SURVIVAL AFTER SURGICAL RESECTION OF PULMONARY METASTASES AND SECOND PRIMARY SQUAMOUS CELL LUNG CARCINOMAS IN HEAD AND NECK CANCER

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Abstract: Background. Patients with head and neck squamous cell carcinoma (HNSCC) are at risk for developing both pulmonary metastasis and second primary lung cancer (SPLC). The objective of this study was to determine survival characteristics of patients with pulmonary lesions after curative treatment for HNSSC.

Methods. Lung resection or biopsy specimens of 36 patients, curatively treated for HNSSC between 1978 and 2002, were defined as second primary squamous cell lung cancer or metastasis by loss of heterozygosity (LOH analysis). Twenty-two of them underwent surgical resection. Survival characteristics were estimated using Kaplan-Meier analysis according to the LOH characterization.

Results. The number of resected lung lesions ranged from 1 to 3. Median overall survival after lung surgery was 23.1 months for SPLC (n = 14) and 25.1 months for lung metastases (n = 8). Fourteen patients, SPLC (n = 6) and metastases (n = 8), did not undergo surgical resection, and their median overall survival was 3.7 and 4.4 months, respectively.

Conclusion. Survival after resection of metachronic lung lesions following curative treatment of HNSSC is similar for lesions characterized as second primary squamous cell lung cancer and those characterized as metastases.

Keywords: head and neck cancer; metastases; second primary lung; carcinoma; LOH (loss of heterozygosity); survival

Pulmonary malignancies are a major problem in curatively treated head and neck cancer patients. Per follow-up year, 3% to 7% of patients surviving head and neck squamous cell carcinoma (HNSCC) develop a second malignancy in the upper aerodigestive tract.1 The relative risk of developing lung cancer after treatment for HNSSC is 3 to 6 times higher than the risk in the normal population.2
which is due to common predisposing factors. In a recent study of 1257 patients, a 5-year incidence rate of 5% emerged for second primary lung cancer (SPLC) in laryngeal carcinoma patients and 3% in oral carcinoma patients. Small series reported overall incidences ranging from 4.5% to 14%. Regional data on lung cancer as a second primary carcinoma in HNSCC patients of the “Integraal Kanker Centrum Amsterdam” (Comprehensive Cancer Centre Amsterdam) support this number with a relative risk of 4.9.

In HNSCC patients, pulmonary metastases account for 66% of all distant metastases and the incidence of pulmonary metastases ranges from 1.6% to 40%. Although in these series tumor stage seemed related to the incidence of metastases, criteria like stage, radiology, and time interval between primary and secondary lesion are of little help for the differentiation between SPLC and HNSCC metastases in the lungs. Histological appearance of HNSCC metastases and second primary lung lesion (squamous cell carcinoma) are often similar as well. On the basis of molecular analysis using the ‘loss of heterozygosity’ (LOH) technique, in a recent study we demonstrated that >50% of the squamous cell lesions, clinically diagnosed as metastases, actually were found to be secondary primary tumors. This may have an impact on treatment planning for secondary lung lesions, assuming that a resectable SPLC justifies local treatment.

To test this hypothesis, we calculated the survival of patients with molecularly defined (LOH analysis) SPLC and HNSCC metastases after curative treatment for head and neck cancer.

PATIENTS AND METHODS

Patients. The PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief; ie, pathologic anatomic national automated archive of The Netherlands) database was searched for all cases between 1978 and 2002 at The Netherlands Cancer Institute coded as a primary HNSCC followed by a squamous cell carcinoma of the lung. During this study period, 3056 patients were curatively treated for HNSCC, of whom 208 (7%) developed radiologically defined lung metastases or SPLC. Patients were selected on the basis of availability of paraffin-embedded material for LOH analysis on. (For details see Geurts et al.) Forty-four patients were identified, of whom 8 were excluded: 5 patients had signs of locoregional recurrence in the head and neck at the time of diagnosis of lung carcinoma, in 1 patient there was not enough tissue to perform LOH analysis, 1 patient had a primary lung carcinoma prior to HNSCC, and 1 patient had multiple metastases and a second primary adenocarcinoma of the lung at the same time.

Methods. Lung lesions were primarily detected either by yearly chest X-ray or CT scan during follow-up. For every patient, we collected data on treatment of the primary tumor, interval between treatment and diagnosis of the lung lesion, the number, dimensions and radiological localization of lung lesions, and details concerning the thoracic surgery.

Indications for treatment of pulmonary lesions were discussed in the multidisciplinary thoracic oncology team. Medically operable patients were candidates for surgery if there were no signs of locoregional recurrence or extrathoracic disease, and if the lung lesions were resectable, as defined by CT scan imaging of the thorax. Patients seen with more than 3 lesions were not eligible for surgery. The aim was to achieve clear surgical margins while saving as much lung tissue as possible. If intraoperative frozen section of a solitary lesion suggested SPLC, an anatomic resection, preferably lobectomy, was performed in patients with adequate cardiopulmonary reserve. None of the patients received adjuvant chemotherapy. Two surgically treated SPLC patients and 1 patient with resected metastasis were irradiated postoperatively. All surgical specimens were reviewed by a pathologist who specialized in head and neck cancer, and were further processed for LOH analysis. In patients treated nonsurgically, materials for LOH analysis were obtained by biopsy or at autopsy. Also the nonsurgical patients were considered free of locoregional head and neck recurrences at the time of diagnosis of the lung lesion, and they had no signs of metastatic spread outside the lungs.

Loss of Heterozygosity Analysis. This paragraph summarizes the LOH analysis and algorithm as published in Clinical Cancer Research for discrimination between SPLC and distant metastasis. The paraffin sections were deparaffinized and a region containing over 50% tumor cells was microdissected from the glass slide using a scalpel. We analyzed DNA isolated from tumor tissue as well as normal tissue by using 12 markers distributed on 11 chromosome arms using polymer-
ase chain reaction (PCR). These markers were selected within chromosomal regions that show frequent loss in lung or head and neck cancer, according to the literature. An automatic sequencer to measure the peak intensity of the fluorescent labeled PCR product was used. The intensity ratio between the 2 allele-peaks of heterozygotes was calculated, and this ratio was subsequently divided by the ratio of the normal alleles for normalization resulting in an index. An index below 0.75, which is frequently used in literature as a cut-off value, was interpreted as LOH; above this value it was considered as "retention of heterozygosity" (ROH).

Calculation of the probability of occurrence of concordant LOH patterns by chance was not allowed because the occurrence of LOH on different chromosome arms is not an independent event (as is also known from literature). Since there is also no consensus procedure to evaluate the use of LOH patterns in deciding on clonality, a new strategy was developed as described previously and formalized in a diagram (Figure 1). The 36 tumor pairs were then categorized according to this diagram.

Division of Groups. Patients were categorized into 4 groups based on the LOH findings for definition of second primary tumor lung cancer (SPLC) or HNSSCC metastasis and type of treatment (surgical resection (R+) or not (R−); Table 1).

Statistical Analysis. Survival was analyzed from the date of diagnosis of the lung lesion(s) to the date of last follow-up or death using the Kaplan-Meier method.

RESULTS
The study population consisted of 36 HNSSCC patients, all treated with curative intent, 29 men and 7 women; with a mean age of 60 years (range, 37–85 years). Primary tumor sites were: larynx (n = 19), oral cavity (n = 8), oropharynx (n = 6), hypopharynx (n = 3). The initial stage of the head and neck cancer was: stage I (n = 5), stage II (n = 8), stage III (n = 10), and stage IV (n = 13; Table 1). The median interval between primary HNSSCC and lung lesion was 21 months in both the resected SPLC patients (SPLC R+) and patients who had metastases that were resected (SPLC R+) and 13.5 months in those that were not resected surgically (SPLC R− and LMR−).

Twenty-two patients had complete resection of their lung lesions again with curative intent. In the other 14 patients, pulmonary surgery was not performed for the following reasons: ≥4 lung lesions (n = 7), mediastinal lymph node involvement (n = 2), locally advanced tumor growth (n = 1), second primary HNSSCC (n = 1), age ≥86 (n = 1), multiple bilateral lesions (n = 1), and unclear (n = 1).

Numbers of lung lesions were as follows (Table 1): resected SPLC: 1 lesion (n = 13), 2
lesions \((n = 1)\), 3 lesions \((n = 0)\), and 4 or more lesions \((n = 0)\); nonresected SPLC: 1 lesion \((n = 2)\), 2 lesions \((n = 1)\), 3 lesions \((n = 0)\), and 4 or more lesions \((n = 3)\); resected lung metastasis: 1 lesion \((n = 4)\), 2 lesions \((n = 3)\), 3 lesions \((n = 1)\), and 4 or more lesions \((n = 0)\); nonresected lung metastasis: 1 lesion \((n = 2)\), 2 lesions \((n = 2)\), 3 lesions \((n = 0)\), and 4 or more lesions \((n = 4)\).

Diameters of lung lesions ranged from 0.4 to 12 cm (mean, 3.1; median, 2.5), with the largest diameters found in patients who underwent surgery for their SPLC. Details on number and diameter of lung lesions are summarized in Table 1.

The following thoracic surgical approaches were used: 5 pneumonectomies, 5 lobectomies, and 4 wedge resections in patients with SPLC; no pneumonectomies, 3 lobectomies, and 5 wedge resections in patients undergoing resection for metastases (Table 1).

The pathologic staging of the resected SPLC was as follows: stage IA \((n = 6)\), stage IB \((n = 5)\), stage IIA \((n = 1)\), stage IIIB \((n = 0)\), stage IIIA \((n = 2)\), stage IIIB \((n = 0)\), and stage IV \((n = 1)\); Table 2).

At the last moment of follow-up, 1 patient was still alive without evidence of disease (12 years), 2 patients died of other causes, 1 patient was lost to follow-up after 30 months, and the other patients \((n = 32)\) died due to tumor progression.

In the group of patients who underwent resection of their SPLC, 6 (43%) died of recurrent lung cancer and 75% died of recurrent HNSCC in the group of patients who underwent metastasectomy. The median recurrence-free survival was 13 months and 19 months, respectively (1 patient was lost to follow-up after 30 months). Median overall survival was 23.1 months for patients with resection of SPLC and 25.1 months for patients with resected metastases. The overall 5-year survival of the group of patients who underwent resection (both SPLC and metastases) was 29.3% (95% CI, 8.7%–50.0%). Figure 2 shows the survival curves for the surgically treated patients. Median survival for nonresected SPLC and metastasized patients was 3.7 and 4.4 months, respectively, with all patients dying of disseminated disease.

**DISCUSSION**

Reports on survival after pulmonary surgery for second primary squamous cell lung carcinoma in head and neck cancer patients do not differentiate
between SPLC and metastases because until now a reliable method for differentiation is not available. In a previous article, we reported on a method to differentiate between these 2 types of lesions based on an interpretation strategy of multiple LOH markers on different chromosome arms (Figure 1). A considerable number of squamous cell lung lesions (50% in this study), clinically interpreted as metastases, were in fact reclassified as second primaries by LOH analysis. With the availability of this new tool, we now describe the survival characteristics of patients with LOH-confirmed secondary lung cancer and lung metastases.

Although it may be expected that cure rates in cases of SPLC are better than lung metastases, we were not able to demonstrate such a difference. Median survival of SPLC and lung metastasis was 23 and 25 months after resection, respectively. Also, in the nonresected patients, the median survival was similar for both SPLC and patients with lung metastases (3.7 vs 4.4 months, respectively).

Before the analysis, we hypothesized, from their HNSCC, that patients with an early stage second primary non-small cell lung carcinoma would have a better survival than patients with pulmonary metastases. Surprisingly, this could not be confirmed. It cannot be ruled out that certain factors contribute to the lack of difference in survival. A higher incidence of pneumonectomy in the group of patients undergoing resection for SPLC may represent a bias of the treating surgeon, as more aggressive treatment was considered justified when SPLC was suspected. The increased risk of aspiration and pulmonary complications in this group may add to the morbidity and possible mortality. On the other hand sublobar surgery (wedge resections) in patients with suspected metastases, while dealing with a SPLC, may represent inadequate surgery, although the recent literature on early NSCLC suggests that less invasive surgery yields comparable long-term results. Additionally, tumors in our series differed considerably in size, ranging from 0.4 to 12 cm. The new IASLC lung cancer staging project data show that tumor size is a major prognostic factor. Depending on size, tumors with different prognosis can be discriminated even within the existing T1 and T2 subgroups with a 5-year survival ranging from 53% in cT1a tumors smaller than 2 cm to 26% in cT2c tumors larger than 7 cm. Although the interval between primary head and neck cancer treatment and lung surgery may also be of prognostic significance, we did not determine time interval differences between the various subgroups (see also Table 1).

Patients with proven metastasized HNSCC had an unexpectedly good 5-year survival, provided that the primary tumor was controlled, less than 4 metastases were present, and the patients were fit for resection. This type of patient selection might preferentially pick out the patients who are prone to survive longer, regardless of their therapy. Nevertheless, we suppose it is fair to assume that the resection has contributed to the pulmonary control of the disease and as such contributed to outcome of the study. Other studies have published similar data as summarized in Table 3, which supports the assumption that (selection of patients for) surgery probably still is a key factor for survival. The definite proof for improved survival after lung surgery should come from randomized phase III trials comparing surgery versus optimal nonsurgical treatment for second primary lung lesions after curative treatment of head and neck cancer. Nevertheless, in selected patients, surgical removal of second primary lung lesions translates into favorable survival,
provided that limited lung surgery is performed to minimize morbidity. Whether screening for pulmonary lesions contributes to long-term survival in curatively treated HNSCC remains a matter of debate. It is suggested that pulmonary lesions are detected earlier in time, without improvement of survival rates. The authors suggest that this could be explained by unfavorable tumor biology parameters. Also, screening for lung cancer in high-risk populations for a long period of time did not seem useful in their retrospective analysis. In contrast, Henschke et al published a remarkably good 10-year survival of 92% for stage I lung cancer detected by annual screening using spiral CT. Although these data have been disputed, they may support the development of spiral CT–based screening protocols for curatively treated head and neck cancer patients, who are at risk for developing a second lung cancer.

Our survival data suggest that differentiation between second primary lung tumor and metastasis of HNSCC is not important for prognosis. However, the differentiation does influence the type of resection, because SPLC would be treated preferably by anatomic resection including hilar and mediastinal lymph node sampling, whereas wide local (tissue-sparing) resection can be used for metastasectomy. Unfortunately, LOH analyses may be very time consuming for delivery of relevant information at or before surgery for all patients. In selected patients, eg, an elderly HNSCC patient needing pneumonectomy, this method can be used to support the treatment choice.

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REFERENCES

Table 3. Literature data on resection of histologically defined pulmonary squamous cell carcinoma metastases following HNSCC treatment.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients resected</th>
<th>Age</th>
<th>Male/ Female</th>
<th>Primary HNSCC site</th>
<th>Stage</th>
<th>No. of lesions per patient</th>
<th>Found by follow-up</th>
<th>5-y or median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nibu Ket al</td>
<td>32</td>
<td>31-73, mean 57</td>
<td>23/9</td>
<td>O = 1</td>
<td>I = 3</td>
<td>1 = 26 pat</td>
<td>?</td>
<td>5-y survival = 32%</td>
</tr>
<tr>
<td>Liu D et al</td>
<td>41</td>
<td>?</td>
<td>?</td>
<td>O = 9</td>
<td>P = 13</td>
<td>1 = 10, 2 or more = 8</td>
<td>Yes</td>
<td>5-y survival = 34%</td>
</tr>
<tr>
<td>Finley RK et al</td>
<td>18</td>
<td>21-78, mean 61.5, median 63.5</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>34/10</td>
<td>O = 10</td>
<td>5-y survival = 29%; Median survival = 28 months</td>
</tr>
<tr>
<td>Mazer TM</td>
<td>44</td>
<td>21-78, mean 61.5, median 63.5</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>1 = 28 pat; Multiple = 16 pat</td>
<td>Yes</td>
<td>5-y survival = 43%</td>
</tr>
<tr>
<td>Younes RN et al</td>
<td>26</td>
<td>38-69, median 53</td>
<td>24/2</td>
<td>O = 3</td>
<td>I = 3</td>
<td>1 = 17 pat</td>
<td>?</td>
<td>Median survival = 23 mo</td>
</tr>
<tr>
<td>Present study</td>
<td>22</td>
<td>37-78, mean 60</td>
<td>17/5</td>
<td>O = 3</td>
<td>P = 5</td>
<td>2 = 4 pat</td>
<td>Yes</td>
<td>5 year survival = 29.3% (95% CI: 8.7%–50.0%); Median survival = 23-25 mo</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; L, larynx; O, oral cavity; Ot, other; P, pharynx; ?, unknown or not described.