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Main Article

Resection of secondary pulmonary malignancies in head and neck cancer patients

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Abstract

Background: This study aimed to evaluate a single institute's experience with resection of metachronous pulmonary malignancy in patients treated for squamous cell carcinoma of the head and neck.

Methods: Sixty-three consecutive patients treated curatively for head and neck squamous cell carcinoma underwent surgical resection of malignant lung lesions. Survival was estimated and potential prognostic factors investigated.

Results: The median overall survival for the total group was 22.2 months. Fifty-one patients (81 per cent) had one lung lesion, while the remainder had multiple lesions (range, two to seven). In the 63 patients, 35 lobectomies, 4 pneumonectomies and 24 wedge resections were performed. For patients with pulmonary squamous cell carcinoma ($n = 52$), the three-year survival rate was 35 per cent (95 per cent confidence interval, 22–48); for patients with resected adenocarcinoma ($n = 10$), it was 50 per cent (95 per cent confidence interval, 18–75). The overall five-year survival rate was 30 per cent (95 per cent confidence interval, 19–42).

Conclusion: In patients treated curatively for head and neck squamous cell carcinoma, resection of secondary pulmonary cancer is associated with favourable long term overall survival, especially for patients with adenocarcinoma lesions.

Key words: Head And Neck Neoplasms; Tumour Metastasis; Lung; Adenocarcinoma

Introduction

In head and neck cancer patients who have undergone curative treatment, the value of post-treatment follow up and screening for secondary lung malignancy is an ongoing topic of debate. Head and neck cancer metastases occur most frequently in the lung (66 per cent), and patients with head and neck cancer also have a far higher risk of developing a second, primary lung cancer.[1–5] It remains difficult to distinguish clinically between pulmonary head and neck cancer metastases and a second, primary lung cancer, although nowadays differentiation on a molecular level is possible. Although such techniques are time-consuming, they are becoming more and more suitable for routine application.[6–8]

Reported five-year survival rates after resection of metachronous lung lesions range from 19 to 43 per cent; however, as in the current series, these percentages are still based on small patient cohorts ($n \leq 55$).[4,5,9–11] Winter *et al.* found a significantly better survival, comparing operated and non-operated patients by matched pair analysis, in 67 patients with pulmonary metastases of head and neck cancer.[1] However, since adequate controlled trials have not been performed, the scientific evidence for benefit from resection is lacking. It is likely that survival results may have been positively driven by lead-time bias.[12] A number of authors have commented on the controversial issue of chest imaging in asymptomatic head and neck cancer patients.[13–16] In our institute, all patients are offered a standard follow-up programme consisting of regular physical checks and yearly chest X-rays. The decision to resect secondary lung lesions is based on clinical evaluation indicating either resectable early-stage second primary cancer or oligometastatic disease.[17,18] All our patients are reviewed in a multidisciplinary setting considering anaesthetic fitness, co-morbidity and tumour resectability.

This study aimed to evaluate surgical treatment and results for secondary lung tumours in a cohort of consecutively treated patients, and to compare these with published results.

Materials and methods

We included in the study all patients treated curatively for squamous cell carcinoma (SCC) of the head and neck and surgically treated for a secondary

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lung tumour in The Netherlands Cancer Institute between 1978 and June 2006. Since 1978, our cancer registry has held electronic recurrence and survival data for all our head and neck cancer patients. Additional patient and treatment data were obtained directly from patient medical records. For every patient, we collected the following data: treatment(s); interval between treatments; diagnosis of secondary lung lesion(s) and their number, dimensions and radiological localisation; and details of thoracic surgery.

Patients were offered, as standard care, a follow-up programme consisting of regular physical checks and a yearly chest X-ray. The investigation of secondary lung lesions consisted of bronchoscopy, computed tomography scan and, since its introduction in 2000, [18F]-fluoro-deoxy-glucose positron emission tomography. Pulmonary function testing was performed, followed if necessary by exercise tests.

Treatment for pulmonary lesions was discussed by the multidisciplinary thoracic oncology team. Criteria for resection comprised the clinical presence of either resectable early-stage second primary cancer or oligometastatic disease (i.e. less than five nodules of <5 cm).[18]

The goal was to achieve free surgical margins while preserving as much lung tissue as possible. When intra-operative frozen section analysis of a solitary lesion suggested a second primary non-small-cell lung cancer, an anatomical resection (preferably lobectomy, occasionally pneumonectomy) was performed in patients with adequate cardiopulmonary reserve (Table I). Only histological appearance (i.e. adenocarcinoma versus SCC) could be evaluated intra-operatively. As demonstrated in our previous publications on the molecular analysis of secondary pulmonary malignancies, histological differentiation between lung metastasis and second primary lung cancer is often difficult.[7,8]

Survival was analysed from the date of resection of the secondary lung lesion(s) to the date of last follow-up or death, using the Kaplan–Meier method. In case of multiple resections, survival was calculated from the date of the first resection of a lung lesion.

TABLE I

PATIENT CHARACTERISTICS

Characteristic	Value
Gender (pts; *n*)	
Male	50
Female	13
Age (y)	
Mean	59
Range	37–78
H&N SCC localisation (pts; *n*)	
Larynx	31
Oral	11
Oropharynx	11
Hypopharynx	7
Nasopharynx	2
Maxillary sinus	1
H&N SCC stage (pts; *n*)	
I	17
II	13
III	16
IV	17
H&N SCC – lung Ca interval	
Median (mth)	29
Mean (mth)	41.7
1–12 mth (pts; *n*)	14
13–24 mth (pts; *n*)	13
25–36 mth (pts; *n*)	9
>36 mth (pts; *n*)	27
Range (mth)	0–171
Lung tumours (pts; *n*)	
1	51
2	7
3	2
≥4	3
Total lung tumours (*n*)	88
Lung tumour size (mm)	
Mean	2.7
Median	2
Range	0.4–12
Lung tumour site (pts; *n*)	
Peripheral	47
Central	15
Both (multiple)	2
Lung tumour histopathology (pts; *n*)	
SCC	52
Adenocarcinoma	10
Carcinoid	1
Resection type (pts; *n*)	
Pneumonectomy	4
Lobectomy	35
Wedge resection	24
Total pt parameters (mth)	
Follow up, mean	40.3
Survival time, range	0–221
Survival time, median	22.2

Pts = patients; y = years; H&N SCC = head and neck squamous cell carcinoma; H&N SCC – lung Ca interval = median disease-free interval between curative primary H&N SCC treatment and lung malignancy diagnosis; mth = months

Results

During the study period (1978–2006), 3866 patients with head and neck SCC were treated with curative intent. Of these, 320 patients (8 per cent) developed secondary pulmonary lesion(s). Of these 320, 64 patients (20 per cent), requiring treatment for metachronous lung tumours following curative treatment for head and neck SCC, were identified as surgical candidates. All these patients were asymptomatic. One patient received chemotherapy for lung carcinoma prior to a wedge resection, and was excluded from analysis.

The total study group thus consisted of 63 patients, comprising 50 men and 13 women. These patients' original head and neck malignancy sites were: larynx ($n = 31$ patients), oral cavity ($n = 11$), oropharynx ($n = 11$), hypopharynx ($n =$ seven), nasopharynx ($n =$ two) and maxillary sinus ($n =$ one). Their original head and neck tumour stages were: stage I ($n = 17$ patients), stage II ($n = 13$), stage III ($n = 16$) and stage IV ($n = 17$).

The resected lung lesions comprised lung SCC ($n =$ 52 patients), adenocarcinoma ($n = 10$) and carcinoid ($n =$ one). The median disease-free time interval between curative treatment for primary head and neck SCC and the diagnosis of lung malignancy was 29 months (range, one to 171 months).

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TABLE II

PATIENT CHARACTERISTICS BY LUNG TUMOUR HISTOPATHOLOGY

Characteristic	SCC	AdenoCa
Total pts (*n*)	52	10
H&N SCC stage (pts; *n*)		
I	11	6
II	10	2
III	14	2
IV	17	0
H&N SCC – lung Ca interval		
Median (mth)	30	9
0–12 mth (pts; *n*)	8	6
13–24 mth (pts; *n*)	12	0
25–36 mth (pts; *n*)	9	0
>36 mth (pts; *n*)	23	4
Range (mth)	0–171	0–150
Lung tumours (*n*)		
1 (pts; *n* (%))	40 (77)	10 (100)
2 (pts; *n*)	7	0
3 (pts; *n*)	2	0
≥4 (pts; *n*)	3	0
Total lung tumours (*n*)	77	10
Lung tumour size (cm)		
Mean	2.63	3.19
Median	2	3.5
Range	0.4–12	0.7–5
Lung tumour site (pts; *n* (%))		
Peripheral	41 (77)	4 (40)
Central	10 (19)	6 (60)
Both (multiple)	2 (4)	0 (0)
Total pt parameters (mth)		
Follow up, mean	37.5	56.5
Survival time, range	0–221	13–195
Survival time, median	19.6	32

SCC = squamous cell carcinoma; adenoCa = adenocarcinoma; pts = patients; H&N = head and neck; mth = months

At thoracotomy, all palpable lesions were removed. Therefore, in some patients ($n = 4$) the number of resected lesions was more than expected pre-operatively. In the majority of patients ($n = 51$), one lesion was removed; however, two lesions were removed in seven patients, three lesions in two, five lesions in two and seven lesions in one. In five patients, a bilateral two-stage thoracotomy approach was used. Multiple lesions were found only in patients with SCCs, apart from one patient with four SCCs and one adenocarcinoma (Table II). Four patients underwent pneumonectomy, 35 lobectomy and 24 wedge resection.

Free surgical resection margins were achieved in 54 patients. Eight patients with incomplete resections and one with pathologically unclear surgical margins received post-operative radiotherapy.

At the time of analysis, 36 patients had died from recurrent disease, three had died within 90 days post-operatively from complications (i.e. bleeding, pneumonia and ischaemic cardiac disease) and 11 had died of other causes (three from cardiac disease, two from pneumonia due to a swallowing disorder, and six from other malignancies (i.e. prostate cancer, sarcoma and melanoma)). Eleven patients had remained disease-free. Two patients had been lost to follow up. One patient had been transferred to another hospital after a cerebrovascular accident one month after surgery. The other patient had remained well, with no evidence of disease, 30 months after surgery.

The three-year survival estimates were 50 per cent (95 per cent confidence interval (CI), 18–75) for patients with adenocarcinoma ($n = 10$) and 35 per cent (95 per cent CI, 22–48) for patients with SCC ($n = 52$) (Figure 1). This difference was not statistically significant ($p = 0.16$). The median overall survival time for the whole group was 22.2 months (95 per cent CI, 17.6–34.3). The five-year survival rate was 30 per cent. The median survival time in patients undergoing multiple SCC resections was 26.5 months. The one patient with carcinoid died of metastases from a third primary carcinoma (cerebral metastases from a non-small-cell lung carcinoma) after 24 months.

Discussion

After curative treatment for head and neck SCC, patients have a continuous risk of developing a second, primary lung cancer, the incidence of which is approximately 0.6–1.0 per cent per year.[19] In addition, patients with advanced head and neck SCC have an even higher risk of recurrent locoregional disease and distant metastasis (mainly to the lung).[20,21] This risk of recurrence remains relatively

TABLE III

REPORTED DATA FOR H&N SCC PATIENTS WITH SUBSEQUENT LUNG CARCINOMA

Author	Year	Pts resected (*n* (lung Ca type))	5-yr survival (% (median ST; mth))
Present study	2010	52 (SCC)	26 (19.6)
		62 (AdenoCa + SCC)	30 (22.2)
Winter *et al.*[1]	2008	55 (SCC)	19.4 (15.2)
		67 (Mixed)	20.9 (19.4)
Liu D *et al.*[10]	1999	41 (SCC)	34
Younes *et al.*[41]	1997	26 (Mixed Ca)	Unknown (23)
Nibu *et al.*[11]	1997	32 (SCC)	32
Wedman *et al.*[9]	1996	21 (Mixed Ca)	59
Finley *et al.*[4]	1992	18 (SCC)	29 (28)
Sercarz J *et al.*[42]	1989	17 (Mixed Ca)	31.3*
Mazer *et al.*[5]	1988	44 (SCC)	43
Mountain *et al.*[43]	1984	48 (Mixed Ca)	40.9

*Three-year survival. H&N SCC = head and neck squamous cell carcinoma; Ca = carcinoma; pts = patients; yr = year; ST = survival time; mth = months; mixed = combination of adenoCa, SCC, undifferentiated Ca, epidermoid Ca and salivary gland Ca

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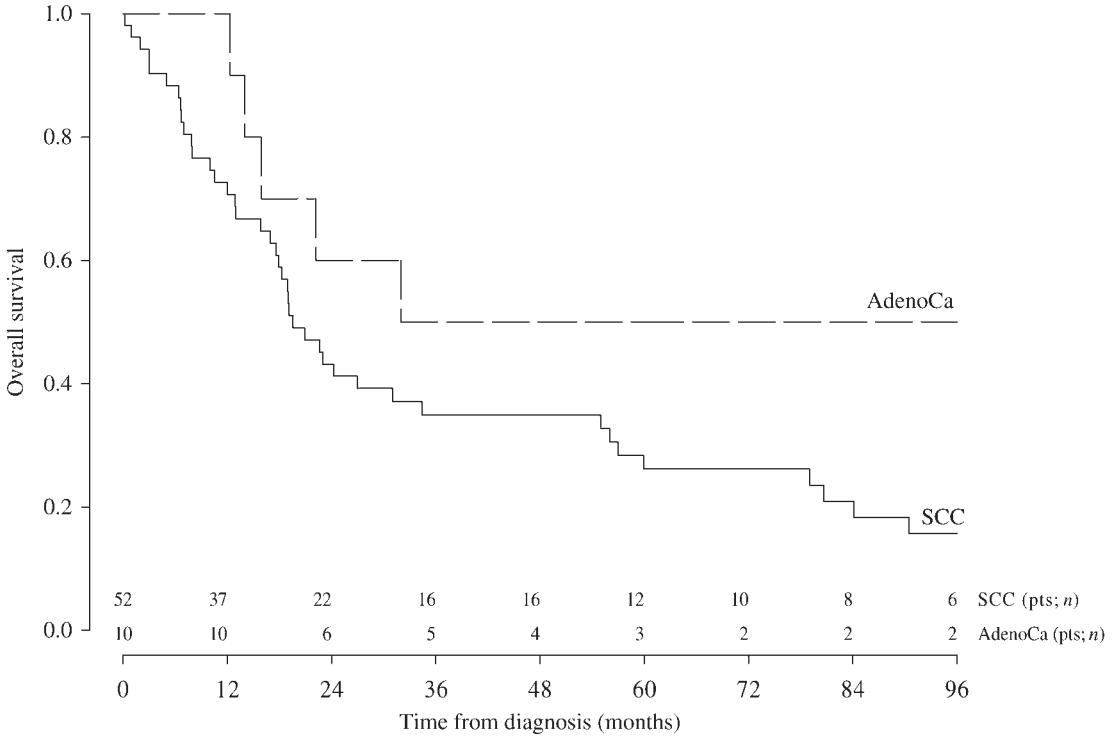

FIG. 1

Overal survival for head and neck squamous cell carcinoma (SCC) patients with resected secondary lung lesions. $p = 0.159$, SCC *vs* adenocarcinoma (adenoCa); log rank test, two-sided. pts = patients

small compared with that for other solid malignancies.[2] Only a limited proportion of patients with secondary lung lesions are eligible for thoracic surgery. The 63 patients in our series who underwent resection for metachronous lung malignancies represented approximately 2 per cent of all head and neck cancer patients treated in our institute over almost 30 years. This figure is compatible to reports from other institutions.[1,10,14]

- **Patients undergoing resection of metachronous lung lesions have five-year survival rates of 19 to 43 per cent; however, these rates are based on small cohorts ($n \leq 55$), and adequate controlled trials have not been performed, so firm evidence of benefit from such resection is lacking**
- **This study evaluated a single institute's experience of resection of metachronous pulmonary malignancy in 63 patients treated curatively for head and neck squamous cell carcinoma (SCC)**
- **In these patients, resection of secondary lung cancer was associated with favourable long term overall survival, especially for adenocarcinoma lesions**

Our data indicated that patients undergoing surgical treatment of a secondary adenocarcinoma of the lung had a more favourable outcome compared with those undergoing SCC resection, although this difference was not statistically significant. There are conflicting reports on survival outcomes for adenocarcinoma and SCC patients. Some authors describe better survival for adenocarcinoma patients, whereas others report no survival difference.[22–29] However, these studies have dealt mainly with primary lung cancer; it is therefore questionable whether these results are representative for patients with secondary lung lesions.

In the current study, multiple (repeated) resections for SCC were associated with favourable median survival. This phenomenon was related to the selection of patients with slowly growing lung lesions. Relatively good outcomes for repeat metastasectomies have recently also been demonstrated for patients with recurrent colorectal cancer, provided that there were long intervals between resections.[30] Other reports have emphasised the prognostic influence of a longer disease-free interval between completion of head and neck SCC treatment and detection of pulmonary lesions.[5,31] The longer the time interval, the better the likelihood of cure, although there is no general agreement or rule.[18] Therefore, we did not use time intervals when analysing treatment decisions.

Molecular techniques are available to differentiate metastases from second primary lung cancer, for tumours sharing the same histology.[6–8,32,33] However, these techniques are complex and sometimes time-consuming, and not universally available for pre-operative analysis of tumour tissue. Although one might have expected better survival rates after treatment for second primary lung cancer, compared with treatment for lung metastases, we were not able to demonstrate such a difference in

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a group of patients with molecularly defined lung SCC lesions.[34] However, the trend towards better survival in adenocarcinoma patients suggests that, in these patients, curative treatment should be planned in the same manner as for patients with primary lung cancer.

Conclusion

The results of the current study indicate that curatively treated head and neck SCC patients who are diagnosed with a solitary (or a limited number of) metachronous lung lesion(s) during follow up may benefit from surgical treatment of those lesions. Unfortunately, due to our study's limited number of patients, long duration and retrospective nature, the results of our cohort cannot be used to refine criteria for the treatment of head and neck cancer patients with metachronous, resectable lung lesions. Nevertheless, the observed survival data support the consideration of surgical resection for solitary or oligometastatic lung lesion(s) (Table III).

Thus far, the US Services Preventive Task Force has not made any recommendation on lung cancer screening, since no clear evidence has emerged from randomised, controlled trials on this subject.[35] Such studies require thousands of patients to undergo long follow up, and are not to be expected in the near future. Currently, only a small minority of patients with curatively treated head and neck SCC receive a standardised follow-up programme involving chest X-ray imaging. However, newer endoscopic and imaging techniques, and analysis of exhaled volatile compounds, may improve the efficacy of detection and treatment of secondary lung malignancy.[11,36–40] Since evidence to support pulmonary surveillance in curatively treated head and neck SCC patients is lacking, any screening strategy should be employed only in a trial setting.

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