Lung Cancer 137 (2019) 23–30

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Let us not underestimate the long-term risk of SPLC after surgical resection of NSCLC

Taylor Leroy[a,b], Elisabeth Monnet[c], Stéphane Guerzider[d], Pascale Jacoulet[d], Bernardino De Bari[e], Pierre-Emmanuel Falcoz[f,g,h], Marie Gainet-Brun[d], Jean Lahourcade[d], Faraj Alfreijat[i], Hamadi Almotlak[i], Olivier Adotevi[j,k], Didier Pernet[d], Jean-Charles Polio[d], Maxime Desmarets[c,k], Anne-Sophie Woronoff[a,b,*,1], Virginie Westeel[d,k,1]

[a] *Doubs and Belfort Territory Cancer Registry, Besançon University Hospital, F-25000 Besançon, France*
[b] *EA3181, University of Bourgogne-Franche-Comté, F-25000, Besançon, France*
[c] *INSERM CIC 1431, Besançon University Hospital, F-25000 Besançon, France*
[d] *Department of Respiratory Diseases, Besançon University Hospital, F-25000, Besançon, France*
[e] *Department of Radiotherapy, Besançon University Hospital, F-25000, Besançon, France*
[f] *University Hospital of Strasbourg, Nouvel Hôpital Civil, F-67000, Strasbourg, France*
[g] *University of Strasbourg, F-67000, Strasbourg, France*
[h] *INSERM UMR 1260, Regenerative Nanomedicine (RNM), FMTS, F-67000 Strasbourg, France*
[i] *Department of Respiratory Diseases, Nord Franche-Comté Hospital, F-90400 Trévenans, France*
[j] *Department of Oncology, Besançon University Hospital, F-25000 Besançon, France*
[k] *INSERM UMR 1098, University of Bourgogne-Franche-Comté, F-25000 Besançon, France*

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Surgery
Second primary lung cancer
Postoperative radiotherapy
Follow-up

ABSTRACT

Objectives: Several studies have reported that patients operated on for non-small cell lung cancer (NSCLC) are at high risk of second primary lung cancer (SPLC). However, widely varying estimates of this risk have been reported, with very few studies taking into account that these patients are at particularly high competing risk of death, due to recurrence of the initial disease and to comorbidities. Risk factor evaluation over time has significant repercussions on the post-surgery surveillance strategy offered for NSCLC. This study primarily sought to measure the risk of SPLC in a long-term follow-up series, using statistical methods considering competing risks of death.

Materials and methods: The cumulative SPLC risk was estimated using the cumulative incidence of patients with completely resected Stage I-III NSCLC diagnosed between 2002 and 2015 based on the Doubs and Belfort cancer registry (France). A proportional sub-distribution hazard model ($_{sd}$RH) was used to investigate factors associated with SPLC risk in the presence of competing risks.

Results: Among the 522 patients, adenocarcinoma and Stage I or II disease accounted for 52.3% and 75.7% of patients, respectively. Overall, 84 patients developed SPLC (16.1%). The cumulative risk of SPLC was 20.2% at 10 years post-surgery (95% confidence interval [CI]: 15.3–23.2), and 25.2% (CI: 19.4–31.3) at 14 years post-surgery. On multivariate analysis, the SPLC risk was significantly higher in patients with postoperative thoracic radiotherapy ($_{sd}$RH 2.79; 95% CI: 1.41–5.52; p = 0.003).

Conclusion: This study using appropriate statistical methods to consider competing risks showed that after

* Corresponding author at: Registre des tumeurs du Doubs et Territoire de Belfort, Bâtiment bleu, CHRU Besançon, 3 boulevard Alexandre Fleming, 25030, Besançon Cedex, France.

E-mail addresses: taylor-lucrece.leroy@laposte.net (T. Leroy), elisabeth.monnet@univ-fcomte.fr (E. Monnet), stephane.guerzider@hotmail.fr (S. Guerzider), p1jacoulet@chu-besancon.fr (P. Jacoulet), bdebari@chu-besancon.fr (B. De Bari), pierre-emmanuel.falcoz@chru-strasbourg.fr (P.-E. Falcoz), brun-gainet@wanadoo.fr (M. Gainet-Brun), j.lahourcade@chi-hautecomte.fr (J. Lahourcade), faraj.alfreijat@hnfc.fr (F. Alfreijat), halmotlak@chu-besancon.fr (H. Almotlak), olivier.adotevi@univ-fcomte.fr (O. Adotevi), dpernet@chu-besancon.fr (D. Pernet), dr.jean-charles.polio@laposte.net (J.-C. Polio), maxime.desmarets@univ-fcomte.fr (M. Desmarets), asworonoff@chu-besancon.fr (A.-S. Woronoff), virginie.westeel@univ-fcomte.fr (V. Westeel).

[1] Equal contribution

https://doi.org/10.1016/j.lungcan.2019.09.001
Received 25 June 2019; Received in revised form 29 August 2019; Accepted 2 September 2019
0169-5002/

complete NSCLC resection, the cumulative incidence function of SPLC was high, with patients receiving postoperative thoracic radiotherapy at higher risk. These data support the need for life-long follow-up of patients who undergo NSCLC surgery, with the objective of screening for SPLC.

1. Introduction

Lung cancer is the most common cause of cancer death worldwide [1]. Non-small cell lung carcinoma (NSCLC) accounts for around 85% of lung cancer cases. The standard treatment for patients with stage I and II NSCLC is surgery based, with or without postoperative chemotherapy depending on the pathological T and N status. Treatment for stage III NSCLC consists either of concurrent chemoradiation, or surgery with perioperative chemotherapy with or without thoracic radiotherapy [2]. After surgery, the 5-year survival rates range between 23 and 83%, depending on stage [3].

After surgery, most international guidelines recommend regular follow-up visits and chest computed tomography (CT), but the optimal duration and frequency of follow-up remain unclear. Several studies have shown that lung cancer survivors remain at high risk of developing a second primary (metachronous) lung cancer (SPLC), even more than 5 years after treatment [4–9]. However, studies investigating the risk of SPLC from resected NSCLC series reported widely varying estimates of this risk, with very few of them taking into account that the patients operated on for NSCLC are at particularly high competing risk of death, due to recurrence of the initial disease and to comorbidities.

Therefore, the primary study objective was to estimate the long-term incidence function of SPLC in a population-based cohort of patients operated on for Stage I to III NSCLC while taking account of the competing risks of death during follow-up. The secondary objective was to identify patient and tumor characteristics, as well as perioperative treatments associated with an increased risk of SPLC (while factoring in competing risks of death).

2. Material and methods

2.1. Study population

Patients were identified using the cancer registry for the Doubs and Belfort administrative districts of France. All incident cases of NSCLC diagnosed between January 1, 2002, and December 31, 2015, were retrieved. Of those, all patients aged 18 years or older with a completely resected pathological Stage I to III NSCLC were included. Staging was determined according to the 6th edition of the Union for International Cancer Control (UICC) TNM classification for cases resected before 2009, and according to the 7th edition thereafter [10,11]. Complete resection was defined as microscopically free surgical margins, and either systematic mediastinal lymph node dissection or selective nodal sampling. Patients were also eligible if they had incomplete resection due to carcinoma *in situ* in the resection margins or metastatic tumors due to pulmonary nodules in another ipsilateral lobe according to the 6th edition of the UICC-TNM classification. The exclusion criteria were: death within 30 days of surgery, synchronous lung cancer or a history of prior cancer within the previous 5 years (except for basal cell carcinoma of the skin or carcinoma *in situ* of the uterine cervix). A consensus approach on follow-up had been adopted for the Doubs and Belfort region. The follow-up comprised clinic visits and chest CT every 6 months for 2 years, then every year between years 3 and 5, and lastly chest X-ray or chest CT yearly beyond 5 years.

2.2. Data sources and variables studied

The data, routinely collected by the registry and from medical records, were as follows: date of diagnosis, topography, histology, date of surgery, pathological classification of the primary tumor (pT) and regional lymph nodes (pN), and perioperative treatment (chemotherapy; thoracic radiotherapy). Histology was dichotomized into adenocarcinoma and non-adenocarcinoma (Appendix 1). Pathology reports were retrospectively examined to determine whether the resection was complete. Smoking history was retrospectively collected. Patients were classified as never-smokers (if they had smoked less than 10 cigarettes in their lifetime), former smokers (who had quit > 1 year before diagnosis) or current smokers, and smoking was quantified in pack-years.

A distinction was made between recurrence and SPLC using the Martini and Melamed criteria [12]. According to this definition, a new, distinct pulmonary malignancy was considered a SPLC if it fulfilled any of the following three criteria: 1) histologic type different from that of the index tumor; 2) same histologic type as that of the index tumor but diagnosed at least 2 years later; or 3) same histologic type as that of the index tumor, diagnosed within 2 years, but located in a different lobe or lung, with no involvement of lymphatics common to both, and no evidence of extrapulmonary metastasis [12]. Vital status, date of death, and last available follow-up date were extracted from the medical records and registry database. An active search for vital status at December 31, 2017 was carried out.

2.3. Statistical analysis

Quantitative variables were expressed by median and range, and qualitative variables by number and percentage. The event of primary interest was the occurrence of SPLC. As many patients may die before experiencing the event of interest due to poor NSCLC prognosis or comorbidities, death from any cause was considered as a competing risk. Consequently, we used a competing-risks approach [13]. The time-to-event was calculated from the date of surgical resection. Patients who experienced no event during follow-up were censored at the time of last contact.

We employed the cumulative incidence function (CIF) method to estimate the “net” probability of SPLC over time among survivors of the first lung cancer, *i.e.,* the incidence of this event in the cohort before the occurrence of death, the competing event. Firstly, annualized risks of SPLC, corresponding to the cumulative incidence over 12-month intervals, were estimated along with the corresponding 95% confidence intervals (95% CI). For this estimation, patients who were still at risk were recalculated at the beginning of each follow-up year. CIF curves were estimated from surgery to the last observed time point, and were generated for the whole cohort according to the following variables: gender, age at initial surgery, smoking status and number of pack-years, pT and pN, histology, and perioperative treatment (chemotherapy and/or radiotherapy) of initial lung cancer. The CIF curves were compared using Gray’s test. Then the Fine-Gray model was used to analyze the prognostic effect of each variable on the sub-distribution hazard function of SPLC [14], that is, the relative change in the instantaneous rate of the event occurrence in patients who were event-free or experienced a competing event. Significance was assessed with the Wald test, and all variables with a p value of 0.2 or less were retained for multivariate analysis. Both unadjusted and adjusted sub-distribution relative hazards were estimated along with the corresponding 95% CI [15]. In the final multivariate model, the proportional hazard assumption was verified for all significant covariates using the Schoenfeld residuals method. A time-by-covariate interaction term was added to the model when the assumption was not met [16]. All statistical tests were 2-sided, with a significance level at 0.05. SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used to perform all statistical analyses.

3. Results

A total of 556 patients with completely resected pathological Stage I to III NSCLC were identified (Fig. 1). We excluded 16 patients who died within 30 days of surgery, 2 patients with synchronous lung cancer, and 16 patients with a history of prior cancer within the previous 5 years. Patient characteristics at baseline are summarized in Table 1. In the 522 eligible patients, median age was 64 years (range: 38–86), 73.6% of patients were males, and 15.1% never-smokers. In ever-smokers, the median number of pack-years was 40 (1–160). Adenocarcinoma accounted for 52.3% of all cases, and Stage I or II 75.7%. A total of 233 patients (44.6%) received perioperative chemotherapy (preoperative 68 patients, postoperative 127 patients, both pre and postoperative 38 patients), and 44 patients (8.4%) postoperative thoracic radiotherapy (plus preoperative chemotherapy 8 patients, plus postoperative chemotherapy 24 patients, plus both pre and postoperative chemotherapy 2 patients).

Median follow-up was 59 months (2–190). Eighty-four patients (16.1%) developed a SPLC, 180 (34.5%) died without evidence of SPLC, and 258 (49.4%) were still alive, showing no evidence of SPLC at the end date. The median time from surgery to SPLC was 47 months (1–163). Of the 84 patients who developed a SPLC, 60 (71.4%) died during follow-up. The treatment for SPLC was surgery ± chemotherapy ± radiotherapy in 20 patients (23.8%), stereotactic radiotherapy in 6 patients (7.1%), radiotherapy ± chemotherapy in 13 patients (15.5%), chemotherapy in 32 patients (38.1%), and best supportive care in 12 patients only (14.3%). The treatment for SPLC was unknown in one patient.

The CIF of SPLC during the follow-up period was 20.2% at 10 years (95% CI: 15.3–23.2), and reached 25.2% at 14 years (95% CI: 19.4–31.3; Fig. 2). The risk of SPLC persisted over time (Fig. 3). In eight of the 84 cases, SPLC occurred within 2 years of surgery, and all had a pathological type different from that of the index tumor. The pathological type was unknown in 7 (43%) of the 16 SPLC diagnosed during year 3, in 7 (37%) of the 19 diagnosed during year 4, and in 5 (38%) of the 13 diagnosed during year 5. It was different from that of the index tumor in 4 (25%), 3 (16%) and 6 (46%), respectively. In the first 5 years after surgery, the annual risk peaked at year 4 (5.8%, 95% CI: 3.6–8.6%). The risk persisted beyond year 9, with 7 SPLC cases among the 92 patients alive at the beginning of year 10 after surgery of the index lung cancer. Among these patients, the risk of SPLC during the following 5 years reached 14.3% (95% CI: 9.6–27.0%).

The CIF curves for SPLC according to perioperative index cancer treatment are shown in Fig. 4. Fourteen of the 44 patients who received radiotherapy developed a SPLC. SPLC risks were significantly higher among patients who received postoperative radiotherapy than among those who received surgery or perioperative chemotherapy only (5, 10 and 14-year risks [95% CI]: 25.8% [13.2–40.6], 40.7% [23.6–57.2] and 40.7% [23.6–57.2]; 9.3 [5.8–13.7], 15.5% [10.3–21.5] and 23.0% [14.9–32.1]; 12.8% [8.6–17.9], 18.4% [13.1–24.5] and 24.8% [16.1–34.6], respectively, p = 0.003).

Sub-distribution relative hazards ($_{sd}$RHs) estimated from Fine–Gray univariate and multivariate models are presented in Table 2. On univariate analysis, SPLC hazard was significantly increased for pN2 ($_{sd}$RH [95% CI] 1.84 [1.08–3.15], p = 0.02) compared to pN0/1, and for postoperative radiotherapy (2.88 [1.54–5.38], p = 0.004) compared to

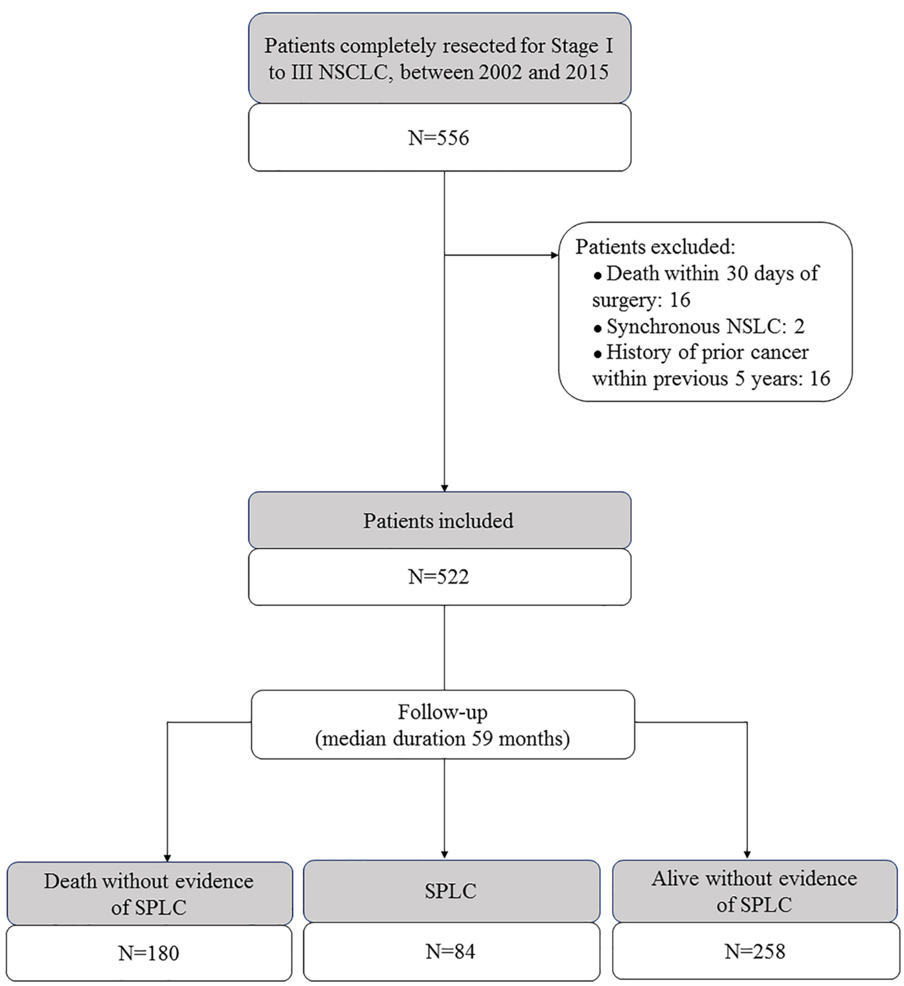


Fig. 1. Flow chart of study patients. NSCLC: non-small cell lung cancer; SPLC: second primary lung cancer.

Table 1
Baseline characteristics (N = 522).

Patients	N = 522 (%)
Age	
< 70 years	367 (70.3)
≥70 years	155 (29.7)
Sex	
Male	384 (73.6)
Female	138 (26.4)
Smoking status	
Never-smokers	79 (15.1)
Current smokers	200 (38.3)
Previous smokers	227 (43.5)
Unknown	16 (3.1)
Pack-years	
[0–10]	99 (19.0)
[11–39]	148 (28.3)
≥40	253 (48.5)
Unknown	22 (4.2)
Tumors	
Time of diagnosis	
[2002–2009]	274 (52.5)
[2010–2015]	248 (47.5)
Histology	
Adenocarcinoma	273 (52.3)
Non-adenocarcinoma	249 (47.7)
pT	
pT0	4 (0.8)
pT1	169 (32.4)
pT2	261 (50.0)
pT3	63 (12.1)
pT4	19 (3.6)
Unknown	6 (1.1)
pN	
pN0	312 (59.8)
pN1	121 (23.2)
pN2	82 (15.7)
Unknown	7 (1.3)
Stage (TNM)	
I	273 (52.3)
II	122 (23.4)
III	117 (22.4)
Unknown	10 (1.9)
Treatment	
Surgery	231 (44.3)
Surgery + Chemotherapy	233 (44.6)
Surgery + Radiotherapy ± Chemotherapy*	44 (8.4)
Unknown	14 (2.7)

pT: pathological classification of the primary tumor; pN: pathological classification of the regional lymph nodes.

* 10 patients received Surgery + Radiotherapy.

surgery alone. As they were associated with the risk of SPLC with a p value < 0.20, the variables time of diagnosis, age, pack-years, pN, and treatment of the index tumor were retained in multivariate modeling. After adjusting for time of diagnosis, age, smoking (pack-years) and pN, the initial perioperative cancer treatment was the main factor associated with SPLC hazard. Compared to surgery alone, postoperative radiotherapy significantly increased SPLC hazard (2.79 [1.41–5.52], p = 0.003), whereas perioperative chemotherapy did not (1.32 [0.77–2.26], p = 0.31). SPLC hazard tended to be higher among patients aged 70 and older compared to their younger counterparts (1.57 [0.98–2.51]). All variables included in the final model met the proportional hypothesis assumption, except for age, for which the time interaction term was significantly associated with the risk of SPLC (p = 0.01). When the interaction term was included in the model, increased age became significantly associated with a higher risk of SPLC up to year 4 after surgery (2.51 [1.39–4.54]). Relative hazard estimations for the other covariates were not modified (data not shown).

4. Discussion

In this exhaustive population series of 522 resected Stage I to III NSCLC patients with a long follow-up (median 59 months, maximum of more than 15 years), our results showed a high risk of SPLC (84 patients, 16.1%). Cumulative incidence, which took account of competing risks of death, was 20.2% at 10 years and 25.2% at 14 years. SPLC cases were observed throughout follow-up, up to year 14 after initial surgery. In a multivariate analysis that took competing risks of death into account, patients who received postoperative radiotherapy (with or without chemotherapy) had a significantly higher risk of developing SPLC than did patients who had surgery with or without chemotherapy (hazard ratio = 2.79; 95% CI: 1.41–5.52).

4.1. Second primary lung cancer

The majority of the mostly retrospective series have reported SPLC rates after surgery for Stage I to III NSCLC of up to 8.6% [4,7,8,17–21]. Only the single-center trial of 124 resected Stage IA NSCLC by Lamont et al. has reported a 15.3% SPLC rate close to ours [22]. In studies with median follow-up durations similar to this study, the highest SPLC rates reported were around 8% [4,17,18]. In a Surveillance Epidemiology and End Results (SEER) cohort including 20032 patients who survived 5 years after an initial diagnosis of lung cancer, the median 10-year risk of SPLC was 8.36% [7].

One of the difficulties in estimating the risk of SPLC revolves around the definition used to distinguish new primaries from lung recurrences. Most studies have applied the same definition as Martini and Melamed, which considers distinct pulmonary malignancies with the same histologic results as being SPLC if they are diagnosed at least two years after the index primary lung cancer [6,17–20]. Others have defined SPLC as a new, distinct lung malignancy diagnosed more than 5 years after the primary tumor, using a stricter definition than the Martini and Melamed criteria [7,8,21]. Comparing radiographic and metabolic appearance, growth patterns, comprehensive histologic assessments, genomic hybridization and biomarker patterns has been proposed to differentiate separate primary lung cancers from metastatic foci in the eighth TNM classification, yet even this is considered to be associated with a substantial rate of misclassification [23]. In our study, all the eight cases of SPLC diagnosed within the two first years of surgery had a histological type different from that of the index tumor, suggesting that these tumors were indeed SPLC. Although the risk of recurrence decreases after two years, misclassifications cannot be eliminated as 13 (27%) of the 48 SPLC had the same histologic type as the index primary lung cancer.

Some differences in patient characteristics are associated with a higher risk of SPLC, and these should also be considered when attempting to understand the risk of SPLC. After surgery for Stage III NSCLC, the risk of recurrence is higher than the risk of SPLC [24]. Even in series excluding resected Stage III NSCLC, the SPLC rate has not exceeded 8.6% [8,20]. Age cannot be the reason for the difference either, since our median age was comparable to that of the published literature [8,18]. The risk of SPLC may also be linked to smoking history [19]. The 15% non-smoker rate in our study was comparable to the rate of non-smokers in other trials [8,18]. A quantification of smoking in pack-years is often lacking in the literature. When available, the number of pack-years was, as in our study, retrospectively collected and therefore at risk of information bias. None of the trials, ours included, has provided information on smoking cessation after surgery. Most of the series published are older, ranging from 1972 to 2012, and taken together they cover more time before the year 2000 than after. Progress over time in clinical and pathological diagnosis may likewise have influenced the 16.1% SPLC rate observed in this series, as may regional surveillance practices with regular follow-up visits and chest CT.

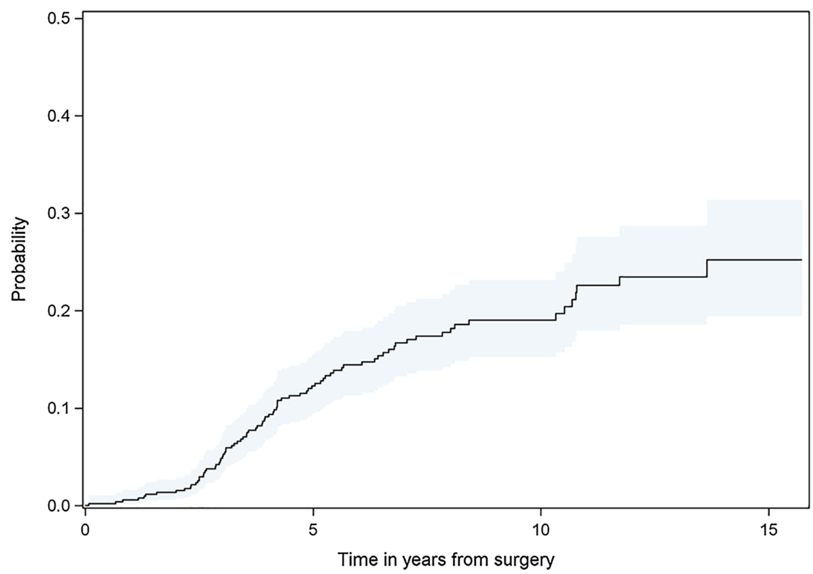


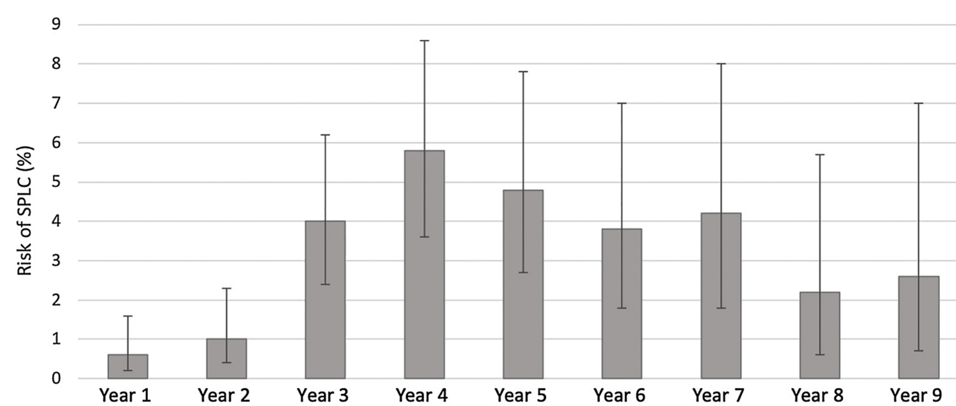
Fig. 2. Cumulative incidence function of SPLC considering the competing risk of death during follow-up (N = 522 patients with surgical resection for NSCLC).
SPLC: second primary lung cancer; NSCLC: non-small cell lung cancer.

Finally, the risk of SPLC is strongly influenced by the number of patients at risk over the study period. Therefore, such an analysis should take into account the actual number of patients at risk over time. Only few studies have considered competing risks, mostly death from comorbidity or recurrence of the index lung cancer [7,18]. In the study by Ripley et al., which only included surgically treated patients and used the same definition for SPLC as in the present study, the CIF of SPLC at 10 years was around 20%, exactly the same as that observed here [18]. Our results were based on a recent series and used appropriate methods to adjust for competing risks, and they clearly show that the risk of SPLC may be even higher than we usually think and should not be underestimated.

Annual SPLC risks increased after the first two years. In the study by Lou et al., the annual SPLC rate increased from 3 to 6 per 100 person-years between years 1 and 5 after surgery [24]. These results are consistent with those observed in our study, and reflect the definition used to distinguish SPLC from lung recurrences [12]. Concordant results were reported in a population-based cohort from the Public Health England National Cancer Registration and Analysis Service, showing an increased incidence of subsequent lung cancer for at least a decade from the first diagnosis [25]. The risk of SPLC persists after 5 years, and even after 10 years, with the SPLC rate being 5.6% in year 14 after surgery. As observed in the literature, the risk of SPLC after lung cancer surgery did not plateau [17,18], proving the need for follow-up of these patients until death.

4.2. Characteristics associated with the risk of SPLC

In multivariate analysis adjusted for age, smoking status, period of diagnosis and pN, thoracic radiotherapy after surgery for the index cancer was the only variable significantly associated with SPLC risk ($_{sd}$RH 2.79; 95% CI: 1.41–5.52). The two periods of diagnosis,



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
SPLC	3	5	16	19	13	8	7	3	3
Deaths	35	47	25	19	21	6	6	4	6
Patients at risk	522	481	425	345	280	223	180	145	118
Risk of SPLC (%)	0.6	1.0	4.0	5.8	4.8	3.8	4.2	2.2	2.6
95% CI, lower bound	0.2	0.4	2.4	3.6	2.7	1.8	1.8	0.6	0.7
95% CI, upper bound	1.6	2.3	6.2	8.6	7.8	7.0	8.0	5.7	7.0

Fig. 3. Annual risk of SPLC after surgery with competing risk of death factored in.
SPLC: second primary lung cancer; Deaths during the year; Patients at risk at the beginning of the year (patients at risk at the beginning of the previous year – number of deaths during the year – number of patients lost to follow-up).

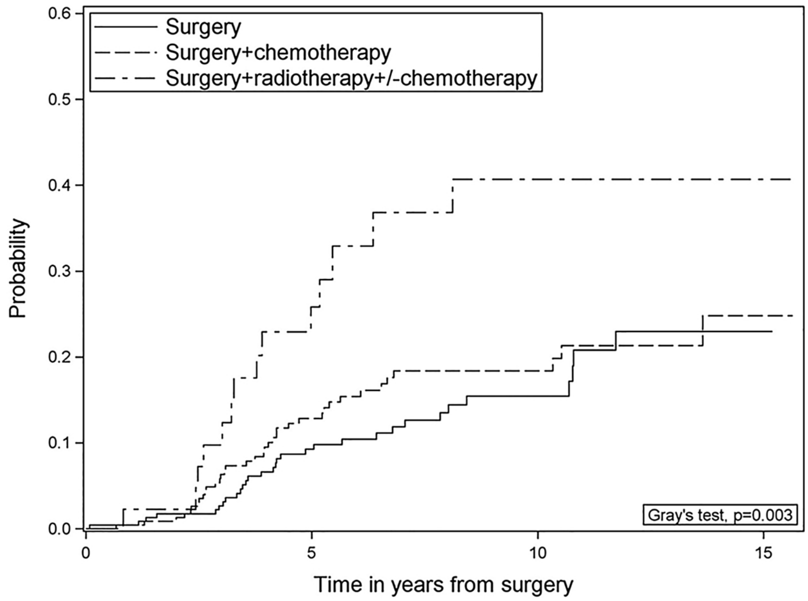


Fig. 4. Cumulative incidence of SPLC by subgroup of first cancer treatment, with competing risk of death factored in. SPLC: second primary lung cancer.

Table 2
Univariate and multivariate analyses of factors associated with SPLC hazard during follow-up (Fine–Gray model).

	SPLC					
	Unadjusted $_{sd}$RH	95% CI	p	Adjusted* $_{sd}$RH	95% CI	p
Age			0.12			0.06
< 70 years						
≥70 years	1.43	0.91–2.23		1.57	0.98–2.51	
Sex			0.72			
Male						
Female	0.91	0.55–1.51				
Smoking status			0.32			
Never-smoker						
Current smoker	1.48	0.73–3.02				
Previous smoker	1.09	0.53–2.27				
Pack-years			0.18			0.21
[0–10]						
[11–39]	1.70	0.87–2.33		1.70	0.87–3.31	
≥40	1.18	0.61–2.29		1.20	0.63–2.31	
Time of diagnosis			0.08			0.18
[2002–2009]						
[2010–2015]	0.66	0.41–1.05		0.72	0.45–1.17	
Histology			0.42			
Adenocarcinoma						
Non-adenocarcinoma	1.19	0.78–1.82				
pT			0.42			
pT0, pT1						
pT2	0.75	0.48–1.19				
pT3, pT4	0.74	0.38–1.45				
pN			**0.02**			0.14
pN0, pN1						
pN2	1.84	1.08–3.15		1.55	0.87–2.78	
Treatment			**0.003**			**0.01**
Surgery						
Surgery + Chemotherapy	1.26	0.78–2.02		1.32	0.77–2.26	
Surgery + Radiotherapy ± Chemotherapy	2.88	1.54–5.38		2.79	1.41–5.52	

SPLC: second primary lung cancer; 95% CI: 95% confidence interval; $_{sd}$RH: relative hazard for SPLC; *: Adjusted for time of diagnosis, age, pack-years, pN; pT: pathological classification of the primary tumor; pN: pathological classification of the regional lymph nodes.

2002–2009 and 2010–2015, were chosen to take into account the change in the TNM classification in 2010, from the 6th to the 7th edition. Because only 10 of the 44 patients who received postoperative radiotherapy had no chemotherapy, the interaction between postoperative radiotherapy and chemotherapy was not tested, meaning that the heightened incidence could have been due to an additive or synergistic effect of radiotherapy and chemotherapy.

There are only a few series in which the correlation between thoracic radiotherapy after surgery and the risk of SPLC have been analyzed. In the SEER database of 20032 Stage I to IV NSCLC patients who survived 5 years after an initial lung cancer, the proportion of patients who received radiotherapy was 20.6% in both the censored and SPLC groups [7]. However, in that series, all NSCLC stages were eligible, and both surgery and thoracic radiotherapy were given to 1435 patients (11%). The treatment variable is reported not to influence the risk of SPLC, but no information on the specific risk of postoperative radiotherapy is available. Patients treated with chemotherapy and radiotherapy for Stage III NSCLC probably have a higher competing risk of recurrence than a risk of SPLC. Of the 1484 patients included in the series by Duke University Medical Center, postoperative radiotherapy did not influence the risk of SPLC, but only 85 patients received such treatment [19]. The postoperative radiotherapy (PORT) meta-analysis of 14 trials and 2343 patients evaluating surgery *versus* surgery plus radiotherapy showed an 18% relative increase in the risk of death after radiotherapy in patients with completely resected NSCLC [26]. The SPLC rate was not reported. Nevertheless, postoperative radiotherapy may be useful for Stage III N2 NSCLC [27], a question which should be answered by the LungART randomized trial [28]. It ought to be noted that, despite its potential interest, we did not perform a pattern of relapse analysis to verify that the SPLC we observed in radiated patients occurred inside the radiation fields, and so we cannot conclude that radiotherapy was directly responsible for the increased incidence of SPLC in our patients. A confusion bias cannot be completely ruled out, as patients who are delivered postoperative radiotherapy were those at high risk of recurrence. However, these patients are more likely to develop an early recurrence and all the SPLC diagnosed within the first two postoperative years had a histologic type different from that of the index tumor. Still, considering the controversial data in the literature on the impact of postoperative radiotherapy on lung cancer patients, and the results of the PORT meta-analysis [26], the significant association that we showed between an increased risk of SPLC and radiotherapy should be particularly borne in mind when postoperative radiation is being discussed.

Of the other variables, only smoking history expressed as pack-years was reported to be associated with an increased risk of SPLC on multivariate analysis in the Duke University series of 1484 patients cited above [19]. In the SEER database, high-risk individuals were defined according to deciles based on age, histology, and disease extent [7]. In our study, there was a trend toward a correlation between increasing age and the risk of SPLC ($p = 0.06$). In the study by Boyle et al., on Cox multivariate analysis per 10 pack-years, smoking was significantly associated with the risk of developing SPLC (hazard ratio 1.08; 95% CI 1.01–1.16; $p = 0.03$) [19]. In contrast, we found that pack-year exposure was not significantly associated with SPLC hazard ($p = 0.21$) on Fine–Gray multivariate modeling. As in our study, CIF curves of SPLC did not differ according to smoking status ($p = 0.16$) in the study by Ripley et al. [18].

To conclude, this study using appropriate statistical methods to take account of competing risks showed that after complete resection for NSCLC the CIF of SPLC was high (around 20% at 10 years and 25% at 14 years) and did not plateau. Patients who received postoperative thoracic radiotherapy were at higher risk of SPLC. These data confirm the need for life-long follow-up of patients who undergo surgery for NSCLC, with the objective of screening for SPLC.

Declaration of Competing Interest

None.

Acknowledgments

The authors thank all those who contributed to the inclusion of cancer patients in the registries, in particular pathologists, medical information staff in public and private healthcare institutions, medical staff of health insurance companies, chest physicians and oncologists, as well as medical practitioners. The authors also extend their gratitude to the registry team for their help in data recording.

French cancer registries are supported by the French National Cancer Institute and Santé publique France, the French national public health agency, as well as by local institutions and the French League Against Cancer.

Appendix 1. Morphology codes

- Adenocarcinoma (morphology codes 81403, 82113, 82303, 82503, 82553, 82603, 82633, 84803, 84813, 85503, 85513, 82653, 82533, 82543)
- Non-adenocarcinoma (squamous cell carcinoma: 80523, 80703, 80713, 80723, 80733, 80743, 80833, 85603, 81233, 80823; large-cell carcinoma: 80123, 80133, 80463, 80203; pleomorphic carcinoma: 80223; undifferentiated carcinoma: 80203; pseudosarcomatous carcinoma: 80333; and non-small cell carcinoma, NOS: 80463)

References

[1] Fact Sheets by Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. (Accessed 10 July 2018).
[2] NCCN Guidelines® Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. (Accessed 17 August 2018).
[3] P. Goldstraw, K. Chansky, J. Crowley, et al., The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming, 8th ed. TNM Classification for Lung Cancer, J. Thorac. Oncol. 11 (2016) 39–51, https://doi.org/10.1016/j.jtho.2015.09.009.
[4] G.L. Walsh, M. O'Connor, K.M. Willis, et al., Is follow-up of lung cancer patients after resection medically indicated and cost-effective? Ann. Thorac. Surg. 60 (1995) 1563–1572, https://doi.org/10.1016/0003-4975(95)00893-4.
[5] N. Martini, V.W. Rusch, M.S. Bains, et al., Factors influencing ten-year survival in resected stages I to IIIA non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 117 (1) (1999) 32–38.
[6] V. Westeel, D. Choma, F. Clément, et al., Relevance of an intensive postoperative follow-up after surgery for non–small cell lung cancer, Ann. Thorac. Surg. 70 (2000) 1185–1190, https://doi.org/10.1016/S0003-4975(00)01731-8.
[7] S.S. Han, G.A. Rivera, M.C. Tammemägi, et al., Risk stratification for second primary lung Cancer, J. Clin. Oncol. 35 (2017) 2893–2899, https://doi.org/10.1200/JCO.2017.72.4203.
[8] D. Rice, H.-W. Kim, A. Sabichi, et al., The risk of second primary tumors after resection of stage I nonsmall cell lung cancer, Ann. Thorac. Surg. 76 (2003) 1001–1008, https://doi.org/10.1016/S0003-4975(03)00821-X.
[9] C.M. Kinsey, K.L. Hamlington, J. O'Toole, et al., Predicting the mortality benefit of CT screening for second lung Cancer in a high-risk population, PLoS One 11 (2016) e0165471, , https://doi.org/10.1371/journal.pone.0165471.
[10] L.H. Sobin, C. Wittekind, International Union against cancer, and editors. TNM classification of malignant tumours, UICC, International Union Against Cancer, 6th ed., Wiley-Liss, New York, 2002.
[11] L.H. Sobin, M.K. Gospodarowicz, C. Wittekind, International Union against cancer, and editors. TNM classification of malignant tumours, UICC, International Union Against Cancer, 7th ed., Wiley-Liss, New York, 2009.
[12] N. Martini, M.R. Melamed, Multiple primary lung cancers, J. Thorac. Cardiovasc. Surg. 70 (1975) 606–612.
[13] J.P. Fine, R.J. Gray, J.P. Fine, Gray RJA proportional hazards model for the subdistribution of a competing risk, J. Am. Stat. Assoc. 94 (1999) 496–509.
[14] P.C. Austin, D.S. Lee, J.P. Fine, Introduction to the analysis of survival data in the presence of competing risks, Circulation. 133 (2016) 601–609, https://doi.org/10.1161/CIRCULATIONAHA.115.017719.
[15] B. Lau, S.R. Cole, S.J. Gange, Competing risk regression models for epidemiologic data, Am. J. Epidemiol. 170 (2009) 244–256, https://doi.org/10.1093/aje/kwp107.
[16] A. Latouche, A. Allignol, J. Beyersmann, et al., A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions, J. Clin. Epidemiol. 66 (2013) 648–653, https://doi.org/10.1016/j.jclinepi.2012.09.017.

[17] M.K. Thakur, J.J. Ruterbusch, A.G. Schwartz, et al., Risk of second lung Cancer in patients with previously treated lung Cancer: analysis of surveillance, epidemiology, and end results (SEER) data, J. Thorac. Oncol. 13 (2018) 46–53, https://doi.org/10.1016/j.jtho.2017.09.1964.
[18] R.T. Ripley, R.R. McMillan, C.S. Sima, et al., Second primary lung cancers: smokers versus nonsmokers after resection of stage I lung adenocarcinoma, Ann. Thorac. Surg. 98 (2014) 968–974, https://doi.org/10.1016/j.athoracsur.2014.04.098.
[19] J.M. Boyle, D.J. Tandberg, J.P. Chino, et al., Smoking history predicts for increased risk of second primary lung cancer: a comprehensive analysis, Cancer. 121 (2015) 598–604, https://doi.org/10.1002/cncr.29095.
[20] F. Lou, J. Huang, C.S. Sima, et al., Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance, J. Thorac. Cardiovasc. Surg. 145 (2013) 75–82, https://doi.org/10.1016/j.jtcvs.2012.09.030.
[21] P.C. Pairolero, D.E. Williams, E.J. Bergstralh, et al., Postsurgical stage I bronchogenic carcinoma: morbid implications of recurrent disease, Ann. Thorac. Surg. 38 (1984) 331–338.
[22] J.P. Lamont, J.T. Kakuda, D. Smith, et al., Systematic postoperative radiologic follow-up in patients with non–Small cell lung Cancer for detecting second primary lung Cancer in stage IA, Arch Surg. 137 (2002) 935–939, https://doi.org/10.1001/archsurg.137.8.935.
[23] F.C. Detterbeck, W.A. Franklin, A.G. Nicholson, et al., The IASLC lung Cancer Staging project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming eighth edition of the TNM classification for lung Cancer, J. Thorac. Oncol. 11 (2016) 651–665, https://doi.org/10.1016/j.jtho.2016.01.025.
[24] F. Lou, C.S. Sima, V.W. Rusch, et al., Differences in patterns of recurrence in early-stage versus locally advanced non-small cell lung Cancer, Ann. Thorac. Surg. 98 (2014) 1755–1761.
[25] M.E. Barclay, G. Lyratzopoulos, F.M. Walter, S. Jefferies, M.D. Peake, R.C. Rintoul, Incidence of second and higher order smoking-related primary cancers following lung cancer: a population-based cohort study, Thorax 74 (5) (2019) 466–472, https://doi.org/10.1136/thoraxjnl-2018-212456.
[26] S. Burdett, L. Rydzewska, J. Tierney, et al., Postoperative radiotherapy for non--small cell lung cancer, The Cochrane Library, John Wiley & Sons, Ltd, 2016 Available at: 10.1002/14651858.CD002142.pub4/full. (Accessed 9 July 2018).
[27] J.-Y. Douillard, R. Rosell, M.D. Lena, et al., Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non–small-Cell lung Cancer Treated with adjuvant chemotherapy: the adjuvant navelbine international trialist association (ANITA) randomized trial, Int. J. Radiat. Oncol. Biol. Phys. 72 (2008) 695–701, https://doi.org/10.1016/j.ijrobp.2008.01.044.
[28] C. Faivre-Finn, C.L. Pechoux, J. Edwards, et al., 169: lung ART: phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy in patients with completely resected non-small cell lung cancer and mediastinal N2 involvement, Lung Cancer. 103 (2017) 79.