Characteristics and outcome of patients with second primary lung cancer

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ABSTRACT Patients with lung cancer are at risk of developing a second primary lung cancer (SPLC). However, the characteristics of patients at risk remain largely speculative.

We reviewed 2816 lung cancer patients from our institution for the occurrence of SPLC. Any SPLC was categorised as synchronous when diagnosed within 2 years of the first primary lung cancer (FPLC) and after direct histological comparison of both tumours. All other SPLCs were considered as metachronous.

139 patients developed a second malignancy including 69 nonsmall cell lung cancer (NSCLC) and 9 small cell lung cancer. The median interval for diagnosis of metachronous SPLC (n=59) after FPLC occurrence was 72 months. SPLC detected within 5 years of FPLC diagnosis had a more favourable stage distribution (p=0.02). After diagnosis of SPLC, patients had a superior median overall survival compared to controls (57.7 *versus* 18.1 months; p<0.0001). Interestingly, comparing only stage IV NSCLC patients, a history of FPLC was also associated with a favourable survival (median 27.4 *versus* 8.97 months; p=0.007).

In summary, previous lung cancer treatment does not lead to impaired prognosis after diagnosis of SPLC. Improved surveillance programmes beyond 5 years after FPLC treatment may result in more favourable disease stages for detected SPLC.

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Introduction

Lung cancer remains one of the most frequent human cancers and the leading cause of cancer-related deaths in the western world [1]. Since most lung cancer patients present with advanced or metastatic disease, the overall 5-year survival rate is only 15% [1]. However, after or during treatment for lung cancer, patients may develop another malignancy, including a second primary lung cancer (SPLC). Some authors have described an increased risk of developing SPLC for lung cancer patients which has been attributed largely to the risks of tobacco consumption [2–4]. The incidence of SPLC has been reported at 1–2% per patient-year [5, 6]. Still, relatively few data have been published about this selected group of patients with sometimes conflicting results. Most of these data have been generated in the 20th century and included low patient numbers, derived either from multiple institutions or over a long time period, that may have rendered conclusions difficult as a result of varying diagnostic procedures and therapeutic developments. Moreover, data regarding clinical characteristics is lacking for patients with first primary lung cancer (FPLC) who might be at risk for developing SPLC. Current surveillance programmes of lung cancer patients do not specifically address the risk of developing a second malignancy [7, 8]. Hence, we conducted a retrospective analysis of SPLC patients diagnosed and treated in our institution within a defined and recent time interval.

Methods

Patients

Retrospectively, we reviewed all lung cancer patients who were treated in our institution between January 1, 2004, and December 31, 2006 using the hospital information system and medical records. In addition, and upon approval by the local ethics committee, patients or their treating physicians were contacted, and the follow-up statuses were completed. The staging of lung cancer was performed according to the sixth edition of TNM (tumour, node, metastasis) criteria; however, all data was also analysed using the seventh TNM classification. Lung cancer patients without a second malignancy served as the control group. The smoking status was assessed at diagnosis of the SPLC. In agreement with other studies, former smoking status was defined for patients with a nicotine cessation of at least 6 months [9, 10]. Patients with a total consumption of less than 100 cigarettes were classified as never-smokers.

Definition of a second primary lung tumour

To identify two lung primary tumours as independent, the criteria established by MARTINI and MELAMED [11] and ANTAKLI *et al.* [6] were used. Briefly, tumours with the same histology must have either an interval of at least 2 years, originate from carcinoma *in situ* or be located in different lungs, lobes or segments without common lymphatics and without distant metastases to be considered as independent primaries. In a similar manner to previous studies, synchronous SPLC was identified if an independent SPLC was evident within 2 years after diagnosis of the FPLC [5, 11]. For synchronous cancers with similar histology, the occurrence of an independent SPLC was confirmed by an independent pathologist after histological

TABLE 1 Locations of a second malignancy after diagnosis of lung cancer

Location of second malignancy	First primary lung cancer		
	NSCLC	SCLC	Total
Another lung cancer	69 (55.6)	9 (60.0)	78 (56.2)
Head neck	8 (6.5)	2 (13.3)	10 (7.2)
Kidney	2 (1.6)	2 (13.3)	4 (2.9)
Bladder	9 (7.4)	0	9 (6.5)
Oesophagus	1 (0.8)	0	1 (0.7)
Colon	6 (4.8)	1 (6.7)	7 (5.0)
Rectum	4 (3.2)	0	4 (2.9)
Breast	5 (4.0)	1 (6.7)	6 (4.3)
Ovary	1 (0.8)	0	1 (0.7)
Liver	4 (3.2)	0	4 (2.9)
Pancreas	2 (1.6)	0	2 (1.4)
Adrenal gland	1 (0.8)	0	1 (0.7)
Prostate	8 (6.5)	0	8 (5.8)
Melanoma	2 (1.6)	0	2 (1.4)
Skin cancer other than melanoma	2 (1.6)	0	2 (1.4)
Total	124 (100)	15 (100)	139 (100)

Data are presented as n (%). NSCLC: nonsmall cell lung cancer; SCLC: small cell lung cancer.

comparison of both tumours. An independent SPLC discovered later than 2 years was labelled metachronous.

Follow-up after therapy of FPLC

All patients entered a follow-up programme with 3-monthly visits for the first 2 years, 6-monthly visits after 2–5 years and yearly visits thereafter [7]. In addition, SCLC patients were seen every 2 months for the first year. All follow-up visits included physical examination, lung function tests and a chest radiograph. In surgically treated patients, a computed tomography scan was performed every 6 months for the first 2 years.

Statistical analysis

The census date was fixed after a minimum period of follow-up of at least 46 months for each patient. As end-points, we used the date of death or survival at the last documented contact with the patient. Collectively, a total of 6326 person-years (4638 person-years for males and 1688 person-years for females) of observation were noted. Patients who died of causes other than lung cancer were censored. Quantitative variables were summarised with their mean or median. Two-sided analysis of variance and the Chi-squared test were performed where appropriate. Survival curves of the different subgroups are presented according to the Kaplan–Meier method. Throughout, $p<0.05$ was considered to be statistically significant.

Results

A total of 139 patients with a second malignancy after diagnosis of lung cancer were identified (table 1) resulting in a prevalence of 2.41% per patient-year. Among these, 78 patients developed a SPLC (prevalence 1.33% per patient-year; 65 nonsmall cell lung cancer (NSCLC) and 13 small cell lung cancer (SCLC); table 2). In 19 patients, SPLCs were diagnosed synchronously. For metachronous SPLCs, the median (range) interval between diagnosis of FPLC and SPLC was 72 (25.4–286) months with most SPLC diagnosed after 5 years of FPLC diagnosis. In contrast, a group of 2675 lung cancer patients developed no further malignancy and served as the control group. While the current health status could not be updated

TABLE 2 Patient characteristics

Characteristics	Patients with SPLC	Control group
Patients	78	2675
Age at time of diagnosis of FPLC		
Median age years	58	64
Age range years	36–78	21–86
Age distribution		
⩽29 years	0	2
30–39 years	2	24
40–49 years	11	237
50–59 years	33	668
60–69 years	21	1032
70–79 years	11	615
⩾80 years	0	97
Sex		
Male	59	1921
Female	19	754
Smoking status		
Current smoker	47 (61.8)	1473 (74.0)
Former	18 (23.7)	372 (18.7)
Never	11 (14.5)	146 (7.3)
Unknown	2	684
Median pack-years	55.0	47.5
Interval FPLC–SPLC		
<1 month	15	
1–6 months	2	
6 months–1 year	0	
1–2 years	2	
2–5 years	24	
5–10 years	18	
>10 years	17	

Data are presented as n or n (%), unless otherwise stated. FPLC: first primary lung cancer; SPLC: second primary lung cancer.

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for 471 patients (11 patients with SPLC; 460 patients in the control group) the mean follow-up was 26.1 months for all patients (median 15.4 months) and 43.9 months for surviving patients (median 43.6 months).

Characteristics of FPLC

Of the 78 patients who later developed a SPLC, 69 and nine patients had a previous NSCLC and SCLC, respectively. Compared to controls, the median age of patients with FPLC was younger (58 *versus* 64 years in controls). Interestingly, while significantly more FPLC patients were former and never-smokers ($p<0.05$), those patients who did smoke had a higher median cigarette consumption (55 *versus* 47.5 pack-years; $p<0.01$). Since most FPLCs were diagnosed in early stages (table 3), most patients underwent surgical resection (86%) or radiation therapy of FPLC (26%). No FPLC was treated with chemotherapy alone. All three first primary NSCLC patients with stage IV disease had lung metastases (ipsilateral in two patients; contralateral in one patient) as the only metastasis location and underwent complete resection of both the primary tumour and metastases, followed by chemotherapy in two cases. One SCLC patient with brain metastasis, that was treated with chemotherapy and cerebral radiation, developed a SPLC after 7 years.

Characteristics of SPLC

At diagnosis of SPLC (65 NSCLC, 13 SCLC), the median (range) age was 64 (45–81) years which was similar to controls. NSCLC and SCLC as metachronous SPLC were diagnosed after a median interval of 77 (25.4–286) and 67 (29–226) months after diagnosis of FPLC, respectively. There were no significant differences between synchronous and metachronous SPLC. All but one SCLC developed as metachronous cancer. No patient with SCLC as FPLC developed another SCLC as a SPLC. In cases of adenocarcinoma or squamous cell carcinoma as FLPC, 65% and 46% of patients also had a similar histology as SPLC, respectively (table 4).

Similar to FPLC, most SPLC were diagnosed as stage I (51.3%) and stage II (11.5%) disease which was independent from the stage of FPLC. Interestingly, SPLC disease detected within or after 5 years after

TABLE 3 Disease and treatment characteristics

	FPLC	SPLC	Control group
Histology			
NSCLC	69 (88.5)	65 (11.5)	2188 (81.8)
Adenocarcinoma	31	33	1070
Squamous cell carcinoma	28	28	717
Large cell carcinoma	8	4	401
NSCLC, not specified	2	0	0
SCLC	9 (11.5)	13 (16.7)	487 (18.2)
Stage distribution NSCLC			
I	40 (57.9)	38 (58.5)	544 (24.9)
II	14 (20.3)	6 (9.2)	166 (7.6)
III	12 (17.3)	11 (16.9)	733 (33.5)
IV	3 (4.3)	10 (15.4)	745 (34.0)
Stage distribution SCLC			
I	1 (11.1)	2 (15.4)	36 (7.4)
II	0	3 (23.1)	11 (2.3)
III	7 (78,8)	3 (23.1)	226 (46.4)
IV	1 (11.1)	5 (38.4)	214 (43.9)
Initial treatment			
Surgery only	54	32	586
Radiation therapy only	3	10	300
Chemotherapy only	0	10	780
Combination therapy			
Surgery and chemotherapy	3	6	210
Surgery and radiation therapy	3	4	132
Radiation therapy and chemotherapy	8	6	403
All modalities	7	6	89
No treatment	0	4	175

Data are presented as n or n (%). FPLC: first primary lung cancer; SPLC: second primary lung cancer; NSCLC: nonsmall cell lung cancer; SCLC: small cell lung cancer.

TABLE 4 Development of second primary lung cancer (SPLC) with regard to the histology of the first primary lung cancer (FPLC)

FPLC		SPLC	
Histology	**n**	**Histology**	**n**
Adenocarcinoma	31	Adenocarcinoma	20
		Squamous cell carcinoma	7
		Large cell carcinoma	2
		SCLC	2
Squamous cell carcinoma	28	Adenocarcinoma	6
		Squamous cell carcinoma	13
		Large cell carcinoma	0
		SCLC	9
Large cell carcinoma	8	Adenocarcinoma	4
		Squamous cell carcinoma	2
		Large cell carcinoma	0
		SCLC	2
SCLC	9	Adenocarcinoma	2
		Squamous cell carcinoma	5
		Large cell carcinoma	2
		SCLC	0
NSCLC, NOS	2	Adenocarcinoma	1
		Squamous cell carcinoma	1
		Large cell carcinoma	0
		SCLC	0
Total	78		78

SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; NOS: not otherwise specified.

diagnosis of FPLC had a different stage distribution (p=0.02; table 5). While SPLC was detected as stage I disease in 65% of cases when diagnosed within 5 years of FPLC detection, this stage was only present in 34% when diagnosed after 5 years of FPLC. In contrast, SPLC was diagnosed as stage III/IV disease in 30% and 46%, respectively, when detected within or after 5 years of FPLC. The most frequent localisation of SPLC was the left upper lobe (35.1%) while FPLC was most often found in the right upper lobe (47.4%). In comparison, lung cancers of the control group were located in the left and right upper lobes in 26.1% and 29.5%, respectively.

Compared to FPLC, stage I and II SPLC underwent less frequent surgical resection (78% *versus* 98%) but were treated more often with radiotherapy (29% *versus* 7%). Of all stage IV SPLC patients, two patients had single lung metastases that were completely resected with the primary tumour. Another patient had brain metastases and received radiation of both the thoracic tumour and brain metastases. Two stage IV patients could not be offered treatment due to poor performance status. All other stage IV patients (n=10) were treated with systemic chemotherapy alone.

Survival

SPLC patients had a median overall survival of 12.6 years (95% CI 197.2–109 months) and 4.8 years (95% CI 79.8–35.6 months) determined from the date of diagnosis of FPLC and SPLC, respectively. In comparison, the control group had a median survival of 1.5 years (19.3–16.8 months; p<0.0001). At the end of data bank closure, 46 (59%) patients with SPLC were still alive including 11 patients who were lost to follow-up. Interestingly, the survival benefit for SPLC compared to controls held true for smokers (median 57.7 *versus* 18.1 months; p=0.01) but not for former (p=0.11) or never smokers (p=0.14). Patients with synchronous SPLC had a better overall survival after diagnosis of SPLC compared to metachronous SPLC patients (median not reached *versus* 42.6 months; p<0.05).

While the survival of SPLC patients with SCLC was not significantly different from controls (median 16.3 *versus* 13.3 months; p=0.64), patients with NSCLC as SPLC lived more than four times longer after SPLC diagnosis than NSCLC control patients (median not reached *versus* 19.8 months, p<0.0001; fig. 1). Comparing NSCLC patients with similar disease stages, a history of FPLC was associated with superior survival for patients with stage IIIA (median 251.6 *versus* 26.5 months; p=0.001) and stage IV disease (median 27.4 *versus* 8.97 months; p=0.006; fig. 2). When all cancers were reclassified using the seventh

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TABLE 5 Stage distribution of second primary lung cancer depending on the time interval after diagnosis of first primary lung cancer

Stage	Interval <5 years	Interval >5 years
I	28 (65)	12 (34)
II	2 (5)	7 (20)
III	6 (14)	8 (23)
IV	7 (16)	8 (23)

Data are presented as n (%).

TNM classification, the difference in overall survival for SPLC NSCLC patients *versus* controls held true (median not reached *versus* 8.8 months; p=0.007). However, SPLC patients with stage IV disease (both NSCLC and SCLC) receiving only chemotherapy were not significantly different to the respective control patients (10 *versus* 650 patients; p=0.14).

Patients with additional malignancies

Besides developing a SPLC, eight patients (10.2%; six male, two female) developed a third malignancy after the FPLC including a third primary lung cancer (two patients), melanoma (two patients), prostate cancer and sarcoma (one patient each). In two cases, the origin of the third malignancy remained unknown. At the end of data bank closure, five of these patients were still alive.

Discussion

To our knowledge, this report reflects on the largest number of patients with SPLC from a single institution with uniform staging and diagnosis criteria. The prevalence of a second malignancy in all lung cancer patients investigated in our study was 2.41% per patient-year, which was somewhat higher compared to data from a large survey including 57 871 cancer patients (5799 with lung cancer) from 1962–1989 from a Japanese institution [12]. In this study, the risk for second malignancy was 0.008% and 1.87% per patient-year for all cancer patients or lung cancer patients only, respectively. Compared to expected values in the general population, the risk of developing a SPLC was 4.6 and 7.8 times higher for male and female patients with lung cancer, respectively. Since 1962, progress in diagnostic and therapeutic options such as the introduction of adjuvant chemotherapy after complete resection has influenced the general outcome of lung cancer with a possible impact on the occurrence of second malignancies. In our study with 2004 as the start entry for collecting data, second primaries were most often located in the lung (55% as compared to only 45% for all other organ cancers combined). In comparison, only 11.04% of all tumour patients being diagnosed in Germany in 2006 had lung cancer [13]. The risk of 1.33% per patient-year for developing a SPLC is in congruence with the estimate of 1–2% per year after the diagnosis of FPLC in other studies [4, 5]. Some authors described a higher risk of SCLC patients for developing a SPLC [2, 14] as compared to the risk for SPLC after NSCLC [5]. However, we did not detect significant differences in this regard.

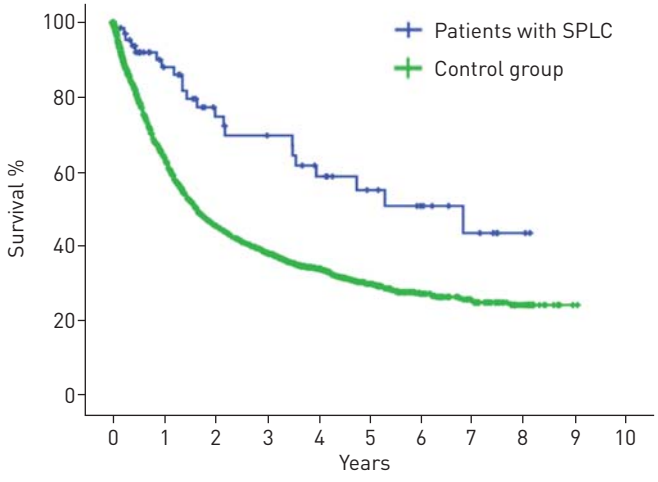

FIGURE 1 Survival of nonsmall cell lung cancer (NSCLC) patients with or without a second primary lung cancer (SPLC). NSCLC patients with a history of a previous primary lung cancer had a significantly superior survival compared to control patients without previous malignancy and diagnosed in the same time interval (p<0.0001).

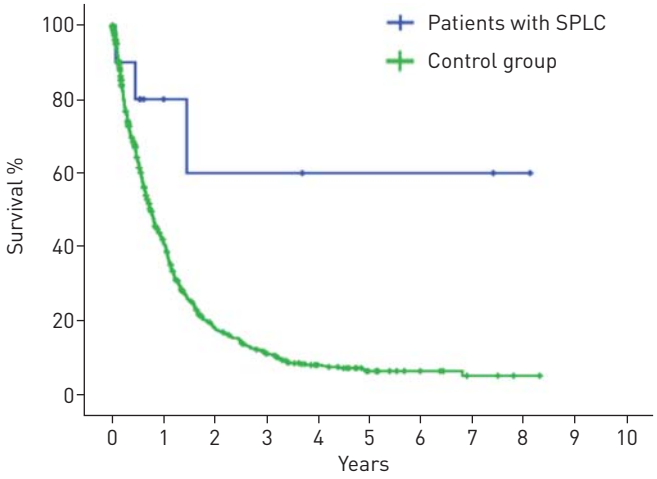

FIGURE 2 Survival of stage IV nonsmall cell lung cancer (NSCLC) patients with and without a second primary lung cancer (SPLC). Patients with SPLC (n=10) had a significantly improved survival after diagnosis of the SPLC compared to controls (n=745; p=0.006).

Patients with SPLC and a smoking history had a significantly higher cigarette consumption compared to controls, which is similar to previous data [15]. In accordance with other data, the predominant histology of SPLC after SCLC was squamous cell carcinoma [14, 16] which may also indicate high nicotine consumption as a risk factor. Collectively, high nicotine consumption remains a major risk factor especially in those patients who continue cigarette smoking after diagnosis of lung cancer [17, 18].

There is an ongoing discussion on the arbitrary distinction between synchronous and metachronous SPLC [19, 20]. In our study, 24% of SPLCs were diagnosed as synchronous tumours. We followed most previous studies in using the definition by MARTINI and MELAMED [11]. Moreover, in cases of similar histology, histological sections from both FPLC and SPLC were compared. This approach may have contributed to a lower incidence of synchronous SPLC compared to others who described approximately one third of all SPLC patients as synchronous [21, 22]. However, the histological pattern may have been changed in relapse tumours. As a perspective, a better identification of the independence of lung primaries may involve molecular assessments such as gene array analyses or patterns of loss of heterozygosity. In a limited number of synchronous and metachronous pulmonary tumours, assessment of loss of heterozygosity patterns demonstrated that the previous classification of synchronous and metachronous tumours based on the criteria suggested by MARTINI and MELAMED [11] held true for most, but not all cases [23].

Most metachronous SPLCs were diagnosed 5 years after diagnosis of the FPLC which is somewhat similar to two retrospective studies on surgical patients developing metachronous SPLC [24–26]. Interestingly, and previously unaddressed, SPLC disease was detected in a more advanced stage when diagnosed more than 5 years after diagnosis of FPLC compared to SPLC patients with a shorter interval. This may have been the consequence of the extension of follow-up visits to a yearly schedule. However, whether a more frequent surveillance programme after 5 years may have led to diagnosis of more SPLC in earlier stages remains speculative and would need to be addressed in larger clinical studies [5].

The 5-year survival rate of 44% of all SPLC patients in our study is congruent with data from 41 resected patients with metachronous lung cancer [26]. Some studies on patients with surgically treated metachronous SPLC report somewhat lower outcomes despite recruiting only patients with early tumour stages (26%–33%) [27, 28]. The finding of earlier studies that support a worse prognosis for patients with synchronous lung tumours compared to metachronous tumours could not be confirmed in our study [6, 26]. Compared to our control group, patients lived significantly longer after SPLC diagnosis, an effect that, at least in part, may be explained by positive patient selection. SPLC patients had more favourable disease stages and were more often never or former smokers. Moreover, one should also consider competing risks caused by major comorbidities, in particular pulmonary and cardiovascular diseases. While this data could not be evaluated for the current manuscript, future evaluations should address this issue as well as possible long-term side-effects caused by the previous treatments.

Comparing the outcome of similar disease stages between NSCLC patients with and without SPLC, stage IV SPLC patients had a significantly better overall survival that held true even after reanalysis using the seventh TNM classification for all lung cancers. Comparing only stage IV NSCLC patients receiving exclusively chemotherapy, the superior outcome failed significance possibly due to low patient numbers. In contrast, the survival of patients after diagnosis of SCLC as SPLC was not different to control patients. Again, the case numbers were low. As a hypothesis, metastatic disease may rather reflect the biology of the disease

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compared to limited stages treated with surgery or radiation. Since various epigenetic and genetic alterations may modify lung cancer risk and development, the better overall survival of patients with SPLC may indicate a distinct epigenetic profile [29, 30].

Reflecting the opportunity of a favourable outcome, as shown in the recent analysis, SPLC should be attributed to an ''as best'' treatment approach. As examples of such an approach selected stage IV NSCLC patients with solitary adrenal gland, brain or contralateral lung metastasis did benefit from complete resection of both primary lung tumour and metastasis resulting in a favourable outcome [31–33]. Moreover, according to the revised staging system, patients with ipsilateral lung metastasis are now classified as having T4 tumours [34].

In summary, our data suggest that lung cancer patients should be closely monitored after treatment with possibly shorter intervals beyond 5 years. Patients with multiple or recurrent thoracic tumours should be carefully staged and, if justifiable depending on expected risks for the patient, be re-biopsied in order to distinguish SPLC from recurrent FPLC. The prognosis of SPLC patients does not seem to be worse compared to other patients with lung cancer and may even be superior in certain circumstances [35].

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