

No evidence for a survival difference between upper and lower lip squamous cell carcinoma

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Abstract. It is generally assumed that upper lip cancer has a worse survival than lower lip cancer, but this notion is not convincingly supported by limited literature. Therefore, we tested whether upper lip cancer has a worse survival than lower lip cancer. All primary squamous cell carcinoma (SCC) of the lip in the North-East of the Netherlands from 1989–2009 were extracted from the Netherlands Cancer Registry database. We calculated overall and relative survival rates. In this series of 979 lower lip and 126 upper lip SCC, men were 2.6 times more often affected, while the proportionate share of upper lip cancer was larger in women. The 5-year overall survival for lip cancer equaled 74% (95% confidence interval (CI) 70–77%), while the relative survival equaled 97% (95% CI 93–100%). The overall and relative 10-year survival rates were 51% (95% CI 47–54%) and 90% (95% CI 84–96%), respectively. The 10-year relative survival rate for patients with SCC of the upper lip was 94% (95% CI 74–111%) compared to 90% (95% CI 83–96%) for patients with SCC of the lower lip. There appears to be little evidence that patients with upper lip SCC have a worse survival rate.

Key words: upper lip; lower lip; squamous cell carcinoma; overall survival; relative survival.

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Carcinoma of the lip is a rare malignancy of the head and neck region, with just over 200 new cases per year in the Netherlands.¹ The vast majority (50–96%) of lip cancers are squamous cell carcinoma (SCC).^{2–7} SCC is the most frequent malignancy on both the upper and lower lip, but in some studies a larger proportion of basal cell carcinoma

(BCC) has been found on the upper lip.^{2,6,7} Approximately 90% of SCCs of the vermilion of the lip are located on the lower lip.^{2,8} The proportion of lower lip cancers has declined significantly from 58.7% to 40.0% over the last 30 years, while the percentage of upper lip cancer has increased from 30.6% to 41.3%.^{3,9}

Men, fair-skinned individuals, and people over 50 years of age have a higher risk of developing lip cancer.^{2,3,10,11} The most important risk factor is cumulative life-time exposure to sunlight, which is related to outdoor occupation^{2,3,12} and rural residency.¹² Additional risk factors are smoking,^{13–15} low socioeconomic

status,^{5,10,12–14} and a suppressed immune system.^{16,17}

SCC of the lip carries a good prognosis, which is attributed to early detection and the relatively infrequent occurrence of regional metastases.^{2,3,5} The 5-year relative survival rate for lip cancer is 91% in Europe.¹⁸ The most powerful predictor of survival is the presence or absence of lymph node metastases.^{19,20} Other prognostic factors are large tumour size^{7,19–21} and surgical margins containing SCC.^{2,19} Increasing tumour thickness, an infiltrative invasion pattern, and perineural invasion are statistically associated with regional metastases.^{19,21}

It is a general belief that cancer of the upper lip has a worse prognosis than cancer of the lower lip. However, conflicting results have been published. Zitsch et al. found a 5-year cause-specific survival rate of 77% for the upper lip and 90% for the lower lip, but this research included both BCC and SCC.² Califano et al. reported a 5-year overall survival (OS) rate of 91% for upper lip SCC and 98% for lower lip SCC.²² In that study, tumours of the upper lip were significantly larger at diagnosis and metastasized more often during follow-up than tumours of the lower lip. Zitsch et al. and Califano et al. hypothesize that upper lip cancer belongs to a more aggressive class of disease.^{2,22} However, neither mentions a possible explanation for this theory. Conflicting results include the findings of Czerninski et al., who found that cancer of the upper lip was associated with a slightly higher cumulative survival rate than that of the lower lip (81% and 77%, respectively).³ Further, another study did not find any difference between the two tumour sites.⁷

These studies^{3,7} included BCC as well as SCC. This might have influenced survival rates since BCC is associated with a better survival than SCC. In our opinion, the presumed worse survival for upper lip cancer has not been supported convincingly by previous research. The aim of this study was to test whether upper lip cancer is associated with a reduced survival compared to lower lip cancer.

Patients and methods

Patients included

For this study, data on a consecutive series of patients with primary SCC of the lip (International Classification of Diseases for Oncology (ICD-O) code C00),²³ registered between 1989 and 2009 in the North-Eastern Region of the Netherlands, were extracted from the Netherlands Can-

cer Registry (NCR). This study was approved by the review board of the NCR. The North-Eastern Region is a subdivision of the nationwide population-based NCR; it covers four provinces of the Netherlands and includes 23 hospitals. Signalling sources for the registry are the automated pathology databank and hospital discharge records. Every year, the NCR updates the cancer database with information on vital status of patients (alive, dead, or emigrated) by linkage to municipal records. The NCR only records primary tumours; recurrences are not included in this study. For the comparison of upper and lower lip, only SCC of the vermillion was included (ICD-O codes no C00.0 and C00.1; M8050–M8084).²³

A total of 1126 primary SCC of the vermillion of the lip, observed in 1105 patients, were included. More than one primary SCC developed in 21 patients. For these patients, the first tumour, or when simultaneous primaries were present the tumour of the highest stage, was selected, leaving 1105 SCC in our database: 979 (88.6%) lower lip SCC and 126 (11.4%) upper lip SCC.

Variables

The variables recorded were sex (male, female), age at diagnosis (<60 years, 60–69 years, or ≥70 years), localization of the tumour, tumour stage, presence of lymph node and distant metastases at presentation, treatment, date of incidence, and vital status.

The tumour site was registered according to the ICD-O-3.²³ Tumour stage was registered according to the TNM classification^{24–27} and divided into low stage (stages I and II) and high stage (stages III and IV; all tumours larger than 4 cm and/or tumours with regional and/or distant metastasis at diagnosis).

Statistics

Associations between variables and localization were analysed using a χ^2 test, Fisher's exact test, or Kruskal–Wallis test, as appropriate.

One patient died on the day of diagnosis and was excluded from the survival analysis, leaving 1104 patients. Survival time was defined as the time from the date of diagnosis to the date of death or date of censoring (date of emigration or date of record linkage to the municipal records to assess the vital status). OS was calculated using the Kaplan–Meier survival estimator, and resulting 5-year OS rates are

presented. Differences between survival curves were tested using the log-rank test.

As lip cancer is associated with a low disease-specific mortality rate, we calculated relative survival rates; with relative survival rates, the ratio of observed survival is related to the expected survival. Paul Dickman's Stata model was used for this purpose.²⁸ The expected survival was based on population life tables stratified by age, sex, and calendar date for the Netherlands.

P-values of <0.05 and 95% confidence intervals that did not include 1 were considered statistically significant. The statistical analyses were conducted using the Stata program (StataCorp. 2011, College Station, TX, USA).

Results

Clinical features

The most frequently involved site was the lower lip at a total of 979 SCC (88.6%); 126 SCC involved the upper lip (11.4%) (Table 1). A male predominance was found, with 801 (72.5%) male and 304 (27.5%) female patients. The male-to-female ratio was 3.3 for the lower lip, while this was 0.7 for the upper lip (female predominance). This difference in site by sex was statistically significant ($P < 0.001$). The median patient age was 70 years and 52.4% were diagnosed at age ≥70 years. The median age was slightly higher for lower lip cancer patients (71 years; 53.6% ≥70 years), compared to upper lip cancer patients (66.5 years; 42.9% ≥70 years).

The age at diagnosis for female patients was higher in comparison to the age for male patients ($P = 0.01$), with median ages of 73 and 70 years, respectively.

Lip cancers were mainly diagnosed at a low stage (stages I and II); only 20 SCC (1.8%) were high stage tumours (stages III and IV) (Table 1). There was no statistically significant difference in tumour stage between the upper lip and lower lip groups. Only 12 patients (1.1%) were diagnosed with lymph node metastases and one patient with a distant metastasis at diagnosis; all were observed in the lower lip cancer group.

Treatment

The vast majority of lip cancer cases (90.0%) were treated by surgical excision of the SCC. A higher percentage of patients in the upper lip cancer group (96.0%) were treated with 'surgery only' in comparison to the lower lip cancer

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