Outcome of oral tongue squamous cell carcinoma has improved in Finland

Short title: Oral tongue carcinoma in Finland

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ABSTRACT

BACKGROUND: Incidence rates for oral tongue squamous cell carcinoma (OTSCC) are steadily rising worldwide.

METHODS: All patients diagnosed with primary OTSCC at the five university hospitals in Finland from 2005 to 2009 were included. The average follow-up time was 43 months (median 54, range 0 – 111).

RESULTS: Three hundred and sixty patients with primary OTSCC were identified. Treatment with curative intent was provided for 328 (91%) patients. The 5-year disease-specific survival rates were as follows: Stage I, 87%; Stage II, 72%; Stage III, 69%; Stage IV, 49%. The 5-year recurrence-free survival in general has improved from 47% in the previous series to 65% in the current series (p=0,000).

CONCLUSIONS: Outcome of OTSCC has statistically significantly improved in Finland. However, the relatively high number of disease recurrences in Stage I and II patients, when compared to Stage III and IV patients, calls for an investigation of new treatment approaches.

Introduction

Oral cancer (including lip cancer) constitutes an important part of the global burden of cancer, accounting for approximately 2% of all cases worldwide (1). Smoking, excessive alcohol consumption and HPV-virus infection are the most commonly cited risk factors in the literature (2,3). However, etiological factors, especially in young people with oral cancer are still mainly unknown (4,5). Squamous cell carcinoma accounts for 90% of all malignancies in the oral cavity (6). The tongue is the most common location, covering approximatively 40% of the cases (7,8). Increasing incidence trends of oral tongue squamous cell carcinoma (OTSSC) have been observed worldwide. Incidence rates vary considerably (0.8-8 per 100 000 per year) between countries, due presumably to diverse risk profiles among populations. (1,9-11) In Finland, oral cancer is the 16th most common cancer, and in the male population the incidence of OTSSC has increased: the age-adjusted incidence rate per 100000 inhabitants was 1.2 in 2002-2006 and 1.7 in 2013 (http://www.cancerregistry.fi). In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), higher survival rates for OTSSC have been reported in females than in males, whose five-year survival rate has remained below 60% during the past 40 years (9).

Large tumor size, significant depth of invasion, intralesional removal or insufficient resection margins and metastasis to regional lymph nodes are considered unfavorable prognostic factors (12). The abundant vascular and lymphatic supply of the tongue apparently facilitates cancer cell invasion and metastasis.

Recommended treatment protocols for OTSSC are still debatable, surgery and radiotherapy being the conventional treatment modalities. Small and local noninvasive tumors are managed mainly by local surgical resection (13). Postoperative radiotherapy has been advocated to patients at high risk of disease recurrence. Combination therapy has been demonstrated to be more effective than surgery alone (14) and some centers administer preoperative radiotherapy in their protocol. Furthermore, superior treatment results have been reported with adjuvant chemoradiotherapy compared with radiotherapy in the treatment of more widespread tumors (15,16).

In Finland, a national treatment protocol for head neck cancer management, set and updated by the Finnish Head and Neck Oncology Working Group, is employed. The purpose of this study was to investigate the implemented treatment modalities and outcomes for OTSSC in Finland during 2005-2009. The results were also compared to the previous Finnish OTSCC survival and treatment data of 235 patients published for the years 1995-1999 (13).

Patients and Methods

All the patients diagnosed with primary OTSCC at the five university hospitals of Finland during the 5-year period between the 1st of January 2005 and the 31st of December of 2009 were included in this study. Subjects were identified from hospital pathology and surgery registries by ICD-10 diagnosis codes (C02.0, C02.10, C02.11, C02.2, C02.3, and C02.9). Only histologically confirmed primary cases of epithelial cancer located in the mobile tongue were included. Patient clinicopathological data obtained from hospital records were reviewed and information were collected on age, sex, smoking and drinking habits, date of pathological diagnosis, tumor location, TNM classification, tumor histopathology, intent of treatment, administered treatment (treatment of the primary tumor, reconstruction, neck dissection, radio- and chemotherapy), surgery date, start and end dates of radiotherapy, disease recurrence (location and date of diagnosis), date of last follow-up and status at last follow-up. Reported TNM classification was based on post-surgical pathological findings, except for patients treated preoperatively with radiotherapy and palliatively treated patients, whose TNM classification was defined before the beginning of treatment. All the study data was collected by the first writer, ensuring uniform TNM stage assignment based on pathological findings across all the centers. The clinical TNM stage assignment retrieved from patients' clinical record is, however, also reported for statistical purposes. Details concerning dates and causes of death were acquired from Statistics Finland. Disease recurrence rates up to a 60-month follow-up time point were calculated for curatively treated patients, in whom disease control was reached (disease-free at 3 months after treatment). Statistical comparisons between treatment modalities were performed using the Z-test for two population proportions.

Patient survival analysis after end of treatment was conducted using the Kaplan-Meier method with IBM SPSS (version 20) and compared statistically according to the log-rank test. Research permission for the study design was granted by the National Institute for Health and Welfare.

Results

Three hundred and sixty patients with new OTSCC were identified (52% were women; mean age of all patients was 64.3 years; median 65.6, range 19 - 97). The average follow-up time after treatment was 43 months (median 54, range 0 – 111). Twenty-nine patients (8%) were lost to follow-up during the first year. Clinical characteristics of the study group are presented in Table 1.

Most OTSCCs were diagnosed at Stage I (n=170, 47%) and the majority of tumors (n=190, 53%) were T1. Clinically, 86 (24%) patients presented with cervical lymph node metastases (cN1 or cN2) and one patient had distant metastases (Stage IVc) at the time of diagnosis. The primary tumor was predominantly (78%) located on the lateral border of the tongue; the ventral surface was the second most common (12%) location.

Treatment with curative intent was provided for 328 (91%) patients. The average treatment delay between diagnosis and surgery was 18 days (median 15, range 1 – 99). Correspondingly, the average treatment delay between diagnosis and start of radio- or chemotherapy was 49 days (median 43, range 14 – 182). The average time between surgery and start of radiotherapy or *vice versa* was 49 days (median 48, range 19 – 260). The primary tumor was surgically removed in 325 (99%) patients (Table 2). Six (2%) total glossectomies were performed. Reconstructive surgery was performed to 129 (39%) patients. A neck dissection was performed, electively, to 156 (48%) and, therapeutically, to 66 patients (20%). Twenty-five

bilateral neck dissections were performed. A sentinel lymph node biopsy was performed to 35 (11%) patients and resulted, subsequently, in a therapeutic neck dissection in 18 cases. Occult cervical lymph node metastases were pathologically diagnosed after completed neck dissection in 86 (39%) patients, 44 (51%) of whom had been clinically classified as N0 (false-negative cervical nodes). T1 and T2 tumors constituted 32% (n=14) and 50% (n=22), respectively, of the false negative cases. True negative cervical nodes represented 82% (n=112) of the pathological negative neck nodes (n=136). The positive and negative predictive values for diagnosis of neck metastatic disease were 64% and 72%, respectively.

Twenty-eight (9%) and 108 (33%) patients, respectively, received pre- and postoperative radiotherapy as part of the curative treatment. Radiotherapy treatment lasted on average 45 days (median 45, range 14 – 74) and the total radiation doses given to the primary tumor and to the neck were, respectively, on average 59.6 (median 60, range 16 – 70) and 54 (median 54, range 16 – 70). Adjuvant cisplatin-based chemotherapy, in addition to radiotherapy, was used for 55 (17%) patients. (Table 2)

In Stage III disease, 60 (90%) patients were treated with curative intent. In this group, 27 (45%) patients received radiotherapy and 17 (28%) radiochemotherapy after curatively intended surgery. There was no significant difference in the disease recurrence rate between Stage III patients treated with surgery and radiotherapy and patients treated with surgery and radiochemotherapy. Stage IV patients treated with curative intent (n=56) mainly received combined treatment consisting of surgery and radiotherapy (n=20, 36%) or surgery and radiochemotherapy (n=32, 57%).

Disease control after primary phase curatively intended treatment was accomplished in 95% (n=312) of the patients. Sixteen patients (Stage I, n=4 (2%); Stage II, n=3 (7%); Stage III, n=1 (2%); Stage IV, n= 8 (14%)) had disease persistence despite all the provided treatment. The rate for locoregional recurrence was 26% (n=81). Distant metastases were diagnosed in 17 (5%) patients during follow-up; four patients had an isolated distant recurrence (all Stage IV patients). The recurrence rates for Stage I and II patients were

locally 15% (n=24) and 13% (n=5), and regionally 12% (n=19) and 18% (n=7), respectively. In Stage I disease, after primary phase treatment, patients treated with curative intent (n=169) with an elective neck dissection had a significantly (p=0.00064) lower number of locoregional recurrences than the patients treated only by surgical removal of the primary tumor. Disease recurrence rates according to Stage and tumor classification for patients treated with curative intent are presented in Table 3.

The five-year overall survival (OS) rate for patients treated with curative intent was 61%. The corresponding 5-year disease-specific survival (DSS) was 76%. There were no statistical differences neither between men and women nor the different University hospitals in the OS and DSS rates. The 5-year DSS rates according to Stage and T class of the tumor are presented in Table 4. DDS according to Stage is also presented in Figure 1. The 5-year recurrence-free survival in this patient series was 65%. The 5-year OS and DSS rates for patients younger than 40 years were both 86%. No statistical differences could be observed either in the Stage distribution or the DDS rates between different age groups.

Discussion

According to the Finnish Cancer Registry (http://www.cancerregistry.fi) the incidence rate of oral tongue squamous cell carcinoma (OTSCC) is steadily rising. Similar increasing trends have been recently documented worldwide (1,9-11). This nationwide study was conducted to investigate the treatment modalities and outcomes for 360 primary cases of OTSCC in Finland during 2005-2009, and to compare these results with our earlier cohort from 1995-1999 (13). The management of head and neck cancer is centralized to the University hospitals in Finland. Some patients with mobile tongue cancer may, however, have been treated at some of the larger non-university central hospitals. The healthcare districts included in this study represent approximately two thirds of the whole population of 5.5 million in Finland.

Throughout the study period, OTSCC was mostly diagnosed at an early stage: Stage I patients covered 47% of the cases, and 53% of tumors were T1. An improvement in early detection of OTSCC in Finland has occurred, since during 1995-1999 only 33% of patients were diagnosed at Stage I and 34% of tumors were T1. Surgical treatment remains the mainstay of therapy for Stage I and II OTSCC patients: 88% of Stage I and 60% of Stage II patients were treated by surgery alone. No statistically significant decrease in the rate of regional recurrences in Stage I and II disease was observed in this study group when compared with the 1995-1999 cohort (13% vs 18%).

In Stage I disease, after primary phase treatment, patients treated curatively with an elective neck dissection had a significantly lower rate of regional disease recurrence than patients treated by surgical removal of the primary tumor only (6% vs. 21%, p=0,00508). In a randomized-controlled trial with 596 patients D´Cruz et al. (17) reported better OS and DSS rates in early-stage oral cancer for patients who underwent an elective neck dissection. This emphasizes the importance of a careful evaluation of the need for elective neck treatment also in Stage I patients. However, elective neck dissection for treating early stage OTSCC has its challenges: one has to consider the risk of occult spread to regional lymphatics and the morbidity associated with neck dissection. Unfortunately, clinical and imaging examinations are far from perfect for the evaluation of neck status in oral cancer patients. In this study, the sensitivity of clinical and imaging examination in detecting cervical lymph node metastases was even lower than reported by others: 0.49 versus from 0.64 to 0.83. Specificity (0.82) was within the range reported in other publications (0.80 to 0.96) related to head and neck cancer (18-20). This reveals the existing difficulty in the preoperative assessment of nodal status by clinical and imaging methods.

Sentinel lymph node biopsy has emerged as a viable alternative diagnostic technique for neck staging in T1N0 oral cancer patients. Negative predictive values of even 97.5-100% have been reported (21,22). Nowadays, sentinel lymph node biopsy is routinely performed in T1-T2N0 cancer of the mobile tongue at our centers. Effort has also been directed towards finding histological prognostic markers, which could identify patients with a high-risk tumor, who might benefit from multimodality treatment (23,24). However,

the use of histomorphological or immunohistological markers in pre- or intraoperative OTSCC tissue samples is not yet a part of everyday clinical pathology practice.

Several studies have emphasized the need for a multidisciplinary treatment approach for improved survival of advanced oral cancer patients (12,14,25). Furthermore, the benefits of combined therapy with adjuvant chemotherapy have been reported (15). In the present study, 72% of the Stage III and 89% of Stage IV patients were treated by combined treatment, as opposed to 82% and 100% in our earlier patient cohort of the 90's. Adjuvant chemotherapy was more frequently used in combination with radiotherapy than previously: 16% of patients, or 43% of Stage III and IV patients, were treated with radiochemotherapy in combination with surgery, whereas a decade earlier only one patient had been similarly treated. In this series, no significant difference could be discerned in the disease recurrence rate between Stage III patients treated with surgery and radiotherapy and patients treated with surgery and radiochemotherapy. Nevertheless, a trend for improved survival for Stage IV patients was observed (5-year DSS: 49% in the present study vs. 33% in the previous cohort, p=n.s.), which may be partly attributed to the use of adjuvant systemic therapy. In Stage III disease, the DSS rate remained constant (5-year DSS: 69% vs. 71%) over the investigated time periods.

The mean time between surgery and start of radiotherapy, or *vice versa* was 49 days. The literature is controversial concerning optimal treatment interval times. While some studies have advocated an interval of less than 6 weeks for better locoregional control (22,26), others have reported no significant differences (27-29). In our study, no differences could be observed in the rate of locoregional recurrence when comparing treatment interval times.

It is noteworthy, that the disease recurrence rates for patients with Stage II, III and IV tumors were rather similar (28%, 31%, 31%, respectively). Together with similar survival outcomes for stage II and III tumors, this raises a suspicion of possible understaging in some of the stage II tumors. An improved staging protocol for these tumors is warranted. The more aggressive treatment approach used for Stage III and IV patients

may account partially for these observed outcomes. Four Stage II patients (7% of Stage II patients) did not undergo an elective neck dissection and were diagnosed with occult metastatic disease during follow-up. It could be speculated, that these patients had been clinically misdiagnosed as neck-disease free. In the present study, the five-year OS and DSS rates for patients treated curatively were 61% and 76%, respectively. The corresponding rates in the 1995-1999 patient cohort were lower; 53% and 64%, respectively. The five-year DSS improvement since the last series reached statistical significance (p=0,018). Notable improvements in the five-year DSS were observed in Stage I and Stage IV patients (80% to 87% and 33% to 49%, respectively), although these changes did not reach statistical significance.

In the current cohort, 8% of patients were younger than 40 years of age at the time of diagnosis. Conflicting results have been reported with respect to survival in young OTSCC patients (30-32). No disparities in DSS rates could be discerned between the different age groups in our study, which is supported by the results obtained by Hyam et al. and Friedlander et al. (30,31).

The 5-year recurrence-free survival in general has improved in OTSCC from 47% in our previous series to 65% in the current series (p=0,000). The survival and recurrence rates for OTSCC at different University Hospitals in Finland were similar. This can be attributed to the homogeneity of treatment level and the use of national treatment guidelines throughout the country. In Finland, OTSCC is mostly diagnosed at an early stage (78% were T1-T2 tumors), which improves treatment outcome. Moreover, the short treatment delay, on average 20 days after diagnosis, contributes to the improved prognosis. Still, the relatively high number of disease recurrences for Stage I and II patients, 22% and 28%, respectively, calls for an improvement in the treatment approaches for OTSCC. Histological prognostic models might be a promising tool to detect high-risk patients, to whom a more aggressive treatment approach could be beneficial and our current research focuses on these alternatives (23,24). Multimodality treatment, involving adjuvant systemic therapy, is advocated for patients with advanced disease.

Statement of author contributions

MR conceived the data. MR and HA analyzed the data. MR, MA, ST and GR conceived and designed the study. MA, LJ, PM, GR, HA and ST provided patient data. All authors had final approval of the submitted and published versions.

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Table 1. Clinical characteristics of 360 OTSCC patients in Finland during 2005-2009.

Clinical characteristics	n	%
Sex		
Male	173	48
Female	187	52
Age		
<30	6	2
30 – 39	21	6
40 – 49	33	9
50 – 59	66	18
60 – 69	100	28
70 – 79	82	23
> 79	52	14
Stage		
I	170	47
II	46	13
III	67	19
IV	76	21
Missing data	1	0
T Class		
T1	190	53
T2	91	25
T3	43	12
T4	35	10
Missing data	1	0
Tobacco use, cigarettes per day		
non-smoking	150	42
<10	24	7

≥10	113	31
no data	73	20
Alcohol use, drinks per week		
>24	51	14

Table 2. Treatment with curative intent given to 328 patients diagnosed with OTSCC in Finland during 2005-2009.

Treatment	n	%
Surgery	192	59
Surgery + radiotherapy	79	24
Surgery + radiochemotherapy	54	16
Radiotherapy	1	0
Radiochemotherapy	2	1
	328	100
Neck treatment		
No treatment	74	23
Neck dissection	104	32
Neck dissection + radiotherapy	118	36
Radiotherapy	16	5
Sentinel lymph node biopsy (only)	16	5

Table 3. Disease recurrence after successful primary treatment for 312 curatively treated OTSCC patients in Finland during 2005-2009.

Stage	n	%
I (n=165)	37	22
II (n=40)	11	28
III (n=59)	18	31
IV (n=48)	15	31
Total (n=312)	81	26
T Class		
T1 (n=189)	43	23
T2 (n=84)	25	30
T3 (n=33)	8	27
T4 (n=22)	5	28
Total (n=312)	81	26

Table 4. Five-year disease-specific survival rates (%) for OTSCC patients diagnosed and treated in Finland during 1995-1999 (see ref. 12) and 2005-2009.

Stage	1995-1999	2005-2009
I	80	87
II	68	72
III	71	69
IV	33	49
T Class		
T1	79	87
T2	65	71
T3	69	54
T4	27	35