
Impact of tumour characteristic and treatment modality on the local recurrence and the survival in patients with oral squamous cell carcinoma

Wpływ charakterystyki guza i sposobu leczenia na powstawanie wznów miejscowych i czas przeżycia u chorych z rakiem płaskonabłonkowym jamy ustnej

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Summary

Purpose of the study. To evaluate the impact of tumour location, local and regional advancement, histological differentiation, status of the surgical margins and radiotherapy on the disease-free time and overall survival rates in patients with oral squamous cell carcinoma. **Material and methods.** A retrospective analysis of 67 patients treated with surgery (61 pts.), radiotherapy (6 pts.) and their combination (28 pts.). Follow time on average 40 months. The probabilities of survival were assessed using the Kaplan-Meier estimates, the differences were calculated with the log-rank test. An analysis of the influence of the neck recurrences on the prognosis was additionally performed. Relationship between independent categorical variables as: primary local advancement, location of the tumour, histological grading and lymph node metastases was evaluated with Fisher's Exact Test. **Results.** Disease-free time rate amounted to 40,1%. There was no independent prognostic importance of primary location, T-staging and N-staging, histological grading of the tumour or radiation on disease-free time, just opposite to the status of the resection margins. However, the number of neck metastases was directly proportional to the tumour dimension and poor histological differentiation. Overall survival rate amounted to 87,5%. Posterior location in the oral cavity, involvement of cervical lymph nodes, surgical margins with the presence of tumour cells, poor histological differentiation and necessity of irradiation negatively correlated with the survival. **Conclusions.** A complete resection of the tumour was the most important independent prognostic parameter for the disease-free and overall survivals in oral squamous cell carcinomas in this study. An adjuvant radiation therapy could improve the results of treatment of oral squamous cell carcinoma also in cases were so far considered only for surgical management.

Hasła indeksowe: rak jamy ustnej, nowotwór jamy ustnej, czynniki prognostyczne

Key words: oral cancer, oral neoplasms, prognostic factors

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INTRODUCTION

Head and neck cancers represent the sixth most common human neoplasm with approximately half a million of new cases annually world-wide [1]. Oral squamous cell carcinoma accounts for more than 90% of them [2]. An aggressive local growth, frequent lymph node metastases and propensity to build second primary focuses characterise these tumours [3]. In the last few decades a considerable progress in

the diagnosis, surgical approach with introduction of free flap microsurgical techniques and the methods of radiotherapy has been noted. Despite of that results of treatment have not improved and remain still unsatisfactory with overall survival rate varying from 40% to 80% and only 40%, 5-year disease-free survival [3, 4].

In consequence, there is a need of repeated assessment of factors influencing the loco-regional control and overall survival of this type of neoplasm to identify

Autorzy nie zgłaszają konfliktu interesów.

Table I. Distribution of the tumours according to the site and local advancement

Localisation	Local advancement				Total
	pT ₁	pT ₂	pT ₃	pT ₄	
Floor of the mouth	8	8	3	7	26
Tongue	8	9	1	3	21
Base of the tongue and Oropharynx	3	5	4	2	14
Cheek	0	2	1	1	4
Palate	1	1	0	0	2
Total	20	25	9	13	67

Table II. Neck staging in relation to the size of the primary focus

Neck staging	pT ₁	pT ₂	pT ₃	pT ₄	Total
pN ₀	17	20	7	5	49
pN+	3	5	2	8	18
Total	20	25	9	13	67

the sources of failures. A better definition of tumour characteristics and clinical parameters having prognostic significance would be of great importance for the prediction of biological behaviour of this cancer and a choice of the best treatment option. To date, several factors have been reported as having independent significance for the prediction of the outcome [5–10]. Nevertheless their prognostic accuracy is not universally recognised and arouses a lot of controversies [11, 12].

The purpose of this study was to evaluate the outcomes in the consecutive series of patients with oral squamous cell carcinoma and to assess the impact of tumour characteristic and treatment modality on the recurrence and the survival.

MATERIAL AND METHODS

A retrospective analysis of the group of 67 patients treated from 1st January 2002 to 31st December 2006 was conducted. There were 22 (32,8%) women and 45 (67,2%) men at the mean age of 60 years (SD 11, range 25–87). Table I shows the distribution of the tumours according to the site and local advancement. The neck staging in relation to the size of the primary focus is presented in the table II. The distribution of histological differentiation according to Broders' amounted to: 24 (36%) G1, 36 (54%) G2 and 7 (10%) G3 cases. Surgery and radiotherapy were primary treatment modalities in 61 and 6 cases respectively. There were 9/61 (14,75%) patients with postoperative positive surgical margins. Radiotherapy supplemented the surgery in 28/61 (45,9%) of the patients in the presence of neck metastases, T3, T4 tumour advancement, after not radical tumour excision, because of a high grade histological malignancy and localisation in the base

of tongue or oropharynx. Sometimes more than one reason justified irradiation. The patients were followed in average for 40 months (SD 31, range 9–60).

As this is a retrospective study, it was considered that no ethical approval was necessary.

The influence of tumour localisation, local (pT) and regional (pN) advancement, histological grading (G), status of the surgical margins (pR) and radiotherapy on disease-free survival as well as overall survival rate were assessed. The patient was classified as having positive surgical margin (pR1) when microscopically the tumour free distance between main tumour and the edge of the resection was lesser than 1 cm. The disease free survival was defined as the period from the end of the surgery to the first recurrence or the second primary tumour. The overall survival rate was defined as the percentage of patients alive for more than 5 years divided by the total number of patients.

The probabilities of survival were assessed using the Kaplan-Meier estimates, the differences were calculated with the log-rank test. An analysis of the influence of the neck recurrences on the prognosis was additionally performed. Relationship between independent categorical variables as: primary local advancement, location of the tumour, histological grading and lymph node metastases was evaluated with Fisher's Exact Test. Statistical analyses were carried out with the use of SPSS for Windows 14.0 (SPSS Inc, Chicago, IL, USA) with significance defined as $p < 0,05$.

RESULTS

The 5-year disease-free survival amounted to 40,1% for the whole study group. There was no statistically significant dependence between primary location of

Table III. Characteristic of the parameters influencing 5-year disease-free survival

Parameter	5-year disease free survival [%]	Log rank test
Local advancement		
pT ₁	52	p=0,98
pT ₂	54	
pT ₃	62	
pT ₄	37	
Neck staging		
pN ₀	51	p=0,79
pN+	40	
Status of the resection margin		
pR ₀	42	p=0,01
pR ₁	13	
Histological grading		
G ₁	36	p=0,2
G ₂	73	
G ₃	27	
Radiotherapy		
No-radiation	54	p=0,18
Radiation	41	
Location of the tumour		
Floor of the mouth	52	p=0,13
Tongue	44	
Base of tongue and oropharynx	32	
Cheek	54	
Palate	30	

the tumour, T-staging, N-staging, histological grading or radiation and the disease-free survival. In the case of patients primary treated with surgery the status of the resection margin predicted the disease-free survival (tab. III). There were 42% disease-free patients presenting negative margins versus 13% without local recurrence, but having positive resection margins.

The number of neck metastases was significantly higher in T3 and T4 tumours ($p = 0,035$) and in those presenting G2 and G3 histological differentiation ($p = 0,048$). The primary location of the neoplasm had no influence on the appearance of lymph node metastases ($p = 0,794$).

Much more factors influenced overall survival rate (tab. IV), which amounted to 87,5% in the study group. Location of the tumour in the anterior part of the oral cavity had a favourable influence on the survival when compared with tumours located more posteriorly. Involvement of the cervical lymph nodes, positive surgical margins, poor histological differentiation and necessity of irradiation negatively correlated with the survival. The local advancement of the tumour had no direct influence on the overall survival rate of the patients in this study.

Table IV. Characteristic of the parameters influencing 5-year disease-overall survival rate

Parameter	5-year overall survival rate [%]	Log rank test
Local advancement		
pT ₁	92	p=0,85
pT ₂	50	
pT ₃	83	
pT ₄	45	
Neck staging		
pN ₀	94	p=0,04
pN+	67	
Status of the resection margin		
pR ₀	88	p=0,001
pR ₁	63	
Histological grading		
G ₁	96	p=0,03
G ₂	79	
G ₃	80	
Radiotherapy		
No-radiation	95	p=0,05
Radiation	76	
Location of the tumour		
Floor of the mouth	76	p=0,01
Tongue	50	
Base of tongue and oropharynx	48	
Cheek	52	
Palate	48	

DISCUSSION

Traditionally recognised prognostic importance of local tumour advancement was reduced in this study. However, we were able to confirm that the frequency of cervical lymph node metastases was significantly higher in more advanced (T3, T4) tumours. Because of that the lack of mathematical significance of T-staging in our Cox multivariate analysis should be interpreted very cautiously and the statement should be rather that a modern surgery is able to provide a complete resection of the tumour, but a complicated biology of the oral cancer causes that the local advancement of these tumours still influences the overall survival.

This study provided the validity of supportive radiotherapy in oral cancer, also in lesser advanced cases were believed could be treated only surgically so far. The survival curves calculated according to the presence or absence of radiation therapy showed similar recurrence rates in irradiated and not irradiated group. However, the patients submitted to radiation presented on assumption more advanced disease. Additionally, no cervical recurrences appeared in the patients with postoperatively positive lymph nodes which were

submitted to adjuvant irradiation. These metastases concerned only initially negative and therefore not irradiated necks.

Our results of the treatment with 40,1% 5-year disease-free survival and 87,5% overall survival rate are consistent with those published in the world literature [4, 13]. Analysis of factors determining the disease-free survival showed that resection of the neoplasm without microscopic remnants was directly correlated with a favourable prognosis. The value of a tumour free resection margin has already been reported and the majority of statements agree with our results. However, this parameter was not a predictor of local recurrence in some other reports [12, 14]. An importance of a complete resection of the neoplasm for overall survival rate, which was also confirmed in this study, is more uniformly accepted [15].

Presence of neck nodal metastases is one of the most significant predictive factors for regional recurrence and survival in patients treated for oral squamous cell carcinoma [1, 10, 16]. An overall survival rate may decrease by approximately 50% when lymph nodes are involved [1]. In the report of Kokemöller et al it drops from 79% to 32% [13]. In our study it fell down from 90% in pN0 patients to 65% in those with microscopically confirmed neck involvement. However, a significance of nodal metastases for disease-free survival could not be confirmed in this study. Such a result seems to be acceptable with reference to the biological behaviour of cancers because it is that the size of the tumour determines the number of metastases. Therefore a reverse relationship should not be expected.

The disease-free and the overall survival rates turned out to be independent from T-staging in this report. Such findings are not common in the literature. The majority of authors claim that the number of failures usually increases with size of the tumour [3, 17–19].

The grade of histological differentiation was not found to have an influence on the number of the local recurrences in our study, but G1 patients presented more favourable overall survival than G2 and G3 cases. The importance of histological maturity is not universally approved. Whereas Oliver et al. ascribed no prognostic significance to the G-staging, it was an important predictor of survival in patients with oral squamous cell carcinoma in the report of Kademani et al. [3, 12]. The other histological features like perineural and lymphovascular invasion were also demonstrated to have a prognostic value but evaluation of these factors was not possible in this retrospective study [5, 6, 9].

Prognostic significance of the location of the primary tumour remains under discussion. In their analysis of head and neck carcinomas Ildstad et al. documented that the survival rate was significantly lower when the cancer was located in the tonsillar area [20]. Beltrami et al. reported about powerful prognostic significance of the primary focus with the most favourable localisation at the lip [21]. Pericot et al. in their multivariate analysis excluded tumour location from the set of the most significant independent prognostic predictors [22]. In this series overall survivals were significantly lower for the locations in the posterior sites of the oral cavity which could be explained by difficulties in detection and surgery. However, there was no influence of the tumour location on the local recurrence rate.

CONCLUSIONS

A complete resection of the tumour is of primary importance for the disease-free and overall survivals in oral squamous cell carcinomas. An independent prognostic significance of the other factors turned out to be much lesser in this study.

An adjuvant radiation therapy could considerably improve the results of treatment of oral squamous cell carcinoma also in cases were so far considered only for surgical management.

REFERENCES

1. Reuther T, Posselt NK, Rabbels J, Kübler AC. Oral squamous cell carcinoma Retrospective analysis of therapy results and prognosis by neoadjuvant, preoperative radio-chemotherapy. *Mund Kiefer Gesichtschir.* 2006; 10: 18–29.
2. Choi KK, Kim MJ, Yun PY, Lee JH, Moon HS, Lee TR, et al. Independent prognostic factors of 861 cases of oral squamous cell carcinoma in Korean adults. *Oral Oncol.* 2006; 42: 208–217.
3. Oliver AJ, Helfrick JF, Gard D. Primary oral squamous cell carcinoma: a review of 92 cases. *J Oral Maxillofac Surg.* 1996; 54: 949–954.
4. Garzino-Demo P, Dell'Acqua A, Dalmaso P, Fasolis M, La Terra Maggiore GM, Ramieri G, et al. Clinicopathological parameters and outcome of 245 patients operated for oral squamous cell carcinoma. *J Craniomaxillofac Surg* 2006; 34: 344–350.
5. Yuen APW, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, et al. Prognostic significance of clinically stage I and II oral tongue carcinoma – a comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez – Gimeno score, and pathologic features. *Head Neck* 2002; 24: 513–520.

6. Bundgaard T, Rossen K, Henriksen SD, Charabai S, Sogaard H, Grau C. Histopathologic parameters in the evaluation of T1 squamous cell carcinomas of the oral cavity. *Head Neck* 2002; 24: 656–660.
7. Va Es RJJ, van Nieuw Amerongen N, Slootweg PJ, Egyedi P. Resection margin as a predictor of recurrence at the primary site for T1 and T2 oral cancer. *Arch Otolaryngol Head Neck Surg* 1996; 122: 521–525.
8. Jones KR, Lodge-Rigal RD, Reddick RL, Tudor GE, Shockley WW. Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. *Arch Otolaryngol Head Neck Surg* 1992; 118: 483–485.
9. Spiro RH, Guillaumondegui O, Paulino AF, Huvos AG. Pattern of invasion and margin assessment in patients with oral tongue cancer. *Head Neck* 1999; 21: 408–413.
10. O'Brien CJ, Lauer CS, Fredricks S, Clifford AR, McNeil EB, Bagia JS, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer-but what thickness? *Head Neck* 2003; 25: 937–945.
11. Hao SP, Tsang NM. The role of supraomohyoid neck dissection in patients of oral cavity carcinoma. *Oral Oncol* 2002; 38: 309–312.
12. Kademani D, Bell RB, Bagheri S, Holmgren E, Dierks E, Potter B, et al. Prognostic factors in intraoral squamous cell carcinoma: the influence of histologic grade. *J Oral Maxillofac Surg* 2005; 63: 1599–1605.
13. Kokemueller H, Brachvogel P, Eckardt A, Hausamen JE. Neck dissection in oral cancer – clinical review and analysis of prognostic factors. *Int J Oral Maxillofac Surg* 2002; 31: 608–614.
14. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol* 2005; 29: 167–178.
15. Binahmed A, Nason RW, Abdoh AA. The clinical significance of the positive surgical margin in oral cancer. *Oral Oncol* 2007; 43: 780–784.
16. Chandu A, Adams G, Smith AC. Factors affecting survival in patients with oral cancer: an Australian perspective. *J Oral Maxillofac Surg* 2005; 34: 514–520.
17. Chen YK, Huang HC, Lin LM, Lin CC. Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan. *Oral Oncol* 1999; 35: 173–179.
18. Ribeiro KC, Kowalski LP, Latorre MR. Impact of comorbidity, symptoms, and patients' characteristics on the prognosis of oral carcinomas. *Arch Otolaryngol Head Neck Surg* 2000; 126: 1079–1085.
19. Aksu G, Karadeniz A, Saynak M, Fayda M, Kadehçi Z, Kocaelli H. Treatment results and prognostic factors in oral tongue cancer: analysis of 80 patients. *Int J Oral Maxillofac Surg* 2006; 35: 506–513.
20. Ildstad ST, Tollerud DJ, Bigelow ME, Remensnyder JP. A multivariate analysis of determinants of survival for patients with squamous cell carcinoma of the head and neck. *Ann Surg* 1989; 209: 237–241.
21. Beltrami CA, Desinan L, Rubini C. Prognostic factors in squamous cell carcinoma of the oral cavity. A retrospective study of 80 cases. *Pathol Res Pract* 1992; 188: 510–516.
22. Pericot J, Escriba JM, Valdes A, Biosca MJ, Monner A, Castellsague X, et al. Survival evaluation of treatment modality in squamous cell carcinoma of the oral cavity and oropharynx. *J Canio-Maxillofac Surg* 2000; 28: 49–55.

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