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The Value of Post-treatment Surveillance for Detection of Loco-regional Recurrences in Oral Tongue Cancer

FREDRIK LANDSTRÖM[1], ELIN ASPENBLAD[2], JOHAN REIZENSTEIN[3] and STEFAN KRISTIANSSON[1]

[1]*Department of Otolaryngology, Örebro University Hospital, Örebro University, Örebro, Sweden;*
[2]*Örebro School of Medical Sciences, Örebro, Sweden;*
[3]*Department of Oncology, Örebro University Hospital, Örebro, Sweden*

Abstract. *Background/Aim: Follow-up after treatment for oral tongue cancer consists of routine follow-up visits for five years. It has been suggested that this program is inefficient for finding recurrences. The primary objective of this study was to investigate how recurrences are detected; at routine follow-up visits, at patient-initiated visits, or incidentally. The secondary objective was to investigate whether the two-year survival after diagnosis of recurrence depended on the manner of detection. Patients and Methods: Patients with recurrences from oral tongue cancer between 1988 and 2016 were included. Survival was analysed by the Kaplan–Meier method and log-rank test. Results: A total of 75 patients were included. In 67% of patients, recurrences were detected at routine follow-up visits, and in 27% at patient-initiated visits. No significant difference in survival between the groups was found (p=0.56). Conclusion: The majority of recurrences were detected at routine follow-up visits. Patient-initiated recurrence detection did not lead to increased survival.*

The oral tongue is the most common location for squamous cell carcinoma in the oral cavity with an incidence of about 160 cases annually in Sweden (1). Surgical resection of the primary tumour is the most common treatment for oral tongue squamous cell carcinoma (OTSCC) usually followed by postoperative radiotherapy. In lymph node-positive OTSCC a neck dissection is usually performed concurrently with the tongue resection. In node-negative OTSCC the strategy has historically been to either do a staging neck dissection, regional radiotherapy or watchful waiting. The national guidelines in Sweden, however, now recommend active treatment of the node-negative neck (2). Reconstruction with either a free or loco-regional flap is sometimes performed especially if the tumour growth involves the floor of the mouth. Postoperative radiotherapy is administered when clinically indicated based on the staging and the pathology report. Existence of lymph node metastasis by the time of diagnosis is associated with higher risk of recurrence and decreased survival (3, 4). The prognosis for patients with recurrences of OTSCC after multimodality treatment is poor (5). The risk of recurrence is relatively high even with clinically lower stage tumours (6). Follow-up after primary treatment for OTSCC serves multiple purposes: detection of early recurrences and second primary tumours, pain management, detection of treatment related side effects and to offer emotional support for the patient and his/her relatives. There is a basic assumption that the earlier a recurrence is found the better the prognosis. The oral cavity is, compared to many other locations, easy to inspect and palpate, not only for the physician but also for the patient. In vigilant patients, this could be an advantage that could lead to earlier detection and treatment of local recurrences, thus improving the prognosis. In a study reported by Zätterström *et al*. where 78% of recurrences were found in visits initiated by the patients in contrast to 22% at routine follow-up visits (7). An exception could be patients that had reconstructive surgery, since recurrences can go undetected, concealed by the flap. The neck is also relatively easy for self-examination but after neck dissection and/or radiotherapy it can be hard to assess even for experienced physicians. The majority of loco-regional recurrences occur within the first two years and almost all within five years after primary treatment (8, 9). This is reflected in the national Swedish guidelines for post-treatment surveillance, that recommend that the patient should be assessed by a physician every third month for the first two years, every sixth months for the next two years and then a last follow-up at five years after treatment (2). There

Correspondence to: Fredrik Landström, Dept. of Otolaryngology, H-Building, Örebro University Hospital, Örebro, Sweden. Tel: +46 196021000, e-mail: fredrik.landstrom@regionorebrolan.se

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Table I. *The demographics, staging, recurrence frequency and survival for all patients and for the groups defined by how the recurrence was diagnosed. The five patients in the incidentally discovered group have been omitted.*

	All patients	Detected at follow-up visit	Detected at patient-initiated visit
Patients			
Total	75	50	20
Female	40 (53%)	26 (52%)	13 (65%)
Male	35 (47%)	24 (48%)	7 (35%)
Age			
Median age (range)	71 (23-90)	62.5 (26-90)	73.5 (23-89)
TNM			
T1	20 (27%)	12 (24%)	7 (35%)
T2	32 (43%)	19 (38%)	12 (60%)
T3	14 (18%)	12 (24%)	1 (5%)
T4	9 (12%)	7 (14%)	0
Stage			
I	20 (27%)	12 (24%)	7 (35%)
II	25 (33%)	15 (30%)	9 (45%)
III	9 (12%)	7 (14%)	2 (10%)
IV	21 (28%)	16 (32%)	2 (10%)
Recurrence			
Local	39 (52%)	26 (52%)	11 (55%)
Regional	36 (48%)	24 (48%)	9 (45%)
Distant*	3	1	0
Treatment of recurrence with curative intention	32 (43%)	21 (42%)	11 (55%)
Median survival after recurrence (range) (months)	9 (0-135)	7 (0-135)	5.5 (0-45)
Median survival after treatment of recurrence with curative intention (range) (months)	15.5 (7-135)	10 (7-135)	19 (8-45)
2-years survival after recurrence (% of group)	15 (20%)	10 (20%)	4 (20%)

*No distant metastases were detected alone but in addition to either local/regional or loco-regional recurrences.

is some controversy regarding the value of routine follow-up in patients treated for oral cavity cancer and it has been suggested that the current surveillance program after primary treatment is inefficient for recurrence detection and does not increase the tumour-specific survival (10-12).

The primary objective of this retrospective study was to investigate how loco-regional recurrences after treatment for OTSCC were detected; at routine follow-up visits, at patient-initiated visits or incidentally. The secondary objective was to investigate if the two-year survival depended on how the recurrences were detected. The hypotheses were, first, that the majority of the recurrences from OTSCC were detected by the patients themselves and, second, that the patient-detected recurrences were associated with a significantly higher two-year survival than recurrences detected at routine follow-up visits.

Patients and Methods

Study group. This retrospective cohort study was based on information from the Örebro Head and Neck Cancer Register and approved by the regional board of ethical evaluation. The register includes all patients treated for head and neck cancer at the Örebro University Hospital since January 1988. All patients treated for OTSCC between January 1988 and December 2016 that had loco-regional recurrences detected in the follow-up period were selected for data acquisition. The data acquired from the register were date of diagnosis, tumour, lymph-node, distant metastasis (TNM)-classification, primary treatment, date and type of recurrence and death. Information about how the recurrences were detected and treated were collected from the patient's medical records. Patients where information about recurrence detection and/or survival data was missing were excluded.

Statistical methods. The Kaplan–Meier method was used for survival analysis and the log-rank test was used to compare the two-year survival between the patients in whom the recurrences were detected at follow-up visits and those that recurrences were detected at patient-initiated visits. For the significance level 0.05 was chosen. SPSS Statistics v 25.0 (Armonk, NY, USA) was used for the statistical analysis.

Results

Mode of recurrence detection. There were, from a total of 406 patients, 114 patients in the register with recorded loco-regional recurrences after primary treatment for OTSCC. This makes the total recurrence rate 28.1%. Thirty-nine patients were excluded because information about how the recurrences

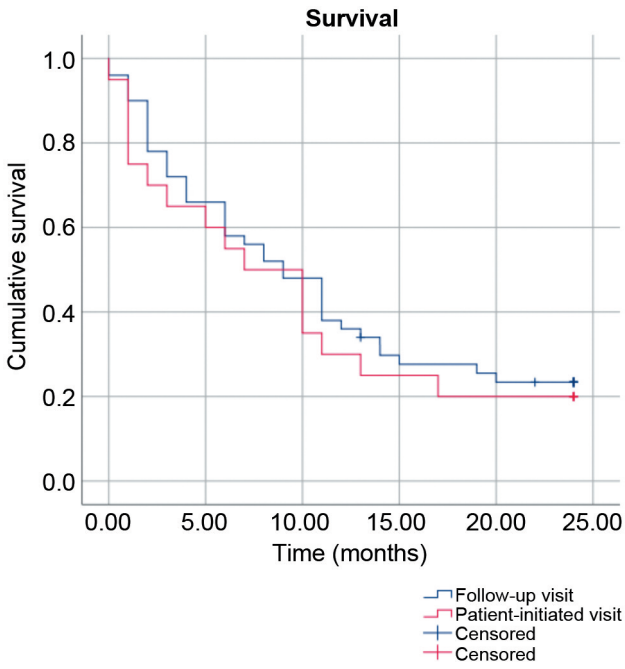

Figure 1. *Kaplan–Meier curve for the two-year survival after recurrence for patients where recurrences were detected at follow-up visits (blue) or at patient-initiated visits (red). No statistically significant difference in survival was found (p=0.56) (N=70).*

were detected and/or survival were lacking. The remaining 75 patients were eligible for inclusion in the study. The study group consisted of 35 men and 40 women, and the median age was 71 years (Table I). TNM classification, staging, loco-regional recurrences, and survival for the overall study group and for groups stratified for recurrence detection, are reported in Table I. A few patients (One in the follow-up group and 2 in the incidental group) had distant metastases at the time of detection of the loco-regional recurrences. The histopathology in all patients was squamous cell carcinoma. All patients had been treated with surgical resection followed by postoperative radiotherapy in most cases. The exception was patients with T1 tumours with low risk Brandwein score, who did not receive primary radiotherapy (13). The management of the N0 neck varied throughout the study period. From 1988 to 2010 watchful waiting was quite common. Since 2010, more staging neck dissections have been performed. Office based ultrasound was introduced at the Otolaryngology department of Örebro in 2006 and has since become a cornerstone of follow up, especially for the neck.

Overall, two thirds of the loco-regional recurrences (50/75) were detected at scheduled routine follow-up visits (Table I). Twenty recurrences (27%) were detected at patient-initiated visits. In five patients, the recurrences were detected incidentally when radiological examination was performed for other reasons. Since this mode of detection was not relevant to the secondary objective of the study, this group was excluded from the survival analysis. The median time from primary treatment to detection of recurrence was seven months. 75% of the recurrences were detected within the first year, 88% the first two years and 95% within the first three years after primary treatment.

Treatment and survival. The treatment of the recurrences varied between extensive salvage surgery and best supportive care. Of the 70 patients that had recurrences in both groups, 32 patients were treated with salvage surgery and, in one patient, electrochemotherapy was performed with curative intention. In the follow-up visit group, 21 patients (42.0%) were treated with curative intention compared to 11 (55.0%) in the patient-initiated group, 29 (58.0%) and 9 (45.0%) patients were treated with palliative chemotherapy and best supportive care, respectively. There was no statistically significant difference in overall survival between the patients where the recurrences were detected at routine follow-up visits and those detected at patient-initiated visits (p=0.56) (Figure 1). The groups were, however, somewhat different in the distribution of age, sex and staging (Table I). In the patient-initiated group there were relatively more women and the patients were older. In the follow-up visit group 95% of the patients had primary T1-T2 tumours compared to 62% for the patient-initiated group. Only 15 of the 75 patients were alive two years after diagnosis of the loco-regional recurrence (20%). The overall median survival after detection of recurrence was nine months. In the small subgroups that received treatment with curative intention of the recurrences the median survival in the follow-up visit group was 10 (range=7-130) months compared to 19 (range=8-45) months in the patient-initiated group (Table I). This difference was not statistically significant.

Discussion

The results reported in this study are yet another reminder that the prognosis for OTSCC recurring after primary treatment is bleak. Only 20% of the patients in the study group were alive two years after diagnosis of a loco-regional recurrence. There are many good reasons to have scheduled follow-up visits after treatment for OTSCC. For instance, for the detection treatment-related side effects like osteoradionecrosis or accessory nerve paralysis, and for emotional support for both patients and their relatives. However, the role of routine follow-up visits for early detection of cancer recurrence and thereby, increased survival, remains controversial (10-12).

A significant majority of the recurrences in the 75 patients in this study were found at the scheduled follow-up visits contrary to our hypothesis. This differs from the results

reported by Zetterström *et al*. where 78% of recurrences were found at patient-initiated visits (7). In addition, in our study there was no statistically significant survival difference at two years after the diagnosis of recurrence between the patients that had their recurrence diagnosed at the scheduled visits and the patients that were diagnosed after an extra visit initiated by the patients themselves. The null hypothesis could thus not be rejected. This result is in accordance with the results reported by Zätterström *et al*. where there was no difference in survival between the groups (7). When the recurrences were detected, there was a small but not statistically significant difference where 55% of the recurrences in the patient-initiated group were treated with compared to 42% in the follow-up group. There was also a difference in median survival after treatment of the recurrence that was not statistically significant (19 vs. 10 months).

There are several limitations to consider when the study results are interpreted. First of all: It is a very small study even if all patients in the register with sufficient information in their medical records were included in the study. Even if the patients that were excluded because of insufficient information had been included the sample size would still be small and probably not sufficiently powered to detect a possible difference in survival. Secondly: the groups were not equal, in the patient-initiated group there were relatively more women, they were older, and they had smaller primary tumours. As a consequence, the primary treatment varied between the groups; a larger percent was treated with surgery alone in this group. The results suggest that these patients were generally more vigilant, which possibly led to an earlier diagnosis of the primary tumour. This hypothesis is interesting and could be the basis for a subsequent study, especially since the incidence of OTSCC is increasing in younger patients (14). The fact that the patients in this group were older, an eleven-year median age difference, could perhaps also partially explain that there was no detectable survival difference in spite of this supposed vigilance. The patients in the scheduled visit group had larger tumours on average resulting in more reconstruction than in the patient-initiated group and thus making self-examination more difficult.

Almost all recurrences in this study (95%) were found within three years after the primary treatment and 88% within two years. This is in accordance with the recommendations of the Swedish national guidelines for clinical follow-up visits every third month during the first two years (2). However, it has been questioned if it is really necessary to follow the patients for 5 years. Boysen *et al*. concluded that routine follow-up visits for more than three years after primary treatment is rarely indicated (9). Furthermore, Merkx *et al*. have reported that nine of ten local recurrences occurred within the first two years after primary treatment, which agrees with the results of this study (8). One of the main arguments against a five-year surveillance program is that these resources could be better used since so few recurrences are found three years after treatment. However, the follow-up program for the last two years of surveillance recommends visits only every sixth month and could therefore be considered a reasonable extra precaution rather than a misuse of resources. Additionally, the detection of recurrence is not the only reason for routine follow-up visits. These visits also have important roles in the emotional support of the patient, as well as providing an opportunity to assess the functional outcome and rehabilitations as well as managing potential complications. The follow-up visits also present an opportunity to detect second primary tumours in the oral cavity and to support the patient in reducing risk factors especially smoking (15). The results of this study also raised some questions about the follow-up guidelines. Despite diagnosis of recurrences, the survival was discouragingly low, which raises the question if the current follow-up guidelines in Sweden are insufficient. Could mandatory radiological controls with positron emission tomography/computed tomography (PET/CT) or magnetic resonance imaging (MRI) lead to earlier detection of loco-regional recurrences and increased survival?

The value of surveillance after primary treatment for OTSCC will likely remain controversial until definite studies have been performed. It is important that the surveillance program is evidence based. This study seems to support the current national guideline for follow-up, however, further investigation in a national prospective study is recommended.

Conflicts of Interest

The Authors have no conflicts of interest to report in relation to this study.

Authors' Contributions

Fredrik Landström contributed the idea, design and was the principal author of the manuscript. Elin Aspenblad have done the data collection and have co-authored the manuscript. Stefan Kristiansson and Johan Reizenstein have co-authored the manuscript.

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