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Survival Comparison in Different Sites of Lip Cancer

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Advances in the management of patients with lip Squamous Cell Carcinoma (SCC) have confounded the prognostic value of the primary site. The purpose of this retrospective study is to estimate the outcome of patients with lip SCC and to determine if the location of primary site is a significant prognostic factor of overall and/or disease-free survival. The records of 188 patients that underwent surgery for resectable lip SCC treated at a single institution from 1995 to 2003 were identified. Patients with positive surgical margins, high grade histology, aggressive biologic behavior, or advanced stage disease underwent adjuvant radiotherapy or chemoradiotherapy. The demographics, site, stage, pathology, treatment and survival data were collected and statistically analyzed in an attempt to identify prognostic parameters of loco-regional control and disease-free survival. Patients were divided into 2 groups: those with lip commissure (n = 13) and all other sites (n = 175). The Cox proportional hazards model was used to distinguish different survival rates between the groups. Criteria for inclusion in the study met 188 patients, 157 males (83%) and 31 females (17%). Overall and disease-free survival rates were 94 and 93% respectively. There was no significant difference in survival between patients with lip commissure and other sites in the lip ($p = 0.8$, $\chi^2 = 0.04$, 1 degree of freedom). In this retrospective study, no survival difference between patients with lip commissure and cancers located at other sites in the lip was found.

Key words: Lip cancer, mouth neoplasms, survival analysis

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INTRODUCTION

Oral Squamous Cell Carcinoma (SCC) is the sixth most common malignancy in the world, with regional variations in incidence and mortality noted, due in part to the prevalence of known etiologic risk factors, such as tobacco use (Parkin *et al*., 1993; Johnson, 1991; Moore *et al*., 2000). The most important factor affecting the outcome of patients with oral SCC is the stage of disease at initial diagnosis (Shiboski and Schmidt, 2005; Kademani *et al*., 2005; Shah, 1990a,b; McGuirt *et al*., 1995; Bloom and Spiro, 1980; Maddox *et al*., 1971; Shaha *et al*., 1984, 1990; Lindberg, 1972; Candela *et al*., 1990). However, the presence of clinically positive lymph nodes is the single most important clinical prognostic factor in determining survival (Shah, 1990a). Clinical and histopathologic regressors (independent variables) influencing the frequency of occurrence of cervical metastasis are: site of the primary tumor, T stage, grade, depth of invasion, biologic tumor markers, perineural invasion and patient observance (Kademani *et al*., 2005; Shah, 1990a, b; McGuirt *et al*., 1995; Shah *et al*., 1993; Bloom and Spiro, 1980; Maddox *et al*., 1971; Shaha *et al*., 1984, 1990; Lindberg, 1972; Candela *et al*., 1990). The occurrence of nodal metastasis in oral SCC increases with regard to the primary tumor's site, as one moves from the lips to the oro-pharynx (Shah, 1990a, b; McGuirt *et al*., 1995; Shah *et al*., 1990; Carew *et al*., 2003). Additionally, there is some evidence to suggest that site of the tumor can influence outcome (Patel and Shah, 2003).

Lip cancer, in particular, has been shown to have a lower mortality rate than other anatomic subsites in the oral cavity (Zitsch *et al*., 1995). It is thought that this difference is related to the inherent tumor biology and the earlier detection of the lesion.

There is a variation in the incidence of lymph node metastasis that depends on the location of the primary tumor in the oral cavity, but it is unknown if this variation is correlated with differences in survival, particularly for patients treated in a multi-modal fashion. Advances in diagnostic modalities, adjuvant therapies and ablative and reconstructive surgery have affected the management of patients with oral SCC during the last 2 decades since many of the studies documenting site as an independent factor in outcome were published. Improved imaging and the more widespread use of adjuvant radiation or chemoradiation therapy may confound the influence of location of primary tumor on outcome.

The purpose of this study is to review the outcome of patients with surgically resectable lip SCC, treated by an established treatment protocol and assess if the location of primary tumor is a predictor of outcome.

MATERIALS AND METHODS

The data in this study reflect the outcomes of therapy from Theagenion Cancer Hospital. The patients were treated by surgeons on the Oral and Maxillofacial Surgery Department, in collaboration with a multidisciplinary Oncology board. Patients presenting with resectable lip SCC were managed by an established treatment protocol that consisted of surgical resection with an attempt to achieve 1-cm tumor-free margins. Neck dissection was generally performed in patients with clinically N+ disease. Patients were reconstructed at the time of ablative surgery using ocal or regional rotational flaps. Adjuvant radiation or chemoradiation therapy was considered for patients with locally advanced disease, high-grade histology or perineural invasion. The initial evaluation data, operative details, pathology reports, adjuvant therapy and longitudinal follow-up data were collected and maintained on a computerized database.

The records of 188 consecutive patients who underwent surgical treatment for resectable SCC of the lip from 1995 to 2003 were retrospectively identified from the hospital Cancer Data Registry. Inclusion criteria were: histologically proved SCC, resectable tumor of the lip with or without regional metastatic lymphnode disease, age>18 years. Patients with unresectable disease, distant metastases on presentation, synchronous tumors, inadequate information or follow-up were excluded from this study. Data entered into a computer database (MS Excel software). Variables recorded and evaluated included age, gender, tumor site, histologic diagnosis, stage, grade, presence of regional or distant metastasis, surgical treatment, margin status and perineural invasion. Outcome measures were defined as time to loco-regional recurrence and survival (death with or without disease). Disease-free survival was defined as the time between surgery and the first recurrence. Descriptive statistics were calculated for each prognostic variable. For purposes of comparison, the patients were divided into groups based upon the site of occurrence: group 1 = lip commissure; group 2 = all other lip sites. Actuarial survival was calculated using the Kaplan-Meier method. Prognostic factors were assessed using the Cox proportional hazards model.

RESULTS AND DISCUSSION

Data from 188 patients were collected and reviewed. 157 (83%) were males and 31 (17%) females, with an average age at diagnosis of 69 years (SD±13). Average tumor size was 1.95 mm (SD±1.3). Stage and histologic grade are summarized in Fig. 1.

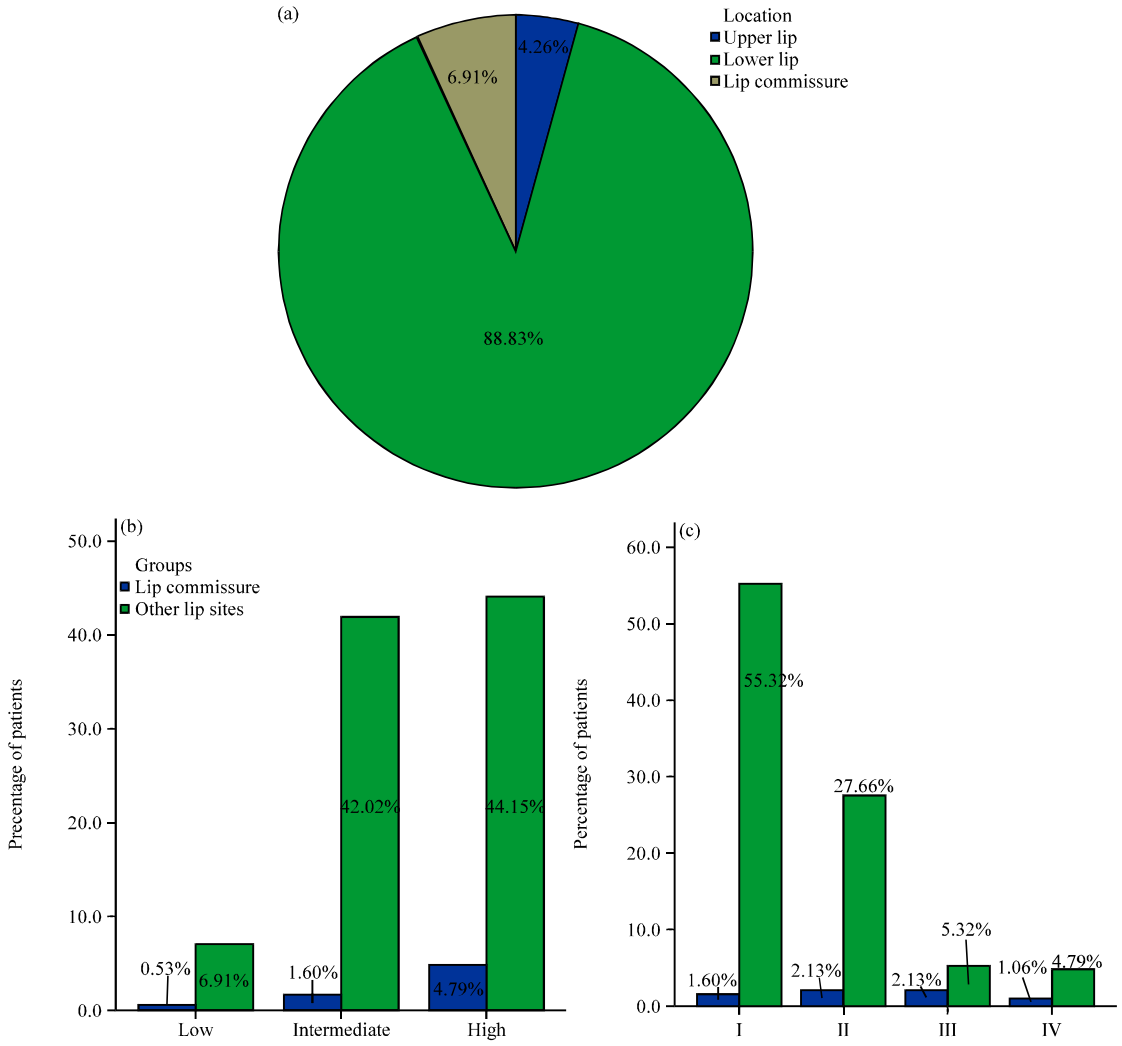

Fig. 1(a-c): Patient demographics, (a), Anatomic subsite distribution, (b) Histologic grade distribution. Percentage of patients with low, intermediate and high-grade tumors in group 1 and group 2 and (c) Stage distribution. Percentage of patients arranged according to stage of disease at presentation in group 1 and group 2

Site distribution was as follows: 13 (6.9%) lip commissure, 8 (4.3%) upper lip, 167 (88.8%) lower lip. Group 1 made up the primary study cohort and consisted of 13 patients with lip commissure tumor; group 2 consisted of 175 patients with tumors from other lip sites. Overall 5-year survival and disease-free survival for both groups combined was 94 and 93%, respectively (Fig. 2, 3).

Survival probabilities and site: Groups 1 and 2 were compared using the Cox proportional hazards model to see if one could distinguish different survival rates for patients with lip commissure when compared with all others. We were unsuccessful in distinguishing among them (likelihood ratio $\chi^2 = 0.04$, 1 degree of freedom [df], $p = 0.8$). The 95% Confidence Interval (CI) for the relative monthly survival of others to lip commissure ranged from 0.40 to 2.08. The Kaplan-Meier survival curves illustrate this relationship in Fig. 4.

Survival probabilities and stage for patients with lip commissure: Among the 13 patients with lip commissure, survival probabilities were evaluated with regard to the effect of stage by using the Cox proportional hazards model. Stage 1 tumors consisted of 3 of 13 or 23%. Stage 2 consisted of 4 cases (31%), stage 3 consisted of 4 cases (31%) and stage 4 consisted of 2 cases (15%). The Cox proportional hazards model was unsuccessful in rejecting the null hypothesis that survival curves for all stages were alike (likelihood ratio test = 1.44 on 2 df, $p = 0.486$).

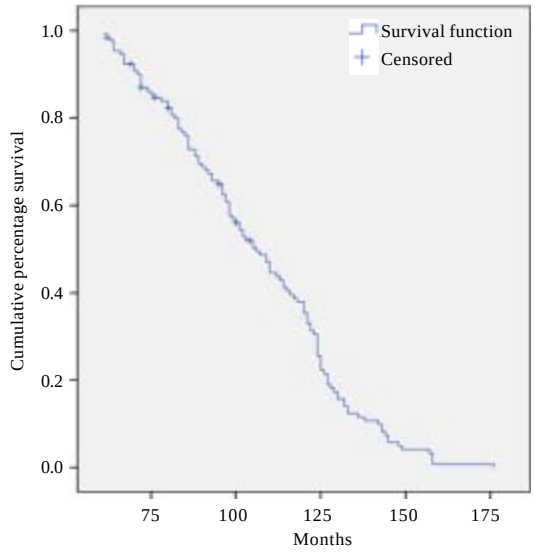

Fig. 2: The Kaplan-Meier survival curve. Survival at 5 years was 94%

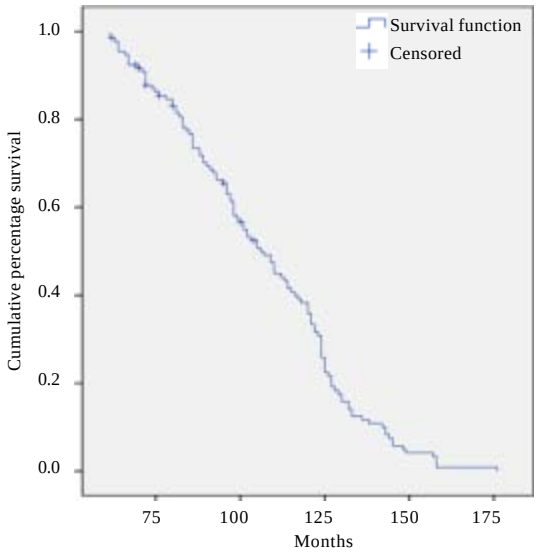

Fig. 3: The Kaplan-Meier disease-free survival curve. The 5-year disease-free survival was 93%

Survival probabilities and tumor grade for patients with lip commissure: Likewise, survival probabilities were evaluated with regard to the effect of grade on survival in patients with lip commissure. There was 1 patient with grade 1 tumors (8%), 3 patients with grade 2 tumors (23%) and 9 patients with grade 3 tumors (69%). Using the Cox proportional hazards model, we attempted to distinguish different survival curves for the 3 grades and found that they were not significantly different (likelihood ratio $\chi^2 = 0.30$, 1 df, $p = 0.58$).

Disease-free survival probabilities and site: The Cox proportional hazards model was used to see if one could distinguish different disease-free survival rates for the 13 patients with lip commissure when compared with all others. We were unsuccessful in distinguishing among them (likelihood ratio $\chi^2 = 0.04$ on 1 df, $p = 0.85$). The 95% CI for the relative monthly survival of others to lip commissure ranged from 0.41 to 2.10.

Disease-free survival probabilities and stage for patients with lip commissure: The Cox proportional hazards model

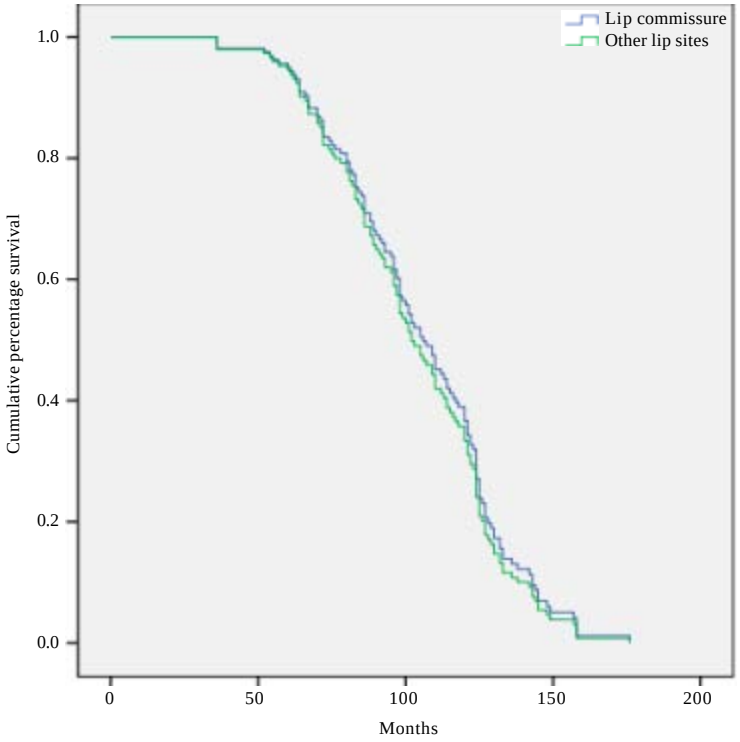

Fig. 4: Kaplan-Meier survival curve for lip commissure (blue line) compared with all other sites (green line). There was no difference in survival between the 2 groups (likelihood ratio $\chi^2 = 0.04$ on 1 degree of freedom, $p = 0.8$). The 95% confidence interval for the relative monthly survival of others to lip commissure ranged from 0.66 to 1.67

was unsuccessful in rejecting the null hypothesis that survival curves for all stages were alike (likelihood ratio $\chi^2 = 1.44$ on 2 df, $p = 0.49$).

Disease-free survival probabilities and tumor grade for patients with lip commissure: The Cox proportional hazards model was used to test the null hypothesis that survival curves for the 3 grades were alike. This hypothesis was unsuccessful in rejecting (likelihood ratio $\chi^2 = 0.302$ on 1 df, $p = 0.58$).

Failure to reject the null hypothesis in all statistical tests described previously, suggesting that there may be no difference in survival outcome, is found in contrast to other studies of oral cavity cancers. Ildstad *et al.* (1983), Spiro *et al.* (1986) and Zelefsky *et al.* (1993) found significant differences between anatomic subsites within the oral cavity that affect treatment outcome.

CONCLUSION

The results of this study suggest that there may be no difference in survival outcome for patients with lip commissure treated in a multi-modal fashion, as indicated based on known risk factors when compared to patients with cancers in other sites of the lip treated in similar fashion.

As stated earlier, there is good evidence to suggest that the occurrence of nodal metastasis in oral SCC increases with regard to the primary tumor's site, as one moves from the lips to the oro-pharynx (Kademani *et al.*, 2005; Patel and Shah, 2003; Shah *et al.*, 1990; Shah, 1990b; Carew *et al.*, 2003). Because the presence of cervical lymph node metastasis is the single most important predictor of survival, the inference is that subsites within the oral cavity affect survival outcome, independent of other factors. When overall survival is analyzed, however, little difference is found based on anatomic subsite alone, as is shown in the current study.

It is apparent that oral SCC is a biologically diverse disease with variable clinical presentations and behavior that is dependent upon many factors. The results of this study suggest that the site of presentation within the lips may play less of a role in survival outcome of patients treated with multi-modal therapy than previously described.

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