Prediction of occult cervical lymph node metastasis in clinically negative supraglottic squamous cell carcinoma

R Zeng1†, Q Dai1†, Z Peng1, P Cai2, W Hu3†

Abstract

Objective
Supraglottic laryngeal carcinomas are often accompanied by occult cervical lymph node metastasis. The aim of this study was to explore predictive factors of cervical lymph node metastasis in clinically negative supraglottic squamous cell carcinoma.

Methods and materials
From January 1990 to December 2009, a series of 221 patients with clinically negative cervical nodal metastases in supraglottic laryngeal squamous cell carcinoma were treated at Sun Yat-sen University Cancer Center. The overall survival rate and occult cervical lymph node metastasis-free survival rate were calculated using a life-table method. The survival curves were constructed by the Kaplan–Meier method and compared using a log-rank test. The relative significant factors in predicting occult cervical lymph node metastasis-free survival were assessed by multivariate Cox proportional hazards model.

Results
The 5-year overall survival rate in 221 patients was 58.6%. The 5-year overall survival rates of the positive cervical lymph node metastasis group and negative cervical lymph node metastasis group were 63.1% and 44.1%, respectively (p = 0.020). The 5-year occult cervical lymph node metastasis-free survival rate in 221 patients was 76.7%. Smoking index, histological differentiation, T stage, resection margins and treatment modality of surgery combined with post-operative radiotherapy for the primary site, were found to be associated with occult cervical lymph node metastasis-free survival by univariate analysis. By multivariate analysis, the significant predictors were found to be histological differentiation (hazards ratio, 1.507; 95% confidence interval, 1.006–2.257) and a combination treatment of surgery plus post-operative radiation for the primary tumour (hazards ratio, 1.035; 95% confidence interval, 0.892–3.494).

Conclusion
Cervical lymph node metastasis in clinically negative supraglottic squamous cell carcinoma results in lower 5-year overall survival rates. The histological differentiation and the treatment modality of surgery combined with post-operative radiotherapy for the primary tumour site, were found to be independent predictors for occult cervical lymph node metastasis-free survival.

Introduction
Supraglottic laryngeal carcinomas have a known tendency to metastasize to cervical lymph nodes because of the extensive lymphatic network. The incidence of cervical lymph nodes in supraglottic laryngeal cancer is about 35%, as reported in the literature. It is now known that occult nodal metastasis is a relatively common occurrence in head and neck cancer, particularly in supraglottic laryngeal carcinoma. The identification of occult lymph node metastasis represents an important role as it is associated with a significant reduction of survival rate and a higher risk for development of local recurrence of primary tumour and distant metastasis. The manual palpation of the neck is not infallible when detecting neck node metastasis. Resnick et al. showed that the combined predictive values of clinical and radiographic examination in positive and negative cervical nodal metastases are only 76% and 83%, respectively. Recently, most studies have confirmed the value of immunohistochemistry. However, when locoregional control and survival are closely examined, most studies fail to demonstrate a statistically significant association between micrometastatic disease and poor outcome. The status of occult cervical lymph nodes cannot be effectively predicted in a clinical setting.

Previous clinicopathological studies have shown that the presence of occult neck metastases in patients with laryngeal carcinoma is significantly associated with some features of the primary tumour, such as the degree of differentiation, tumour growth pattern, T stage and the quality of surgical resection. As reported in the literature, little attention has been given to host factors, such as tobacco smoking, alcohol consumption and age, which affect occult lymph node metastasis. The treatment modality used for the primary tumour and management of negative cervical nodal metastases may also account for differences in the clinical outcome. However, few reports have analysed the treatment-related variables of occult lymph node metastasis.

Licensee OA Publishing London 2012. Creative Commons Attribution License (CC-BY)

The aim of this study was to evaluate the clinical, pathological and treatment modality factors used to predict occult cervical lymph node metastasis in clinically negative supraglottic squamous cell carcinoma (SCCA).

**Materials and methods**

**Patient enrolment criteria**

A retrospective review of patients from Sun Yat-sen University Cancer Center revealed 2136 patients with primary SCCA of the larynx between January 1990 and December 2009. There were 734 patients with SCCA arising in the supraglottic larynx. Of these, 236 patients had biopsy-proven SCCA of the supraglottic larynx and were previously untreated, with a clinically negative neck demonstrated by a combination of palpation, computed tomography (CT) and/or magnetic resonance imaging (MRI). Among these 236 patients, the enrolment criteria were as follows: (1) each patient had complete clinical and pathological data including age, gender, blood style, stage, smoking index, alcohol consumption, histological differentiation and treatment status; (2) patients were restaged according to the guidelines of the 2002 Union for International Cancer Control by the cancer staging system. No patient had distant metastasis at the time of initial staging; (3) patients were initially treated with the goal of a cure at our institution by one or a combination of the following three modalities: surgery, radiation therapy and chemotherapy. Because this was a retrospective study, no informed consent from individual patients was needed in our jurisdiction.

A total of 221 patients were evaluated in this analysis according to the aforementioned criteria. There were 212 male (95.9%) and 9 female (4.1%) patients and the median age at diagnosis was 61 years (range 26–85 years). There were 18 cases of T1, 59 cases of T2, 86 cases of T3 and 58 cases of T4. There were 133 cases of good differentiation, 49 cases of moderate differentiation and 39 cases of poor differentiation.

**Treatment**

For the treatment modality of the primary site, 116 patients received surgery alone; 24 patients received 68–76 Gy radiation alone; 63 patients received surgery plus 60–66 Gy post-operative radiotherapy and 18 patients were treated with combined cisplatin-based chemotherapy, including 4 cases of neoadjuvant chemotherapy and surgery, 1 case of surgery and adjuvant chemotherapy, 3 cases of neoadjuvant chemotherapy and radiotherapy, 9 cases of concurrent chemo-radiotherapy and 1 case of surgery with concurrent chemo-radiotherapy.

In the surgical treatment of the neck, 82 patients were managed by neck dissection, including 25 cases with modified radical neck dissection and 57 cases with selective neck dissection. Seventeen patients underwent 50–60 Gy neck radiation alone. Seven patients had combined neck dissection with 40–50 Gy post-operative radiotherapy. Seven patients were given cisplatin-based chemotherapy alone. Ninety-seven patients received no active therapy and were observed. Eleven patients had combined cisplatin-based chemotherapy, including 1 case of neoadjuvant chemotherapy plus surgery, 1 case of surgery plus adjuvant chemotherapy, 2 cases of neoadjuvant chemotherapy plus radiotherapy and 7 cases of concurrent chemo-radiotherapy.

**Follow-up time and method**

Follow-ups were conducted mainly via outpatient check-ups. The follow-up duration was calculated from the day of diagnosis to either the day of death or last follow-up. Follow-up examination was started after treatment. Patients were seen every 2 months during the first year, every 3 months for the subsequent 2 years and then every 6 months thereafter until death. All locoregional tumours were diagnosed by clinical examination, MRI or intensive CT, fiberoptic endoscopy and biopsy. Distant metastases were diagnosed by clinical symptoms, physical examinations and imaging methods, including chest X-ray, bone scan, abdominal sonography, MRI, intensive CT and positron emission CT. Occult cervical lymph node metastasis was defined as metastasis that was diagnosed after treatment in an initially clinically negative cervical nodal metastases.

In our study, the last follow-up was 29 November, 2011, with a median follow-up time of 69.5 months (range, 2–237 months). Four patients were lost to follow-up at <5 years and these were statistically considered to be tumour-related events (occult cervical lymph node metastasis and death). Eleven patients were tumour free for >5 years and then lost to follow-up; these patients were statistically considered as treatment successes (no occult cervical lymph node metastasis and survival). Three patients had unknown causes of death and were statistically handled as tumour-related events (occult cervical lymph node metastasis and death).

**Statistical analyses**

The primary end point of this study was 5-year occult cervical lymph node metastasis-free survival (OCLNM-FS) and overall survival (OS). OCLNM-FS was defined as the length of time between the date of diagnosis and first failure at any site of cervical lymph node metastasis. OS was defined as the length of time between the date of diagnosis and death from any cause or since the last follow-up. SPSS 12.0 statistical software (SPSS Inc., Chicago, IL) was used. The survival rate and univariate analysis were performed by the Kaplan–Meier method and a log-rank test. Multivariate analyses with the Cox proportional hazards model were used to test the independent significance by forward
elimination of insignificant explanatory variables of different parameters. A two-tailed p value of <0.05 was considered statistically significant.

**Results**

**Survival**

At the last follow-up, 107 patients were alive and 114 patients were dead. Among the 114 deaths, 86 were due to tumour-related diseases. Additionally, 44 patients presented with occult cervical lymph node metastasis after treatment. The lymphatic metastasis rate was 19.9%. The 5-year OS rate in 221 patients was 58.6% (Figure 1). The 5-year OS rates in the positive and negative cervical lymph node metastasis group were 63.1% and 44.1%, respectively ($\chi^2 = 5.423, p = 0.020$) (Figure 2). The 5-year OCLNM-FS rate in 221 patients was 76.7% (Figure 3).

**Univariate analysis**

Clinical and pathological factors that may affect the prognosis of occult cervical lymph node metastasis encompass age, gender, blood type, smoking index, alcohol consumption, histological differentiation, T stage and resection margin status. Analysis showed that smoking index, histological differentiation, T stage and resection margin status were factors that affected OCLNM-FS (Table 1). Univariate analysis was also performed by treatment modality, including treatment of primary tumour and neck. A significant predictor was found only with the treatment of a combination of surgery and postoperative radiation for the primary tumour (Table 2).

**Multivariate analysis**

Multivariate analysis was performed to adjust for significant various predictors in univariate analysis. The following parameters were included in the Cox proportional hazards model by forward elimination of insignificant explanatory variables: smoking index, histological differentiation,
T stage, resection margins and treatment modality of surgery plus post-operative radiotherapy for the primary site. Histological differentiation and the combination treatment of surgery plus post-operative radiation for the primary tumour were significant predictive factors for OCLNM-FS (Table 3).

**Discussion**

A clear decrease in the 5-year OS rate in patients with occult lymphatic metastasis (63.1% vs 44.1%, p = 0.020) was observed in our study. Much attention should be paid to occult lymphatic metastases. The development of occult lymph node metastasis may be influenced by some predictive factors, including smoking index, histological differentiation, T stage, resection margins and treatment modality of the primary tumour. The pathological grade with good differentiation (hazard ratio (HR), 1.507; 95% confidence interval (CI), 1.006–2.257) and the treatment of surgery combined with post-operative radiotherapy for the primary tumour (HR, 1.035; 95% CI, 0.892–3.494) may decrease the cervical lymph node metastasis rates in clinically negative supraglottic SCCA.

Between 0% and 62.5% of patients with clinical N0 supraglottic laryngeal cancer have occult cervical nodal metastasis, according to studies of serial sections of whole neck dissection specimens. In the present study, the rate of occult metastasis was 19.9%. However, this rate may be undervalued because as per the definition, occult metastatic neck disease in our study is that which occurs after treatment, which is also referred to as delayed lymph node metastases in literature. The incidence of delayed neck metastases can be assumed to be somewhere between 4% and 42% based on previous studies. A series of data demonstrated that the 5-year OS rate in clinically negative supraglottic SCCA ranged from 46.4% to 72.3%. Our results showed that the 5-year OS rate of patients was 58.6%, which was consistent with rates reported in the literature.

Significant predictive factors of occult cervical lymph node metastasis were evaluated among supraglottic patients in previous studies. It has been reported that the T stage and histological differentiation influence the prognosis of occult lymph node metastases in supraglottic cancers of the larynx, and numerous studies have identified tumour differentiation as a predictor of lymph node metastasis. Significant factors for tumours with a higher incidence of occult metastases were compared. The general conclusion of Esposito’s study is that the incidence of occult metastases was higher for the less differentiated tumours and for tumours with a higher T value; the effects of both factors are combined, thereby increasing the rate of occult metastases. Ozdek et al. showed a strong correlation between infiltrating tumour margins and neck metastasis; however, poorer differentiation is more aggressive and has a
According to multivariate analyses, T stage and resection margins did not exhibit favourable prognostic factors, but both univariate and multivariate analyses showed that differentiation is a significant prognostic factor for 5-year OCLNM-FS. The heterogeneity of the tumour may somehow influence lymph node metastasis. A combination of histological parameters and molecular characterization warrants further study.

Multiple studies have found that the relative risk for developing SCCA of the larynx increases in a dose-dependent manner with increasing cigarette consumption30–33. Some reports demonstrated that nicotine-induced activation of the apoptotic pathway affects the signalling of the cell death pathway31. The second-most predominant risk factor for the development of laryngeal cancer is alcohol consumption. Many studies also found that alcohol demonstrated its effect on the risk for supraglottic cancer, although the effect was not as profound as that of tobacco30,32. Our research placed these two variables as predictors into analysis. In univariate analysis, the data showed that the 400-cigarette smoking group had poorer OCLNM-FS rates. There was a trend toward decreased occult neck metastasis and increased survival advantage in patients who did not consume alcohol, although it did not reach statistical significance. Further study is needed to investigate the relationship between tobacco and alcohol consumption with occult metastases in clinically negative supraglottic SCCA.

Patients with head and neck SCCA require careful evaluation by a multidisciplinary team to determine optimal management34. Surgery and radiotherapy remain the most important treatment modalities, although there is an increasing role for chemotherapy and some centres have included the modality of biologic therapy. Failure to control the primary site is the leading cause of decreased survival.

higher tendency towards lymphovascular invasion14. These results were similarly confirmed by our study, in which univariate analysis showed that the T3 + T4 group (p = 0.022), resection margins and a poor degree of differentiation (p = 0.022) carried a negative prognostic value.

Table 2  Treatment modality univariate analysis for OCLNM-FS

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Cases</th>
<th>5-year OCLNM-FS (%)</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment modality of primary site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>116</td>
<td>78.7</td>
<td>0.021</td>
<td>0.885</td>
</tr>
<tr>
<td>No</td>
<td>103</td>
<td>74.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>82.8</td>
<td>0.415</td>
<td>0.519</td>
</tr>
<tr>
<td>No</td>
<td>197</td>
<td>76.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery and post-operative radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>82.2</td>
<td>16.816</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>158</td>
<td>65.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy with chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>94.1</td>
<td>1.844</td>
<td>0.175</td>
</tr>
<tr>
<td>No</td>
<td>203</td>
<td>75.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment modality of neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97</td>
<td>80.8</td>
<td>1.252</td>
<td>0.263</td>
</tr>
<tr>
<td>No</td>
<td>124</td>
<td>73.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified radical neck dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>83.5</td>
<td>0.517</td>
<td>0.472</td>
</tr>
<tr>
<td>No</td>
<td>196</td>
<td>75.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective neck dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57</td>
<td>70.1</td>
<td>2.208</td>
<td>0.137</td>
</tr>
<tr>
<td>No</td>
<td>164</td>
<td>79.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>79.4</td>
<td>0.138</td>
<td>0.710</td>
</tr>
<tr>
<td>No</td>
<td>204</td>
<td>76.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery and post-operative radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>71.4</td>
<td>3.014</td>
<td>0.076</td>
</tr>
<tr>
<td>No</td>
<td>214</td>
<td>78.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>100.0</td>
<td>6.899</td>
<td>0.343</td>
</tr>
<tr>
<td>No</td>
<td>214</td>
<td>76.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy with chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>87.5</td>
<td>1.019</td>
<td>0.313</td>
</tr>
<tr>
<td>No</td>
<td>210</td>
<td>76.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Licensee OA Publishing London 2012. Creative Commons Attribution License (CC-BY)

survival due to an increased risk of locoregional recurrence and distant metastatic spread. Spector et al. showed that delayed metastasis was significantly related to advanced primary disease and locoregional tumour recurrence. We found that the 5-year OCLNM-FS rate of patients receiving surgery plus post-operative radiotherapy to the primary site was higher than those who did not (82.2% vs 65.1%; p < 0.001) and that this was an independent factor affecting OCLNM-FS through multivariate analysis. Post-operative radiotherapy is widely advocated for patients with head and neck SCCA, who are considered to be at a high-risk of recurrence after surgical resection. Some studies now have demonstrated that concurrent post-operative chemotherapy and radiotherapy significantly improve the rates of local and regional control and disease-free survival. It may become meaningful to determine a promising approach for the primary site to reduce the probability of nodal failure and distant metastasis.

The treatment of neck-negative patients is a matter of great controversy. Indeed, prophylactic neck dissection and radiotherapy eliminate the risk of late metastases in negative cases, but exposes the patient to a higher morbidity. Another possible disadvantage of prophylactic treatment is the local reduction of the immunological host defence, which may facilitate the spread of residual tumour cells. Therefore, Session et al. suggest that patients with negative disease may be observed safely with no loss of survival advantage. But, we did not find the treatment of neck for OCLNM-FS in either univariate or multivariate analyses.

The data collected were not originally designed for a research application. This report does not include molecular predictive factors or biological therapy. Some molecular factors, responsible for the ultimate treatment outcome, may have been omitted in the analysis, thereby contributing to bias.

Conclusion

Our findings showed that occult cervical lymph node metastases in clinically negative supraglottic SCCA led to lower 5-year OS rates. The histological differentiation and treatment of surgery combined with post-operative radiotherapy for the primary tumour site were found to be independent predictors for OCLNM-FS. Our results warrant confirmation with other large, prospective studies with long-term follow-up.

Abbreviations list

CI: confidence interval, CT, computed tomography; HR, hazards ratio; MRI, magnetic resonance imaging; OCLNM-FS, occult cervical lymph node metastasis-free survival; OS, overall survival; SCCA, squamous cell carcinoma.

References


Licensee OA Publishing London 2012. Creative Commons Attribution License (CC-BY)