy has reduced the risk of metastases in comparison with protocols of RT and/or surgery alone. We found that 15% of all deaths were not related to oral cancer. Among these, second carcinoma of the thorax (4.1%) or in the head and neck region (3.2%) were predominant and occurred more frequently than distant metastases. In agreement with a report by Woolgar et al.[28], other causes of death and metastases did not show any significant distribution over time. As a consequence, follow-up should be focused on locoregional recurrence within the first three years and screening for second carcinoma and metastases should be routinely performed for the patients' lifetime. As a suitable tool for detection of early stage thoracic neoplasm Diederich et al.[5] suggest low-dose computed tomography in high-risk patients.

In conclusion, this survey demonstrates the high efficacy of a multimodal treatment concept with preoperative concomitant RCT and radical surgery. Comparing the reported results with outcome data of other treatment modalities for advanced head and neck cancer, the neoadjuvant multimodal concept deserves high recognition.

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Address:
Clemens Klug
University Hospital of Cranio-Maxillofacial and Oral Surgery
Medical University of Vienna
AKH Waehringer Guertel 18-20
A-1090 Vienna
Austria.
Tel: +43 1 40400 4252
Fax: +43 1 40400 4253
E-mail: clemens.klug@univie.ac.at