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Evaluation of a Post-treatment Follow-up Program in Patients with Oral Squamous Cell Carcinoma

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Abstract

Objectives

The duration and the frequency of follow-up after treatment of oral squamous cell carcinoma are not standardized in the current literature. The purpose of this study was to evaluate our local standard post-treatment and follow-up protocol.

Materials and methods

Overall, 228 patients treated curatively from 01/2006 to 07/2013 were reviewed. To evaluate the follow-up program, data on the secondary event were used. To determine risk groups, all patients with tumor recurrence were specifically analyzed. Relapse-free rate were estimated by the Kaplan-Meier product limit method. The chi-square test was used to identify independent risk factors for tumor relapse.

Results

In total, 29.8 % patients had a secondary event. The majority of the relapse cases (88.2 %) were detected within 2 years postoperatively, 61.8 % of them within the first year. Most events were local recurrences (34.7 %). UICC-stage IV was significantly associated with tumor recurrence ($p = 0.001$). Gender ($p = 0.188$), age ($p = 0.195$), localization ($p = 0.739$), T-stage ($p = 0.35$), N-stage ($p = 0.55$), histologic grade ($p = 0.162$), and tobacco and alcohol use ($p = 0.248$) were not significantly associated with tumor recurrence. Patients with positive neck nodes relapsed earlier ($p = 0.011$). The majority of relapses (86.3 %) were found in asymptomatic patients at routine follow-up.

Conclusions

The results of this study suggest an intensified follow-up within the first 2 years after surgery.

Clinical relevance

Given the higher relapse rate of patients exhibiting an UICC-stage IV and/or positive neck nodes, it seems to be from special interest to perform in this group a risk-adapted follow-up with monthly examinations also in the second year.

Keywords

Oral squamous cell carcinoma Follow-up Tumor recurrence Risk groups

Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignant tumor of the mouth. Worldwide, its estimated incidence is around 275,000 cases per year [1]. Despite great progress in surgery and adjuvant radio- and chemotherapy in the last decades, the prognosis of OSCC is still poor with a 5-year survival rate at about 50 to 55 % [2]. Main reason besides the aggressive local invasion and metastasis is tumor relapse. A recurrence rate from 35.5 to 47.1 % has been reported [3, 4].

For an early detection of recurrences and to offer the patient a promptly second curative therapy, a post-treatment follow-up protocol is indispensable for these patients. Some authors argue that too much follow-up is costly and labor intensive [5, 6, 7], while others believe that a reduction in the follow-up period is irresponsible due to a high risk of tumor relapse [8, 9].

The purpose of this presented study was to evaluate our local standard treatment and follow-up protocol in patients with oral squamous cell carcinoma and to identify risk groups for tumor recurrence.

Materials and methods

All patients included signed consent for the evaluation of their medical records. The medical records of 228 patients with histological confirmed diagnoses of OSCC who underwent surgery at the Jena University Hospital from 01/2006 to 07/2013 with curative intent without previous malignancy were reviewed. The follow-up program was started after completion of adjuvant radiotherapy or combined radio-chemotherapy, if necessary, and postoperative rehabilitation. To determine risk groups, all patients with tumor recurrence were specifically analyzed.

Surgical regimen and clinical classification

All patients underwent curative resection of OSCC. Neck dissection was routinely performed in all patients. Resection specimens were pathologically diagnosed using primary and neck dissection tissues. Tumor stage was classified according to the TNM classification of the International Union against Cancer (UICC) [10]. Tumor size (T), lymph node metastasis (N), and distant metastasis (M) were staged based on clinical and histopathologic findings in addition to images from computed tomography (CT), ultrasonography (USG), and chest x-ray examination. Tumor histological grade (G) was defined according to the WHO classification.

Follow-up program

Routine follow-up included monthly clinical examinations in the first year, trimonthly examinations in the second year, and biannual examinations thereafter for up to the end of fifth year. After the fifth postoperative year, only high risk patients were still examined biannually. Each visit included a short medical history, inspection and palpation of the oral cavity, palpation, and a routine USG of the head and neck region. Routine CT with contrast agent was performed after 6, 12, and 24 months, postoperatively. Chest x-ray was taken every 12 and 24 months after treatment to detect lung metastasis. USG of abdomen were performed after 12 and 24 months. In addition, CT, chest x-ray and USG of abdomen were performed after 36, 48, and 60 months in patients with $T > 2$ and/or positive neck nodes and/or $M = 1$ and/or $R > 0$ and/or $G > 2$.

Secondary event

A secondary event was defined as local recurrence, regional recurrence, locoregional recurrence, distant metastasis, or a second primary tumor. Local recurrence was defined as tumor growth at the same location within a period of 5 years after primary treatment with curative intent. Tumor growth at a different site in the aerodigestive tract or at the same location in the oral cavity more than 5 years was considered as second primary tumor. Regional recurrence was defined as tumor regrowth in lymph nodes of the neck and locoregional recurrence as tumor regrowth at the same location in combination with regrowth in lymph nodes of the head and neck. Distant metastasis was defined as tumor spread from the aerodigestive tract to distant organs or distant lymph nodes outside the head and neck region.

Statistical analysis

To evaluate the follow-up program, data on the first tumor recurrence or first second primary tumor and also further events in the head and neck region or elsewhere in the body were used. Statistical analyses were performed using SPSS 21.0 for Windows (Chicago, IL). Relapse-free rate for patients with secondary event were estimated by the Kaplan-Meier product limit method. Relapse-free rates were calculated with local recurrences, regional recurrences, locoregional recurrences, distant metastases, and second primary tumors. Statistical significance was compared using the log-rank test. Chi-square test was used to identify independent risk factors for tumor recurrence. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics are summarized in Table 1. In total, 228 patients were included: 177 men (78 %) and 51 women (22 %) with median age of 58 years. Mean age of 60 years ranged from 24 to 89 years at the time of surgery. The most prevalent site of tumor localization was the floor of mouth in 90 patients (39.5 %), followed by tongue in 50 patients (21.9 %), multiple areas in 28 (12.3 %), lower jaw in 19 patients (8.3 %), retromolar region in 13 patients (5.7 %), upper jaw in 10 patients (4.4 %), buccal mucosa in 9 patients (3.9 %), and soft palate in 9 patients (3.9 %). One hundred seventy-six patients (77.2 %) underwent follow-up visits strictly according to protocol. Twenty-six patients (11.4 %) participated irregularly, and further 26 patients (11.4 %) did not take part in the follow-up program or shown up at other hospitals.

Table 1 Patient characteristics and appearance of a secondary event

Characteristics	No. of patients (%)	No. of patients with a secondary event (%)	*p* value
All patients	228 (100)	68 (100)	
Gender			0.188
Male	177 (77.6)	49 (72.1)	
Female	51 (22.4)	19 (27.9)	
Age			0.195
≤49	39 (17.1)	15 (22.1)	
≥50	189 (82.9)	53 (77.9)	
Site			0.739
Oral floor	90 (39.5)	31 (45.6)	
Tongue	50 (21.9)	14 (20.6)	
Lower jaw	19 (8.3)	6(8.8)	
Retromolar region	13 (5.7)	5 (7.4)	
Upper jaw	10 (4.4)	1 (1.5)	
Buccal mucosa	9 (3.9)	2 (2.9)	
Soft palate	9 (3.9)	3 (4.4)	
Multiple areas	28 (12.3)	6 (8.8)	
T-stage			0.35
T1	75 (32.9)	28 (41.2)	
T2	82 (36.0)	20 (29.4)	
T3	22 (9.6)	6 (8.8)	
T4	49 (21.5)	14 (20.6)	
N-stage			0.55
N-	134 (58.8)	41 (60.3)	
N+	94 (41.2)	27 (39.7)	
UICC-stage			0.001
I	63 (27.6)	15 (22.1)	
II	49 (21.5)	8 (11.8)	
III	30 (13.2)	6 (8.8)	
IV	86 (37.7)	39 (57.4)	
Histologic grade			0.162
Well	24 (10.5)	5 (7.4)	
Moderately	145 (63.6)	40 (58.8)	
Poorly	59 (25.9)	23 (33.8)	
Risk factors			0.248
Alcohol	6 (2.6)	1 (1.5)	
Tobacco	66 (28.9)	14 (20.6)	

Alcohol and tobacco	95 (41.7)	32 (47.1)	
No risk factors	61 (26.8)	21 (30.8)	

N+ positive neck nodes, *N−* negative neck nodes

Tumor relapse

Sixty-eight of 228 patients (29.8 %) had a secondary event. After the secondary event, further 27 events were found in these patients during follow-up. The largest proportion of all events consisted of local recurrences. Thirty-three of these 95 events (34.7 %) were local recurrences. Distant metastases and regional recurrences were detected in 21 events (22.1 %) and 19 events (20.0 %), respectively. Further 12 events (12.6 %) were locoregional recurrences and 10 events (10.5 %) second primary tumors (Table 2). Forty-two secondary events (61.8 %) were detected within 1 year, and sixty events (88.2 %) were detected within 2 years. The mean interval between surgery and secondary events was 13 months (range, 1 to 53 months), and the median interval was 10 months, suggesting that 50 % of these events were detected in the first 10 months of follow-up program.

Table 2 Detecting recurrence in the follow-up

	Site of recurrence				
	Local (%)	Regional (%)	Loco-regional (%)	Second primary (%)	Distant metastasis (%)
Routine follow-up visit (*n* = 82)					
Clinical examination (*n* = 41)	16 (48.5)	7 (36.8)	7 (58.3)	4 (40.0)	7 (33.3)
Radiological examinations (*n* = 31)	11 (33.3)	6 (31.6)	3 (25.0)	4 (40.0)	7 (33.3)
Ultrasound examinations (*n* = 10)	0	6 (31.6)	1 (8.3)	0	3 (14.3)
Self-initiated visit (*n* = 13)	6 (18.2)	0	1 (8.3)	2 (20.0)	4 (19.0)
Total (*n* = 95)	33 (100)	19 (100)	12 (100)	10 (100)	21 (100)

Chi-square test revealed that stage IV was significantly associated with tumor recurrence ($p = 0.001$). In contrast, gender ($p = 0.188$), age ($p = 0.195$), localization ($p = 0.739$), T-stage ($p = 0.35$), N-stage ($p = 0.55$), histologic grade ($p = 0.162$), and tobacco and alcohol use ($p = 0.248$) were not significantly associated with tumor recurrence.

All patients with tumor recurrence were specifically analyzed to determine risk groups. Relapse-free rate for patients with secondary event were estimated by Kaplan-Meier product limit method. No statistically significant differences could be found between patients with different T-stage ($p = 0.3$), UICC-stage ($p = 0.09$), histological grade ($p = 0.507$), gender ($p = 0.738$), localization ($p = 0.7$) and with risk factors tobacco and alcohol use ($p = 0.369$). However, there was a statistically significant difference between patients with negative neck nodes and those with positive neck nodes ($p = 0.011$). Patients with pathologically diagnosed positive neck nodes in the primary operation relapsed earlier. In addition, all patients with tumor recurrence and pathologically diagnosed positive neck nodes in the primary operation were detected within 20 months (Fig. 1).

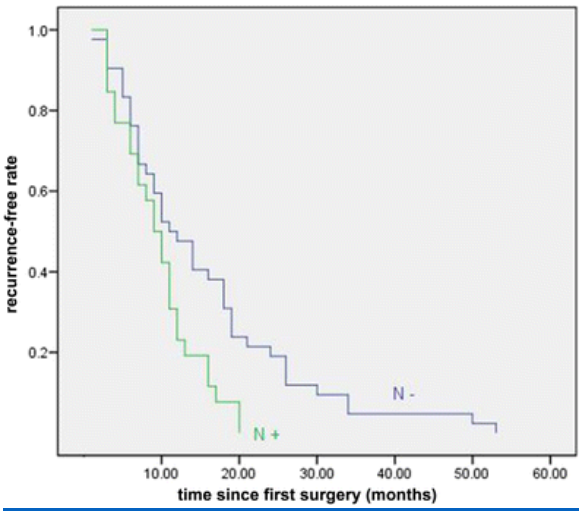

Fig 1 Recurrence-free rate in patients with secondary event by node classification: positive neck nodes (N+; *green line*) and negative neck nodes (N-; *blue line*)

Tumor relapse detected on routine follow-up

Tumor relapse was discovered during a patient-initiated visit for complaints in 13 (13.7 %) events and was found during a routine follow-up visit in 82 (86.3 %) cases. Overall, 41 (43.2 %) events were identified clinically, 31 (32.6 %) were detected by routine radiological examination and further 10 (10.5 %) by USG. In total, radiological examination detected 11 occult local recurrences, 6 regional recurrences, 3 locoregional recurrences, 4 second primary tumors, and 7 distant metastases. USG identified 6 regional recurrences, 1 locoregional recurrence and 3 distant metastases. In the patient-initiated group, the most common site was local recurrence (6 cases). (Table 2).

Discussion

The optimal post-treatment follow-up strategy for patients with OCCC was not yet described in the current literature. The majority of reported follow-up programs were site-specific or applicable to all head and neck sub-sites. Furthermore, follow-up strategies vary substantially among specialized centers. The number of visits ranges from a minimum of 9 visits over 3 years [11] to a maximum of 48 visits over 5 years [12]. Various accepted international guidelines for follow-up treatment protocols are listed in Table 3 [13, 14, 15].

Table 3 International guidelines for follow-up treatment protocols

	Post-treatment year	Follow-up strategy	Imaging
AWMF [13], Germany	First year	Every 3 months	Every 6 months
	Second year	Every 3 months	Every 6 months
	Third year	Every 6 months	Every 12 months
	Fourth year	Every 6 months	Every 12 months
	Fifth year	Every 6 months	Every 12 months
	>Fifth year	Routine screening	–
NCCN [14], United States of America	First year	Every 1–3 months	Within 6 months[a]
	Second year	Every 2–6 months	–
	Third year	Every 4–8 months	–
	Fourth year	Every 4–8 months	–
	Fifth year	Every 4–8 months	–

	>Fifth year	Every 12 months	–
BAHNO [15], Great Britain	First year	Every 4–6 weeks	Within 3 months
	Second year	Every 4–6 weeks	–
	Third year	Every 3 months	–
	Fourth year	Every 6 months	–
	Fifth year	Every 6 months	–
	>Fifth year	Every 12 months	–

AWMF Association of Scientific Medical Societies in Germany, *NCCN* National Comprehensive Cancer Network, *BAHNO* British Association of Head and Neck Oncologists

[a]Imaging is recommended for T3-4 or N2-3 disease only

In our institute, all patients with OSCC are followed according to the evidence-based guideline for oral cavity cancer organized under the aegis of the Association of Scientific Medical Societies in Germany (AWMF). This guideline involves an interval between follow-up visits every 3rd month in the first 2 years and every 6 months in year 3 to 5. After the completed 5th year, patients should attend routine tumor screening [13]. We strictly follow this guideline, with the only exception that we perform a more frequent follow-up with monthly examinations in the first year. The structure of this follow-up program is designed to identify early recurrences, which is known to be more frequent in the first 2 years after completion of primary treatment [16]. Comprehensive Cancer Network (NCCN) guidelines scheduled follow-up visits, every 1 to 3 months for the first year, every 2 to 6 months for the second year, every 4 to 8 months for the third to fifth years, and then annually [14]. Additionally, British Association of Head and Neck Oncologists (BAHNO) recommend clinical examinations every 4–6 weeks during the first and the second year after primary therapy, every 3 months for year 3, every 6 months for years 4–5, and annually thereafter [15].

In this presented study, 61.8 % of the secondary events occurred within the first year, 88.2 % within 2 years, and all events were detected within 5 years. These results could require a stricter follow-up for locoregional control within the first 2 years after surgery and confirmed our monthly visit program during the first year. One point to think about is if patients should be seen more frequently in the second year with monthly or bimonthly examinations. In addition, tumor recurrence was discovered during a patient-initiated visit for complaints only in 13 (13.7 %) events and was detected during a routine follow-up visit in 82 (86.3 %) cases. This confirms the importance of a routine follow-up and endorses our strategy.

Overall, 29.8 % of the analyzed patients had recurrences. This is fewer yet comparable to the literature, with recurrence rates varying between 35.5 and 47.1 % [3, 4]. The most frequent form of relapses was local recurrences which accounted for 34.7 % of all cases. Chi-square test and log-rank test showed that UICC-stage IV was important factor of tumor recurrence ($p = 0.001$) and that pathologically diagnosed positive neck nodes predict earlier relapse ($p = 0.011$). All patients with tumor recurrence and pathologically diagnosed positive neck nodes in the primary operation relapsed within 20 months. Maybe, it seems to be suitable to classify patients with UICC stage IV and/or positive neck nodes as high risk group for tumor recurrence. More frequent follow-up visits with monthly examinations in the second year could be necessary in these patients.

However, the benefit in cancer survival with routine follow-up has not been well proven in the current literature. Studies have not been conclusive with respect to survival, in the physician-detected recurrent disease versus patient-detected [17, 18]. Therefore, several references consider that regular follow-up program does not have any influence on survival outcomes [18, 19, 20].

Due to the anatomical and functional alterations after operation, post-treatment surveillance for the recurrence or distant metastasis of OSCC is a diagnostic challenge. In this presented study, 41 (43.2 %) events were identified clinically. However, clinical examination alone is not sufficient to detect tumor recurrences. Imaging modalities such as USG, chest x-ray, and CT can provide key information for the adequate stages of patients and evaluation of occult recurrences. In all, 31 events (32.6 %) were detected by routine radiological examination and further 10 (10.5 %) by USG in this study.

In our institute, the follow-up program was performed by the same physicians. Therefore, scrupulous head and neck examinations were realized. In addition to inspection and palpation of the oral cavity, and palpation of the neck, routine USG was used. We think that combination of clinical examination and USG is valuable in detecting regional recurrence early. USG findings of cervical lymph node metastasis were shown to change as quickly as within 2 to 4 weeks [12]. Because of its advantages of simplicity, its lack of radiation exposure and lower costs, USG should be routinely performed at each visit. In all, USG had importance for detection of 6 regional recurrences, 3 distant metastases, and 1 locoregional recurrence.

AWMF recommends CT scan of the head and neck region every 6 months in the first 2 years after treatment and every 12 months for the third to fifth years [13]. In the current study, routine CT was used after 6, 12, and 24 months postoperatively. Only in patients with $T > 2$ and/or positive neck nodes and/or $M = 0$ and/or $R > 0$ and/or $G > 2$ CT (besides chest x-ray and USG of abdomen) was performed after 36, 48, and 60 months. Above all, radiological examinations were beneficial in detecting occult local recurrences (11 cases), regional recurrences (6 cases), locoregional recurrences (3 cases), second primary tumors (4 cases), and distant metastases (7 cases). In contrast, other international guidelines are not recommending post-treatment baseline imaging at regular intervals. NCCN suggests a radiological examination within 6 months for patients with T-stage 3–4 or N-stage 2–3. Further imaging investigation are based only on symptoms or signs [14]. In addition, BAHNO recommends imaging examination 3 months after completion of treatment [15]. There are indications in the literature that radiological examinations at regular intervals provide no advantage over improvement of patient outcomes [21]. However, radiological examination can detect recurrence at an early stage in order to provide salvage procedures with curative intent.

In the present study, we used CT with contrast agent and chest X-rays to detect occult recurrences such as second primary tumors and distant metastases. Further imaging modalities are magnetic resonance (MR) imaging and 18-F-fluorodeoxyglucose positron emission tomography (18-FFDG-PET). The advantage of MR over CT is a better soft-tissue differentiation [22]. In contrast, CT has lower cost than MR, a shorter examination time with reduction of motion artifacts.

There are indications that 18-FFDG-PET has a better accuracy in recurrence detection of head and neck cancer than with CT and/or MR [23], but it is not available in all hospitals and is more cost intensive. Generally, the baseline imaging exam should be the same that has been performed in the pretreatment staging [24].

Conclusion

The results of this study suggest an intensified follow-up within the first 2 years after surgery, e.g., in a monthly interval. Imaging examinations are useful to detect occur recurrence and should be performed at regular intervals. Given the higher relapse rate of patients exhibiting an UICC-stage IV and/or positive neck nodes, it seems to be from special interest to perform in this group a risk-adapted follow-up with monthly examinations also in the second year.

Notes

Compliance with ethical standards

Conflict of interest

The authors declare that that they have no conflict of interest.

Funding source

No funding was secured for this study.

Ethical approval

Ethical standards were considered when performing the presented study. All patients gave written consent to the evaluation of their records. Prior to starting the presented study, we asked the local ethics committee of the Medical Faculty of the University Jena for approval. We were informed that ethical approval is not required as the presented study bases on routinely performed and retrospectively evaluated medical records.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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