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CLINICO-PATHOLOGICAL PREDICTIVE FACTORS IN SQUAMOUS CELL CARCINOMA OF THE TONGUE AND THE FLOOR OF THE MOUTH

Abstract: Introduction: The incidence of oral squamous cell carcinoma (OSCC) comprises about 2% of all malignant neoplasms. Despite improvement in treatment modalities in OSCC the prognosis remains poor.
Aim: The aim of this study is to evaluate clinical and histological predictive factors determining the risk of loco-regional recurrence (LRR) and survival of the patients surgically treated for SCC of the tongue and the floor of the mouth (FOM).
Materials & methods: The study group consisted of 60 patients with primary SCC of the tongue and FOM who underwent surgical treatment without prior therapy. Clinical and histological factors, such as: age, sex of the patients, comorbidities, tumour site, stage, grade, lymph nodes and mandible involvement, margin status, type of neck dissection and adjuvant radiation therapy, influencing LRR and 5-year disease-specific survival (DSS) were analysed.
Results: LRR was observed in 26 (43.3%) patients after 9.6 months on average (SD ± 9.47) and DSS reached 53.3% (95%CI: 40.0–66.3). LRR was more frequent in patients with SCC of the base of the tongue (p = 0.024), posterior part of FOM (p = 0.010) and who underwent MRND (p = 0.043). Adverse impact on DSS had advanced stage of the disease (p = 0.048) and tongue cancer (p = 0.045). In multivariate Cox regression analysis SCC of the tongue achieved the status of independent predictor of LRR (p = 0.028) and DSS (p = 0.011). Lymph node involvement was the second independent predictor of LRR (p = 0.008) as well as DSS (p = 0.015).
Conclusions: The analysis of prognostic factors in SCC of tongue and FOM revealed that lymph node involvement was an independent predictor of LRR and DSS. Moreover, higher risk of LRR and death was observed in patients with tongue cancer, especially localised posteriorly.

Key words: squamous cell carcinoma, floor of the mouth, oral tongue cancer, prognostic factors.

INTRODUCTION

In 2008, 263 020 new cases of malignant neoplasms of the lips and oral cavity were registered worldwide. This number of patients, including 170 496 males and 92 524 females constituted 2% of all malignant neoplasms [1]. Highly invasive, metastasizing squamous cell carcinoma (SCC) accounts for over 90% of all malignancies of the oral cavity. In 60% of cases oral squamous cell carcinoma

(OSCC) is localised in the tongue and the floor of the mouth (FOM) [2–4]. The risk of occult metastases in patients with OSCC is estimated to be 45% [5–7]. The presence of cervical metastases is one of the most important prognostic factors affecting the outcome of treatment.

The other clinico-pathological predictive factors in OSCC comprise age of patients, site, stage and grade of the tumour as well as tumour thickness and depth, pattern of invasion, extracapsular extension (ECE), infiltration of bones, muscles, blood vessels and nerves [3, 7–10].

The aim of this study is to evaluate clinical and histological predictive factors determining the risk of loco-regional recurrence (LRR) and survival of the patients surgically treated for SCC of the tongue and FOM.

MATERIALS AND METHODS

The study group consisted of the patients with primary SCC of the tongue and FOM who underwent surgical treatment in the Department of Cranio-Maxillofacial, Oncological and Reconstructive Surgery of the Jagiellonian University in Kraków from 2000 to 2011. Clinical and histological factors influencing LRR and 5-year disease-specific survival (DSS) were analysed. Clinical predictive factors comprised age and sex of the patients, tumour site and stage, also the presence of comorbidities. Histological predictive factors included SCC's grade, confirmed cervical metastases (pN+), infiltration of the mandible. Prognosis was evaluated with regard to radicality of tumour excision, type of neck dissection, postoperative radiation therapy (PORT). Exclusion criteria comprised applied neoadjuvant chemotherapy, synchronous and metachronous neoplasms, incomplete follow-up, inadequate information concerning survival of the patient or death from other causes than OSCC.

Analysis of predictive factors potentially influencing endpoints such as LRR and death caused by SCC of the tongue and FOM was conducted for variables categorised by χ^2 test and the Fisher's exact test for small groups. The Mann–Whitney's test was used to compare groups in cases of continuous variables. The risk of death and LRR in 5-year period was analysed by logistic regression. Graphic analysis of survival was presented using the Kaplan–Meier curves with log-rank test. In the multivariate analysis of the influence of chosen prognostic factors on the probability of death and LRR the Cox proportional hazard model was used. STATA 8.0 was applied, predetermined significance level was $p < 0.05$.

RESULTS

Between 2000 and 2011, 148 patients with SCC of the tongue and FOM were treated in our department. Of these, 60 patients met inclusion criteria. There were 46 males and 14 females in the group, the age ranged from 23 to 81 years

and was 56.5 years on average. Tongue SCC was diagnosed in 24 (40%) patients and SCC of FOM in 36 (60%) cases (Fig. 1, 2). Epidemiologic characteristics of the study group statistically did not differ from the remaining patients (Table 1). The majority of patients, 49 (81.7%) presented in advanced (III or IV) stage of disease. The largest group comprised of 32 (53.3%) patients with moderately differentiated, partially keratinising SCC.

Surgical treatment included neck dissection, resection of the tumour and immediate reconstruction of the postoperative defects of the oral cavity (Fig. 3). Modified radical neck dissection (MRND) on the tumour site was the most common procedure performed in 34 (56.6%) patients. Bilateral neck dissection was carried out in 36 (60%) patients. In SCC of FOM the tumour was resected with underlying mandibular bone in 34 (94.4%) cases.

Cervical metastases, in the postoperative specimen, were diagnosed in 29 (48.3%) patients, ECE occurred in 5 (8.3%) cases. In cN_0 patients occult metastases were diagnosed in the histological examination of the postoperative specimen in 2 (13.3%) patients (Table 2).

LRR was observed in 26 (43.3%) patients from 1 month to 44 months, 9.6 months on average (SD ± 9.47), following surgery. In the study group DSS reached 53.3% (95% CI: 40.0–66.3). Death in 24 (85.7%) patients was caused by LRR, in 3 (10.7%) patients by distant metastases and in one patient by the new primary SCC of the soft palate.

Site of the tumour was predictive for LRR and DSS. Prognosis was significantly poorer in patients with SCC of the tongue ($p = 0.045$) and the tendency to higher risk of LRR in these patients was observed ($p = 0.056$) (Fig. 4). Also posterior localisation of the tumour in patients with SCC of the tongue enhanced the risk of LRR ($p = 0.024$) and influenced DSS ($p = 0.052$). LRR was more frequent in patients with posterior part of FOM ($p = 0.010$). Moreover, advanced stage of the disease had an adverse impact on prognosis. DSS of the patients with stage III and IV reached 46.9% (95% CI: 32.5–61.7) whereas in patients with stage I and II was — 81.8% (95% CI: 48.2-97.7) ($p = 0.048$). Age, sex and comorbidities of the patients had no impact on LRR and DSS in the study group (Table 3).

The presence of cervical metastases in the postoperative specimen had an adverse impact on prognosis. DSS in patients with lymph nodes metastases was 37.9% (95% CI: 20.7–57.7) whereas in patients without cervical metastases — 67.7% (95% CI: 48.6- 83.3) ($p = 0.021$) (Fig. 5). ECE enhanced unfavourable prognosis. Death rate in patients with cervical metastases and ECE was 100% ($p = 0.018$). Patients with lymph nodes involvement had higher risk of LRR ($p = 0.005$). Tumour grade and infiltration of the mandible had no predictive value as well as status of surgical margin and PORT. Higher risk of LRR was observed in patients who were treated by MRND ($p = 0.043$). This was caused by the advancement of the disease (Table 3).

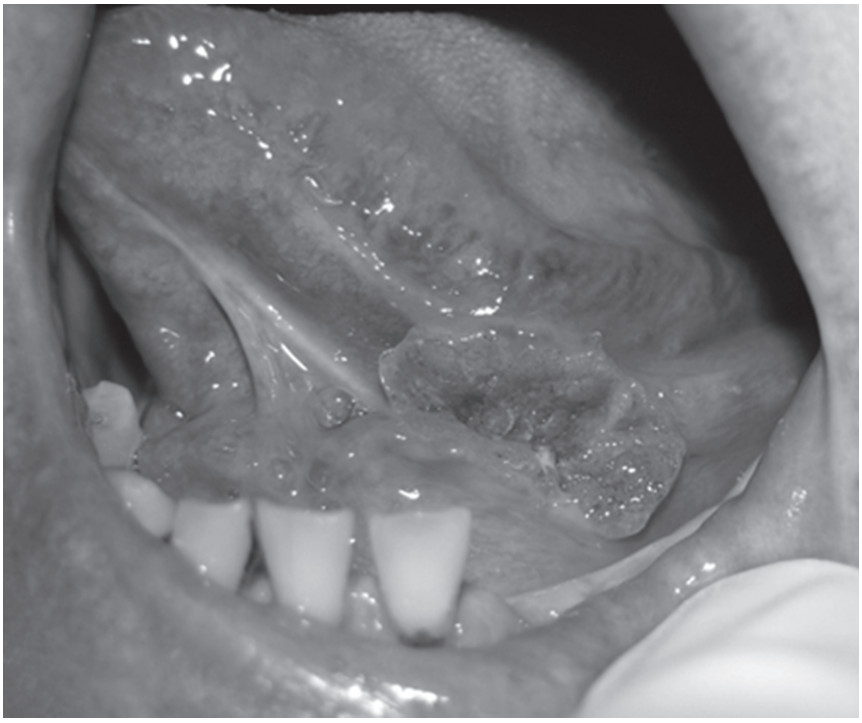

Fig. 1. 51-year old patient with SCC G2 of the anterior part of FOM.

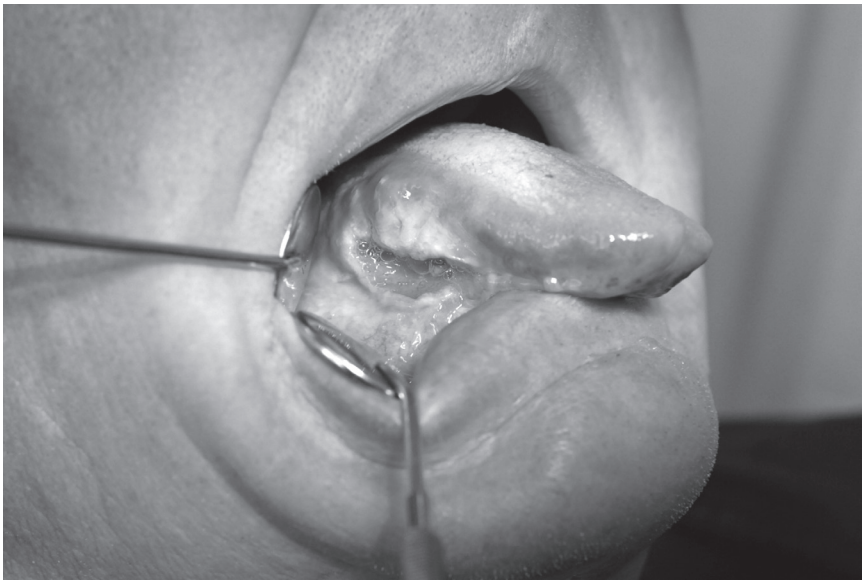

Fig. 2. 64-year old patient with SCC G2 of the mobile tongue.

Table 1

Characteristic of the patients operated due to squamous cell carcinoma of the tongue and the floor of the mouth in the period 2000–2011.

Total number of patients n = 148	Study group n = 60		The rest of patients n = 88		P Value
Age	23–81 years Mean 56.5 ± 11.74 years		24–87 years Mean 57.3 ± 10.82 years		0.628
Sex	Men (M) Women (W) M:W ratio = 3.3:1	46 14	Men (M) Women (W) M:W ratio = 2.7:1	64 24	0.590
Site	Tongue FOM[a]	24 36	Tongue FOM[a]	45 43	0.182
Stage	I II III IV	6 5 13 36	I II III IV Not assessed	8 10 24 41 5	0.594

[a] FOM — floor of the mouth

Table 2

Characteristic of the study group.

	Tongue		Floor of the mouth	
Location	Mobile Base	18 6	Anterior part Medial part Posterior part	16 13 7
Margin status	Adequate Close Positive	15 1 8	Adequate Close Positive	24 4 8
Ipsilateral neck dissection	MRND[a] SND[b]	21 3	MRND[a] SND[b]	14 22
Contralateral neck dissection	No SND[b]	16 8	No SND[b]	8 28
Lymph node metstases	Yes (ECE[c] – 2) No	13 11	Yes (ECE[c] – 3) Mo	16 20
Bone resection	No Rim Segment	21 2 1	No Rim Segment	2 18 16
Bone infiltration	No Periostium Bone	23 0 1	No Periostium Bone	21 5 10
Adjuvant therapy	PORT[d]	10	PORT[d]	16
Loco-regional recurrence	14 (58.3%)	3–44 months Mean 9.1 SD ± 11.1	12 (33.3%)	1–28 months Mean 10.1 SD ± 7.6
5-year disease-specific survival	37.5%	95%CI: 18.8–59.4	63.9%	95%CI: 46.2–79.2

[a] MRND — modified radical neck dissection, [b] SND — selective neck dissection, [c] ECE — extracapsular extension, [d] PORT — postoperative radiotherapy

Fig. 3. 52-year old patient with SCC G2 of mobile tongue (a), 5 days after hemiglossectomy with cervical skin pedicled flap reconstruction (b), 2 months after surgery (c).

Table 3

Predictors of loco-regional recurrence and 5-year disease specific survival.

	Loco-regional recurrence	P Value	Death	P Value
Age				
<60 years	16 (41.0%)	0.623	18 (46.1%)	0.914
≥60 years	10 (47.6%)		10 (47.6%)	
Sex				
men	21 (45.6%)	0.511	21 (45.6%)	0.775
women	5 (35.7%)		7 (50.0%)	
Site				
tongue	14 (58.3%)	0.056	15 (62.5%)	0.045
FOM[a]	12 (33.3%)		13 (36.1%)	
Tongue				
mobile	8 (44.4%)	0.024	9 (50.0%)	0.052
base	6 (100%)		6 (100%)	
FOM[a]				
anterior part	6 (37.5%)		4 (25.0%)	
medial part	2 (15.4%)	0.010	5 (38.4%)	0.362
posterior part	4 (57.1%)		4 (57.1%)	
Stage				
I, II	2 (18.2%)	0.062	2 (18.2%)	0.048
III, IV	24 (49.0%)		26 (53.1%)	
Comorbidities				
no	9 (40.9%)	0.773	11 (50.0%)	0.694
yes	17 (44.7%)		17 (44.7%)	
Grade				
I	3 (27.3%)	0.383	4 (36.4%)	0.630
II	21 (45.6%)		22 (47.8%)	
III	2 (66.7%)		2 (66.7%)	
pN(+)	18 (62.1%)	0.005	18 (62.1%)	0.021
pN(-)	8 (25.8%)		10 (32.3%)	
Bone infiltration				
no	7 (33.3%)	1.000	7 (33.3%)	0.890
periostium	2 (40.0%)		2 (40.0%)	
bone	4 (36.4%)		5 (45.4%)	
Margin				
adequate	9 (56.2%)	0.348	9 (56.2%)	0.429
close	1 (20.0%)		1 (20.0%)	
positive	16 (41.0%)		18 (46.2%)	
Neck dissection				
MRND[b]	19 (54.3%)	0.043	19 (54.3%)	0.162
SND[c]	7 (28.0%)		9 (36.0%)	
Neck dissection				
unilateral	13 (54.2%)	0.167	14 (58.3%)	0.139
bilateral	13 (36.1%)		14 (38.9%)	
PORT[d]				
no	15 (44.1%)	0.889	17 (50.0%)	0.554
yes	11 (42.3%)		11 (42.3%)	

[a] FOM — floor of the mouth, [b] MRND — modified radical neck dissection, [c] SND — selective neck dissection, [d] PORT — postoperative radiotherapy

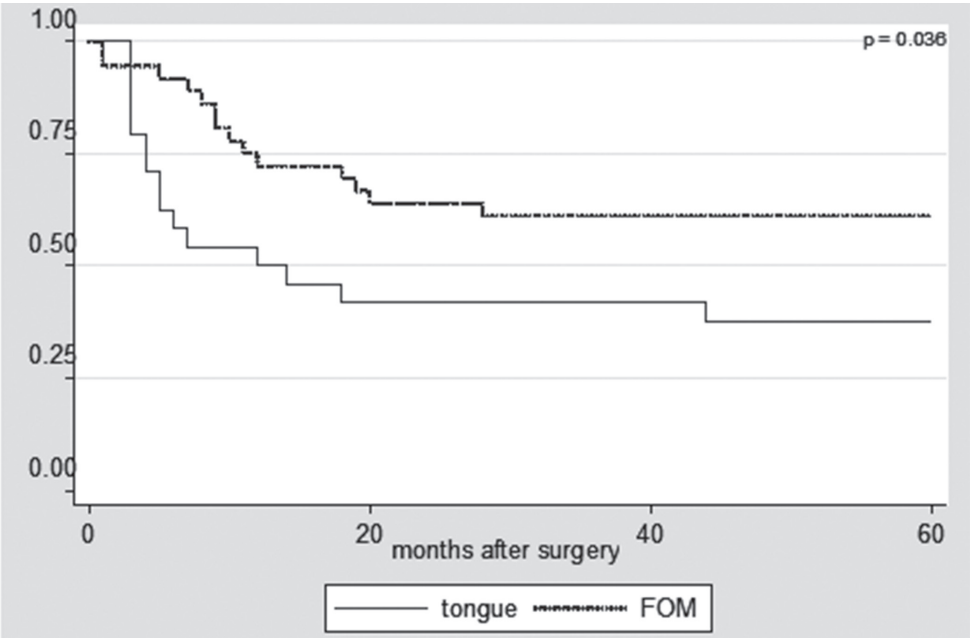

Fig. 4. Kaplan–Meier survival analysis in relation to site of squamous cell carcinoma in the oral cavity.

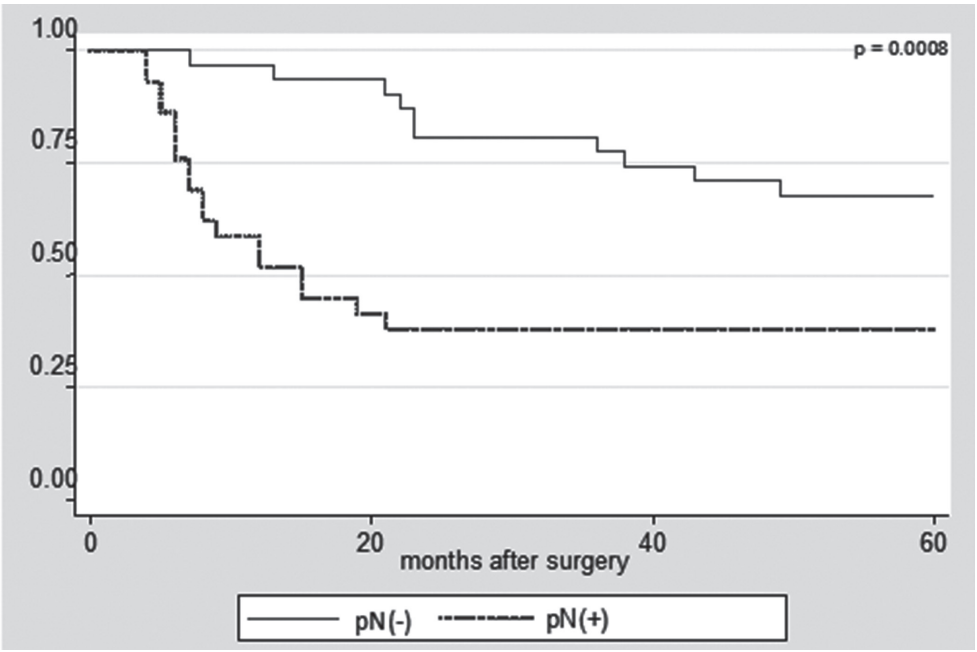

Fig. 5. Kaplan–Meier survival analysis in relation to lymph nodes involvement in the surgical specimen.

Table 4

Univariate and multivariate analysis of prognostic factors.

	Univariate analysis				Multivariate analysis Cox			
	Loco-regional recurrence		Death		Loco-regional recurrence		Death	
Parameter	OR (95% CI)	P Value	OR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Stage (I, II vs III, IV)	4.32 (0.85–22.08)	0.079	5.09 (0.99–26.01)	0.051	3.10 (0.69–13.88)	0.139	3.64 (0.83–16.08)	0.088
Site (FOM[a] vs tongue)	0.36 (0.12–1.04)	0.059	0.34 (0.12–0.99)	0.048	0.37 (0.15–0.90)	0.028	0.33 (0.14–0.78)	0.011
pN(+) vs pN(-)	4.70 (1.57–14.13)	0.006	3.44 (1.19–9.95)	0.023	3.22 (1.35–7.68)	0.008	2.73 (1.21–6.12)	0.015
Neck dissection (MRND[b] vs SND[c])	3.05 (1.02–9.15)	0.046	2.11 (0.74–6.05)	0.164	1.30 (0.49–3.42)	0.593	0.99 (0.41–2.44)	0.992

[a] FOM — floor of the mouth
[b] MRND — modified radical neck dissection
[c] SND — selective neck dissection

In univariate analysis localisation of the SCC in the tongue (p = 0.048) and lymph node involvement (p = 0.023) had an adverse impact on DSS. It was also found that the patients with cervical metastases (p = 0.006) and those who underwent MRND (p = 0.046) had higher risk of LRR (Table 4).

Also in multivariate analysis SCC of the tongue achieved the status of independent predictor, had an influence on higher risk of LRR (p = 0.028) and shorter DSS (p = 0.011). Lymph node involvement was the second independent predictor of LRR (p = 0.008) as well as DSS (p = 0.015) (Table 4).

DISCUSSION

Despite improvement in treatment modalities in OSCC the prognosis remains poor. The 5-year overall survival (OS) rate ranges from 32.8% to 56% and the 5-year DSS rate varies from 41% to 74% [3, 11–13]. Similar results were observed in our study, where 5-year DSS rate was 53.3% (95%CI: 40.0–66.3). The prognosis is highly dependent on the histological subtype of the SCC, stage and the location of the tumour. Good blood supply as well as the lymphatic drainage are the causes of the metastasis in the early stages of cancers of the tongue and FOM. Therefore, despite the absence of clinical and radiological symptoms of tumour spreading, occult metastases are found in 23.1%–45% of patients [2, 5, 6]. In our study only 2 (13.3%) patients had occult metastases. Lymph node involvement comprises one of the predictors of adverse prognostic significance [2, 3, 5]. In the analysed group of patients with confirmed lymph node metastases, the 5-year DSS rate was 37.9% (95%CI: 20.7–57.7) (p = 0.021). Similar findings were reported by Woolgar *et al.*, in their group of patients with lymph node metastases, operated due to SCC of the oral cavity and the oropharynx, the 5-year survival rate was 44% [4]. Also the prognosis is worsen by multiple metastases and their location in the IV and V cervical level [3]. In addition, the risk of death from cancer is increased by the presence of positive lymph nodes with ECE [3, 4, 14]. These findings are in accordance with our results — patients with ECE had 100% mortality rate (p = 0.018).

Widely recognised prognosticator in OSCC is the tumour stage. The 5-year survival rate in stage I and II is estimated between 65.6% and 96% [15, 16]. Similar results were obtained in the present study, in which the 5-year DSS rate in the group of patients with stage I and II SCC was 81.8% (95%CI: 48.2–97.7) compared to 46.9% (95%CI: 32.5–61.7) survival rate in patients with advanced malignancies (p = 0.048).

Controversial prognostic factor in the OSCC is the location of the tumour. Most studies show no predictive value of the location of cancer in the oral cavity [3, 15, 17]. However, the present study showed higher percentage of LRR (p = 0.056) and higher risk of death (p = 0.045) among patients with tongue can-

cer. The 5-year DSS rate in patients with tongue cancer was only 37.5% (95%CI: 18.8–59.4) compared to 63.9% (95%CI: 46.2–79.2) in patients with SCC of FOM. Similar results were obtained by Zelefsky *et al.*, who found frequent recurrence and poorer prognosis in patients with tongue cancer compared to the SCC of FOM [18]. Also Rusthoven *et al.* showed worse prognosis in the tongue cancer than in other sites in the oral cavity [19].

Also patients with more posteriorly located tumours have a lower 5-year survival. Some studies confirmed worse prognosis as a result of frequent metastasis to regional lymph nodes, in SCC of the base of the tongue, as compared to tumours located in the mobile tongue [11, 20, 21]. In the present study we also reported higher rate of LRR ($p = 0.024$) and worse survival ($p = 0.052$) among patients with SCC of the base of the tongue. Also posteriorly localised SCC of FOM had higher risk of LRR ($p = 0.010$).

The size of the primary tumour affects both the choice and outcome of treatment. Clinical tumour staging in the TNM classification is based on tumour greatest surface dimension for categories T1–T3, and involvement of specific structures (such as bone and skin) for T4. Large tumours have a greater risk of local recurrence and metastasis to regional lymph nodes, which is associated with poor prognosis [3, 7, 8]. However, recent reports indicate that the thickness and depth of the tumour are more important than the diameter in predicting nodal metastasis and survival, especially in early stage OSCC [14, 22, 23]. In patients with SCC of the tongue and the depth of tumour greater than 5 mm lymph node involvement is found in over 50% of cases [22]. Tumour thickness is less important predictor, especially in the case of exophytic tumours with minimal infiltration of stroma [5, 24]. However, risk of nodal metastasis increases in SCC of FOM with thickness more than 7.5 mm [23].

The most important feature of SCC is a histological grading. In general, poorly differentiated cancers are more aggressive in relation to the moderate and well differentiated tumours. However, not always the histological grading, especially in the early stages of the disease, correlates with the outcome [2, 5, 22], which was also proved in this study. More important histological features, which influence outcome, are pattern of invasion and perineural invasion. According to Brandwein-Gensler *et al.*, histologic features of cancer, including a widely dispersed pattern of tumour invasion, perineural invasion of large nerves (diameter > 1 mm), and limited or no lymphoid response of the stroma, are all predictors of high risk of local recurrence despite clear surgical margins [10]. Another adverse histologic prognosticators are lymphovascular invasion and muscles involvement [5, 9, 25].

Also controversial prognostic factor in OSCC is bone involvement. Some authors concluded that the presence of tumour infiltration of bone adversely affects prognosis [8, 14]. The other authors do not support these findings [26, 27]. In the present study in the group of patients with and without bone involvement LRR rates were similar and amounted 33.3% and 36.4%, respectively.

Prognosis and adjuvant treatment depend on the status of the surgical resection margins. Distance from invasive carcinoma to surgical margins is measured in millimeters. From the surgical point of view, >5 mm is clear, 1–5 mm is close and <1 mm is an involved margin [10]. A close or involved surgical margin is regarded as a strong predictor of outcome [8, 28]. However, our findings showed that the status of the surgical margins did not correlate with LRR and DSS rate, as well as in the studies of Kademani *et al.* and Brandwein-Gensler *et al.* [10, 29]. This might be the result of using frozen section examination in assessing of the status of the surgical resection margins, as well as a qualification of patients for adjuvant radiotherapy in case of involved margin.

Furthermore, present study showed no predictive value of general and clinical factors such as age, sex, comorbidities and the adjuvant radiotherapy. We found higher risk of LRR in patients who underwent modified radical neck dissection (MRND) ($p = 0.043$). This relationship may be explained by the fact that the MRND was performed in advanced stages of the cancer.

CONCLUSIONS

The analysis of prognostic factors in SCC of tongue and FOM revealed that lymph node involvement was an independent predictor of LRR and DSS. Moreover, higher risk of LRR and death was observed in patients with tongue cancer, especially localised posteriorly. The relatively low 5-year DSS rate in the study group was the result of poor oncological awareness of patients. This influenced the progress of cancer and postponed the patients decision about the treatment.

CONFLICT OF INTEREST STATEMENT

None declared.

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