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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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C. Klug, A. Wutzl, C. Kermer, O. Ploder, I. Sulzbacher, E. Selzer, M. Voracek, M. Oeckher, R. Ewers, W. Millesi:Preoperative radiochemotherapy and radical resection for stages II to IV oral and oropharyngeal cancer: grade of regression as crucial prognostic factor. Int. J. Oral Maxillofac. Surg. 2005; 34: 262–267.

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.

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

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).

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 to BRAUN et al.[1,3] into four regression grades (RG). RG1 corresponds to a full response, without vital tumour cells detected by light microscopy. In RG2, corresponding to partial responders, vital tumour cells are found in areas in less than 5% of the analysed tissue. RG3 and RG4 are classified as non-responders with a significant extent of vital tumour (5 to 50% in RG3, more than 50% in RG4) left.

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. A detailed report of the clinical outcome data of the same cohort including the distribution of causes of deaths and the distribution of recurrences was published before[15].

Statistics

The Kaplan–Meier survival analysis method was used to estimate the events of interest for 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 disease-specific survival functions of different groups. A Cox regression model was calculated to estimate the impact of various prognostic factors, based on disease-specific survival data. Overall, the significance level was set to $\alpha = 0.05$. P values between 0.05 and 0.10 were considered marginally statistically significant. The analyses were performed using SPSS for Windows, version 11.5.

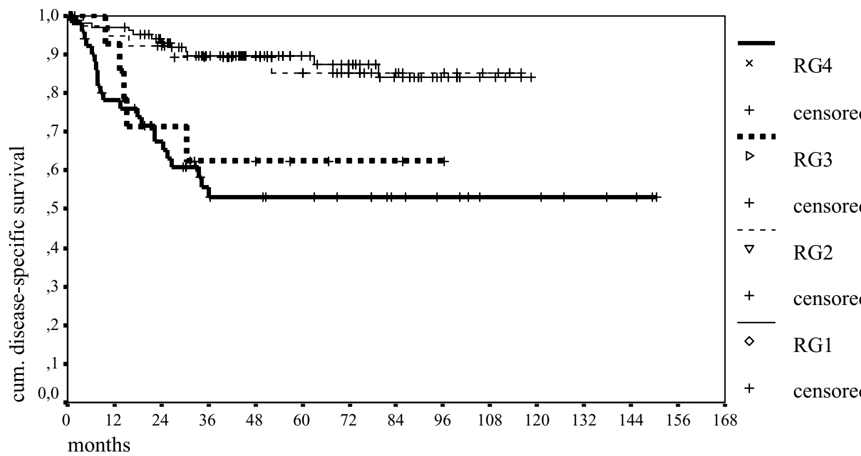

Fig. 1. Disease-specific survival of different groups of histopathological regression grades.

Results

Histopathology of the resected specimen after preoperative RCT revealed complete responses (RG1) in 108 cases (48.3%), minimal tumour remnants (RG2) in 43 cases (19.9%), RG3- and RG4-non-responders in 15 cases (6.6%) and 56 cases (25.2%), respectively.

For all patients overall survival probabilities at 2 and 5 years were 76.2 and 62.4%. The 2- and 5-year overall survival probability in the different groups of histopathological regression grades were: RG1: 87.4 and 73.4%, RG2: 80.9 and 72.1%, RG3: 57.1 and 41.9%, RG4: 56.6 and 37.9%. For group comparisons, disease-specific survival probabilities were analysed: no significant differences in disease-specific survival probability were found between RG1 and RG2 as well as between RG3 and RG4, whereas differences were highly significant between RG1 and both groups of non-responders (RG3, RG4) as well as between RG2 (log-rank test; $P < 0.001$) and both groups of non-responders (RG3, RG4) (log-rank test; $P < 0.001$). See Fig. 1 for disease-specific survival function for different groups of RG. The distribution of recurrences (locoregional and/or distant) among the different groups of RG was 12/108 RG1-patients, 5/43 RG2, 5/15 RG3, and 24/56 RG4, making 17 recurrences among 151 responders and 29 recurrences among 71 non-responders. Locoregional control probabilities at 2 years were 94.2, 92.4, 69.8, and 68.0% for RG1, RG2, RG3, and RG4. Locoregional control for responders and non-responders differed highly significantly (log-rank test; $P < 0.001$), with no significant differences among their subcategories. Table 2 shows the results of the

Table 2. Differences in survival of groups formed according to RG-, T-, N-classifications, and UICC-stages

RG-classification	1	2	3
2	0.906		
3	<0.001[a]	0.013[a]	
4	<0.001[a]	<0.001[a]	0.769
T-classification	2	3	
3	0.005[a]		
4	0.006[a]	0.559	
N-classification	0	1	2
1	0.108		
2	0.066[b]	0.985	
3	0.001[a]	0.067[b]	0.034[a]
UICC-stage	2	3	
3	0.055[b]		
4	0.013[a]	0.821	

[a] Differences in survival between groups are statistically significant.
[b] Differences in survival between groups are marginally statistically significant.

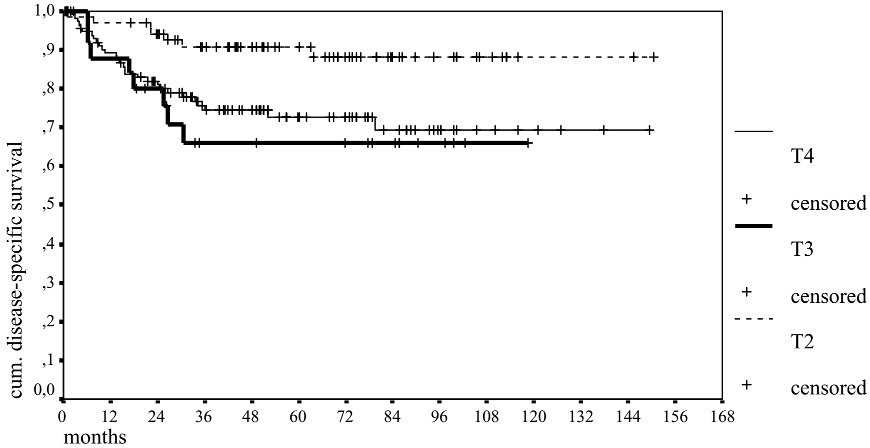

Fig. 2. Disease-specific survival of different groups of UICC T-classification.

Table 3. Distribution of RGs among of T and N stages (percent patients)

	RG1	RG2	RG3	RG4	All
T2	19.4	6.8	0.9	6.3	33.3
T3	6.8	2.7	0.5	2.7	12.6
T4	22.5	9.9	5.4	16.2	54.1
All	48.6	19.4	6.8	25.2	100.0
N0	30.8	11.4	2.2	11.9	56.2
N1	7.6	5.4	1.1	7.0	21.1
N2	7.6	3.2	1.6	4.3	16.8
N3	1.6	0.0	1.6	2.7	5.9
All	47.6	20.0	6.5	25.9	100.0

statistical analyses with a log-rank test comparing different groups of RG, T, N, and stage in respect to their differences in survival. For pretherapeutic histological grading (G) and tumour sites, no statistically significant differences were found with respect to survival time (log-rank test). Figures 2–4 show survival functions for different groups of T, N, and disease stage.

In a multivariate analysis of RGs and various traditional prognostic factors (tumour site, T-classification, N-classification, UICC disease stage, histological grading (G), and patients' sex and age) we found RGs to have the strongest predictive value for overall survival time. Specifically, we calculated a Cox regression model, with survival time as the dependent variable; RG, site, T, N, G, stage, and sex as categorical independent variables; and patients' age as a continuous independent variable. Due to missing values, the results from this multivariate analysis are based on 216 patients. The independent variables were entered stepwise into the Cox regression model, by using the forward-inclusion likelihood ratio algorithm. Overall, the model was statistically significant ($\chi^2 = 30.82$; d.f. $= 5$; $P < 0.0005$). At the first inclusion step, RG was entered into the model ($P < 0.0005$), and at the second inclusion step, T-classification was entered into the model ($P = 0.028$). All further prognostic factors considered for this multivariate analysis had no statistically reliable impact on survival time and thus were not entered into the model.

We did not find any statistically significant association of RG with T- or N-classifications (for the distribution see Table 3). Histological grading (G1 to G3) was neither statistically significantly associated with pathohistological grading (RG1 to RG4), nor with group of responders (RG1 and RG2) versus non-responders (RG3 and RG4).

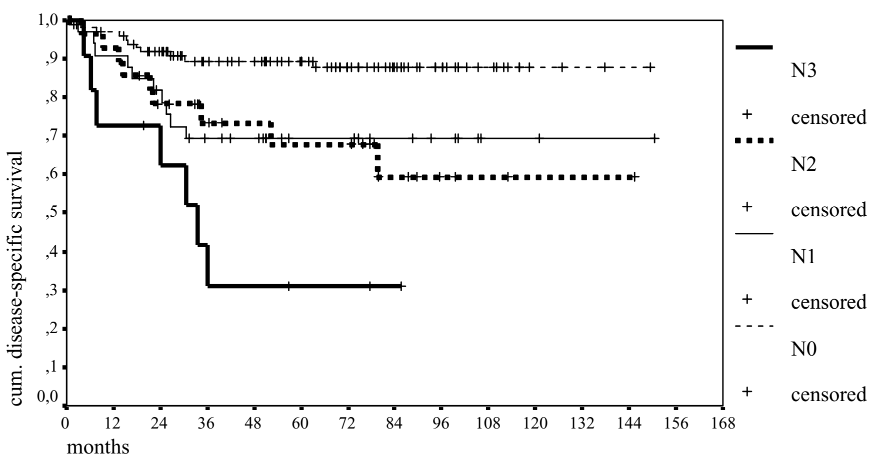

Fig. 3. Disease-specific survival of different groups of UICC N-classification.

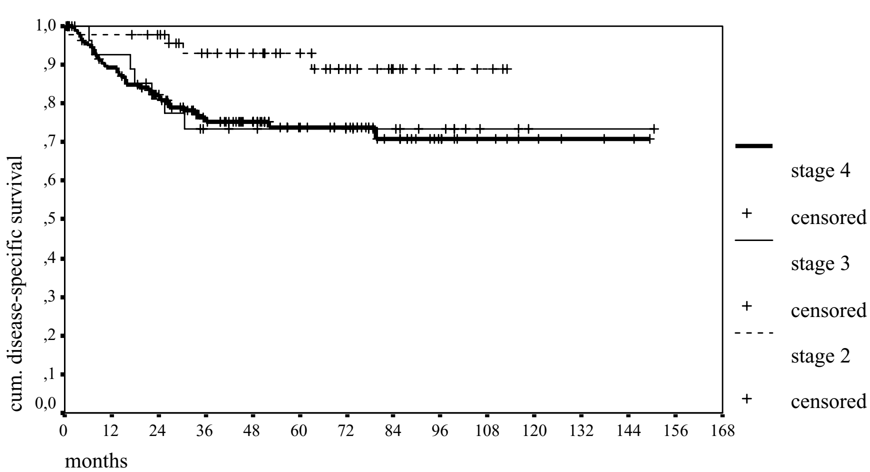

Fig. 4. Disease-specific survival of different groups of UICC disease stage.

Discussion

In this study we analysed the histopathological pattern of response to preoperative RCT with regard to its prognostic value. Response evaluation of the resected tumours was performed in 222 patients according to a score previously described by Braun et al.[1,3]. Complete and nearly complete responses (RG1 and RG2) were found in two thirds (48.3 and 19.9%, respectively) of the patients and poor response was found in one third (RG3 and RG4 in 6.6 and 25.2%, respectively). Association of response with clinical outcome was highly significant. Two- and 5-year survival probability of the different groups of histopathological regression showed significantly better survival for responders than for non-responders.

The results of the multivariate analysis of the prognostic value of various factors as calculated by a Cox regression model revealed RG as the most important predictive factor for survival. In this model T-classification (T2 to T4) as a measure for the primary tumour size also reached significance level in the second step. N-classification, disease stage, histological grading, tumour site, sex, and age did not reach significance level in the multivariate analysis. In the log-rank test statistically significant and marginally statistically significant differences between different groups of N-classification (N0 versus N2, N3) and disease stage (II versus II, IV) were observed. Therefore, we consider RG as the most influential factor for prognosis in this cohort. These findings confirm previous reports of smaller cohorts by Valente et al.[23], Kirita et al.[13], Eckardt et al.[8], and Hermann et al.[11], who emphasised, that response to preoperative RCT was a crucial prognostic factor in a combined neoadjuvant treatment regime. As a consequence, non-responders should be regarded as high-risk patients for local and regional recurrence even when adequate surgery (R0-resection) was accomplished. From the opposite perspective in 42 of 71 non-responders of this cohort, a locoregional recurrence did not occur. This fact underlines the importance of surgical resection in these patients since it may be postulated that further radiation therapy would not have been sufficient to cure these patients. For responders, however, the role of surgery is more controversial. The question arises, whether surgery can be foregone preferring further RCT as reported in organ preservation trials of the larynx[21]. An adequate method enabling the surgeon to make a decision towards or against surgery after RCT is desired. Our study did not show any statistically significant association of pretherapeutic histological grading (G) with the pathohistological grades of regression (RG). Thus, G has to be considered unsuitable as a predictor. Whether macroscopic changes of the tumour under RCT can be correlated with the response on the microscopic level has to be shown. In a recent study, we compared changes of tumour volume in CT scans before and 4 to 5 weeks after RCT with the pathohistological response (RG) and found that in a significant proportion of patients volume changes did not correlate with response[14].

In recent studies about prognostic factors in oral cancer, the status of the resection margin[20] and the extra-capsular spread of metastases[25,26] were shown to have high value in patients who underwent primary surgery. In our patient, collective resection margins were not free of vital tumour in eight cases (3.6%). All of these patients were non-responders and five of them died as a consequence of a locoregional recurrence, even though further surgery was performed in all cases. Other authors investigated the role of microvessel density in oral tumour epithelium and compared it with response to RT and clinical outcome[5]. A high density of microvessels showed to be associated with poor clinical outcome but did not correlate with histopathological response to RT[5]. The search for prognostic factors with predictive value for the individual risk of recurrence is continued on the molecular level. Immunohistochemical assessment of proliferation antigens and markers of apoptosis as well as the level of nitric oxide expression have shown predictive potential in breast[6] and lung cancer[18] and are currently evaluated for head and neck cancer[27]. In future it is hoped, that non-responders may be detected early in the course of therapy or even before therapy with molecular markers, so that individual treatment strategies can be implemented.

Another important aim is to increase the fraction of responders, whose outcome was found to be significantly better. In experimental and clinical trials, it was shown that the level of oxygen in irradiated tumours strongly influences its response to RCT[9,17]. Hypoxia adversely affects the prognosis of carcinoma of the head and neck in patients who received primary RT[4,16]. An argument in favour of surgery before RT is that large tumours with poorly oxygenated and even necrotic centres would be eliminated before RT and eventual microscopic remnants would be more accessible for RT. However, we believe that scar tissue after surgery is less well oxygenated than surgically unaffected tissue. In the context with preoperative RCT and radical surgery we believe that good oxygenation and consequently good response at the tumour borders is relevant. Following the strict concept of en bloc-resection, the less well oxygenated centre of a tumour is eliminated with sufficient safety margins. As a manoeuvre to circumvent the hypoxic effects substitution of recombinant human erythropoetin was successfully implemented in clinical trials[10].

But also for non-responders attempts are to be made in order to increase survival. Consequential to our study additional therapeutic measures after the full course of multimodal treatment should be deliberated for this group of high-risk patients (non-responders, RG3 and RG4). Options are further RCT or preventive measures including 13-*cis*-retinoic acid[12] or non-steroidal anti-inflammatory drugs (NSAIDs)[22].

This study demonstrates the crucial prognostic value of primary pathohistological tumour response to preoperative RCT. In cases of poor response, further therapeutic measures may be necessary to improve survival and to reduce the incidence of local recurrences.

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