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Multiple independent primary cancers do not adversely affect survival of the lung cancer patient☆

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Abstract

Objective: Diagnosis of multiple independent primary cancers is increasing in many settings. Objectives of this study were to analyze clinical characteristics, organ location, and prognosis associated with the presentation of multiple independent primaries when a lung cancer is involved. **Methods:** We analyzed all patients with a histology-proven diagnosis of lung cancer registered from January 1990 to December 2004 at the Tumor Registry of the Hospital del Mar, Barcelona. We compared 1686 patients presenting a lung cancer as unique primary versus 228 patients presenting a lung cancer and another independent primary. Cofactors included age, sex, smoking habit, lung cancer histology and stage, type and intention of treatment, organ location of the other cancer, and survival from the date of lung cancer diagnosis. **Results:** Seventy percent of the other cancers were tobacco-related. Independent risk factors of cancer multiplicity were smoking (OR: 3.99; 95% CI: 1.4—11.2), lung cancer stages I (OR: 1.84; 95% CI: 1.2—2.9) and II (OR: 3.25; 95% CI: 1.7—6.3), and older age (OR: 3.11; 95% CI: 1.9—5.1). Once adjusted by age and sex, the main determinant of survival was lung cancer stage rather than cancer multiplicity. However, patients with multiple cancers presented a slightly better survival than patients with a lung cancer as unique primary. When analyzed by subgroups, survival was higher in patients with the lung cancer first (HR: 0.44; 95% CI: 0.24—0.80), and in patients with the other cancer first (HR: 0.80; 95% CI: 0.65—0.99), but it was not different in the patients with a lung cancer and a synchronous other cancer (HR: 0.80; 95% CI: 0.52—1.15). **Conclusions:** The risk of developing a second independent cancer was strongly associated with tobacco smoking. Cancer multiplicity was not associated with a worse prognosis. As a consequence, when a first primary tobacco-related cancer is treated with curative intention, patients should be closely followed up for an early diagnosis of a possible new independent cancer; and if diagnosed, treatment to cure should be considered as the first option.

Keywords: Lung neoplasms; Second primary neoplasms; Smoking; Survival; Prognosis

1. Introduction

The arising of multiple primary cancers in a same patient was already addressed in 1932 by Warren and Gates, who proposed as diagnostic criteria that each tumor must be histologically distinct, and that the possibility of a tumor being a metastasis of the other must be ruled out [1]. Interest on multiple independent primary cancers is currently renewed as the incidence of second primaries continues to increase in many settings [2—5]. In 2002 the American College of Surgeons defined multiple independent primaries (MIP) as 'two or more tumors arising at different sites or at the same site when histologic characteristics differ' [6].

Several questions arise when MIP involve a lung cancer. Multiplicity may be related to sharing a common etiologic factor such as tobacco smoking or asbestos exposure, to genetically related individual susceptibility, or to improvements in survival due to earlier diagnosis and better medical care [7—9]. Besides, identification of any clinical characteristics as related to cancer multiplicity would possibly be useful as a sign of alarm. Finally, interest is justified in assessing if cancer multiplicity carries differences in prognosis.

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Our study was aimed at analyzing the clinical characteristics, organ location, and prognosis of MIP involving a lung cancer.

2. Materials and methods

The study was based on the clinical information recorded by the Tumor Registry of Hospital del Mar (RTHMar), Barcelona, Spain [10]. Any cancer of any patient visited in our hospital at any time during the disease process is registered, even if the patient has been diagnosed or treated in another center. The clinical information is collected through an exhaustive revision of the medical records, pathology reports, and minutes of cancer committees. Skin basocellular carcinomas are not registered.

We first identified all patients with a diagnosis of lung cancer registered between January 1990 and December 2004, which yielded 2030 patients (12.4% of all cancer patients registered in the period). Of them, we excluded 116 patients (5.7%) without histological proof of lung cancer (which was not obtained due to advanced age, advanced disease or poor general status). The resulting 1914 patients (94.3%) with a diagnosis of lung cancer confirmed by cytology or biopsy entered the analysis. The following variables were used: patients' age at the date of lung cancer diagnosis, sex, date of lung cancer diagnosis, lung cancer histology and stage, type of lung cancer treatment (surgery, chemotherapy, radiotherapy), treatment intention (curative, palliative), and tobacco smoking (registered since January 1993). All additional information available in the RTHMar for patients included in the study regarding any other independent primary cancer was next merged into the database. MIP are registered according to the standard criteria of the International Agency for Research on Cancer [11]. Extension of the lung cancer was staged using the tumor-node-metastasis international system [12]. Based on scientific consensus [7], the following cancers were considered potentially tobacco-related: mouth, pharynx, larynx, lung, esophagus, stomach, liver, pancreas, kidney, urinary bladder, colon-rectum, and uterine cervix.

Patients were grouped as follows: group I included patients presenting a lung cancer as unique primary; group II included patients presenting a lung cancer and another independent cancer. For the analysis of survival, patients in group II were divided as 'synchronous' (when less than two months had elapsed between the diagnosis of the two primaries), and 'metachronous' [13]. Patients with metachronous MIP were further subdivided into those presenting their lung cancer first (group II-lung cancer first), and those presenting their other cancer(s) first (group II-other cancer first). Patients with three or more cancers were included in the group II-lung cancer first, except when the lung cancer was the last one, in which case they were included in the group II-other cancer first. Patients with two primary lung cancers were included in group II-lung cancer first, and the second lung cancer was counted as other cancer.

Univariate statistics were computed as customary. Differences between groups were tested by Fischer's exact test for categorical variables, and by Student's *t* test and ANOVA for continuous variables. Clinical variables significantly associated with the presentation of MIP in the univariate model were tested by stepwise multivariate logistic regression analysis. The response variable was neoplasia multiplicity (dichotomous: 1 representing multiplicity, and 0 its absence). Observed survival was calculated from the date of lung cancer diagnosis to death, loss of follow-up, or end of the study period by the method described by Kaplan and Meier. Differences between groups were tested by the log-rank test. Multivariate survival analyses were performed by Cox proportional hazards regression. Throughout, the level of statistical significance was set at 0.05, and all tests were two-tailed. Analyses were performed using SPSS® version 13.5 for Windows (SPSS Inc, Chicago, IL).

3. Results

The 1914 patients included in the study presented 2167 cancers. Group I included 1686 (88.1%) patients with a lung cancer as unique primary, while group II comprised 228 (11.9%) patients presenting a lung cancer and some other cancer(s). The percentage of patients in the latter group increased from 7.4% in 1990–1995, to 9.6% in 1995–1999, and to 17.6% in 2000–2004. Organ location of the other cancers is shown in Table 1. From the date of lung cancer diagnosis, 86 out of 253 (34%) other cancers were diagnosed within 1 year, and 171 of 253 (67.6%) within 5 years, with no significant differences between tobacco-related and tobacco unrelated cancers.

Clinical characteristics of patients are summarized in Table 2. The male-to-female ratio was 9:1, similar in the two groups. Univariate differences between the groups were significant for age, smoking, lung cancer histology, lung cancer stage, and surgical treatment with curative intention. In group I (lung cancer as unique primary), patients diagnosed at earlier lung cancer stages (I and II) comprised 13.8%, while this percentage was 30% in group II (patients with a lung cancer and another primary). As expected, these figures closely match the percentage of patients undergoing surgical treatment with curative intention, 11.1% and 21.5%, respectively. Adjuvant or neoadjuvant chemotherapy were administered to 70 of 214 (32.7%) surgical patients in group I, and to 15 of 50 (30.0%) patients in group II ($p = 0.87$).

Table 3 summarizes multivariate analyses assessing the probability of presenting MIP involving lung cancer against the probability of presenting lung cancer as unique primary. Clinical characteristics related to a significantly higher probability of cancer multiplicity were tobacco smoking (odds ratio: 3.99), age older than 60 years, and lung cancer stages I and II (Table 3, model A). When the previous three factors were taken into account, the squamous-cell carcinoma histology was also a significant risk factor, while surgery with a curative intent was not (Table 3, model B).

Clinical characteristics of patients with MIP differed by subgroup as shown in Table 4. The only significant difference among subgroups was that the percentage of patients with earlier lung cancer stages (I and II), which are potentially amenable to curative surgery, was higher in group II-lung cancer first (18 of 32, 69.2%), than in group II-synchronous (13 of 43, 37.1%), and in group II-other cancer first (26 of 153,

Table 1
Location of other cancers preceding or following the lung cancer

Cancer locations	Total, *n* (%)	Lung cancer first, *n* (%)	Other cancer first, *n* (%)	Synchronous, *n* (%)
Global	253 (100.0)	40 (100.0)	168 (100.0)	45 (100.0)
Tobacco-related				
Upper aerodigestive tract	73 (28.9)	12 (30.0)	48 (28.6)	13 (28.9)
Uroepithelium	44 (17.4)	5 (12.5)	35 (20.8)	4 (8.9)
Colorectum	22 (8.7)	2 (5.0)	15 (8.9)	5 (11.1)
Stomach	12 (4.7)	3 (7.5)	4 (2.4)	5 (11.1)
Lung	11 (4.3)	6 (15.0)	0 (0.0)	5 (11.1)
Liver	8 (3.2)	2 (5.0)	1 (0.6)	5 (11.1)
Cervix	7 (2.8)	0 (0.0)	7 (4.2)	0 (0.0)
Total	177 (70.0)	30 (75.0)	110 (65.5)	37 (82.2)
No-tobacco-related				
Prostate	27 (10.7)	5 (12.5)	20 (11.9)	2 (4.4)
Skin	16 (6.3)	1 (2.5)	14 (8.3)	1 (2.2)
Lymphoma/leukemia/myeloma	12 (4.7)	2 (5.0)	9 (5.4)	1 (2.2)
Breast	9 (3.6)	1 (2.5)	7 (4.2)	1 (2.2)
Thyroid	1 (0.4)	0 (0.0)	0 (0.0)	1 (2.2)
Soft tissues	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)
Others	10 (4.0)	1 (2.5)	7 (4.2)	2 (4.4)
Total	76 (30.0)	10 (25.0)	58 (34.5)	8 (17.8)

20.2%). Differences in sex, age, smoking, and histology were not significant.

Differences in observed survival were clinically and statistically significant (log-rank test: 42.4, $p < 0.01$) (Fig. 1). Multivariate Cox analyses showed that patients in group II-lung cancer first presented an almost fourfold higher survival than patients in group I (lung cancer as unique primary) (hazard ratio (HR): 0.28, $p < 0.001$), while for

Table 2
Clinical characteristics

	Total, *n* (%)	Group I: Lung cancer unique, *n* (%)	Group II: MIP[a] involving LC, *n* (%)	*p*[b]
Patients	1914 (100.0)	1686 (88.1)	228 (11.9)	
Primary cancers per patient				
1 primary	1686 (88.1)	1686 (100.0)	–	
2 primaries	205 (10.7)	–	205 (89.9)	
3 primaries	21 (1.1)	–	21 (9.2)	
4 primaries	2 (0.1)	–	2 (0.9)	
Sex				
Male	1706 (89.1)	1502 (89.1)	204 (89.5)	
Female	208 (10.9)	184 (10.9)	24 (10.5)	0.860
Age				
mean [SD]	65.7 [11.0]	65.4 [11.3]	68.3 [8.7]	<0.001
Tobacco smoking habit				
Smoker	1433 (92.6)	1243 (92.1)	190 (96.4)	
Non-smoker	114 (7.4)	107 (7.9)	7 (3.6)	0.028
Unknown	367	336	31	
Histology (lung cancer)				
Small-cell carcinoma	297 (15.5)	273 (16.2)	24 (10.5)	
Undifferentiated-cell carcinoma	339 (17.7)	310 (18.4)	29 (12.7)	
Squamous-cell carcinoma	725 (37.9)	618 (36.7)	107 (46.9)	
Adenocarcinoma	510 (26.6)	450 (26.7)	60 (26.3)	
Other	43 (2.2)	35 (2.1)	8 (3.5)	0.004
Stage (lung cancer)				
I	192 (12.0)	153 (10.8)	39 (20.5)	
II	61 (3.8)	43 (3.0)	18 (9.5)	
III	544 (34.0)	494 (35.0)	50 (26.3)	
IV	805 (50.2)	722 (51.1)	83 (43.7)	<0.001
Unknown	312	274	38	
Curative surgery				
Yes	236 (12.3)	187 (11.1)	49 (21.5)	
No	1678 (87.7)	1499 (88.9)	179 (78.5)	<0.001

Lung cancer as unique primary versus MIP involving lung cancer.
[a] MIP: multiple independent primaries (lung cancer first, other cancer first and synchronous).
[b] Fisher's exact test; Student's *t* test.

Table 3
Multivariate analysis of the risk of presenting multiple independent primaries involving lung cancer

	Model A, OR (95% CI)	Model B, OR (95% CI)
Sex		
Male	1[a]	1[a]
Female	1.88 (0.96–3.69)	2.01 (1.02–3.98)
Age (years)		
<60	1[a]	1[a]
60–69	1.99 (1.20–3.32)	1.95 (1.17–3.26)
70–79	3.11 (1.90–5.10)	2.91 (1.77–4.80)
>80	2.27 (1.11–4.63)	2.24 (1.09–4.61)
Stage (lung cancer)		
I	1.84 (1.18–2.87)	1.57 (0.98–2.50)
II	3.25 (1.69–6.25)	2.79 (1.44–5.41)
III	0.79 (0.53–1.16)	0.67 (0.44–1.00)
IV	1[a]	1[a]
Tobacco smoking habit		
Non-smoker	1[a]	1[a]
Smoker	3.99 (1.42–11.21)	3.78 (1.33–10.71)
Histology (lung cancer)		
Small-cell carcinoma	–	1[a]
Undifferentiated-cell carcinoma	–	0.84 (0.43–1.63)
Squamous-cell carcinoma	–	1.75 (1.00–3.06)
Adenocarcinoma	–	1.21 (0.67–2.17)
Curative surgery		
Yes	–	1.16 (0.65–2.07)
No	–	1[a]

OR: odds ratio.
[a] Reference category (odds ratio = 1).

patients with a synchronous or a previous other cancer, survival was not any worse than for group I (indeed, it was slightly better and almost statistically significant) (Table 5, Model A). Results were similar when adjusted by age and sex (Model B). When lung cancer stage (the most important known prognostic factor) was taken into account (Model C), survival in group II-lung cancer first was still higher (more than twofold, HR: 0.44; $p < 0.001$); in group II-other cancer

Table 4
Clinical characteristics of MIP involving lung cancer (group II)

	Lung cancer first, *n* (%)	Other cancer first, *n* (%)	Synchronous, *n* (%)	*p*[*]
Patients	32 (14.0)	153 (67.1)	43 (18.9)	
Sex				
Male	30 (93.8)	135 (88.2)	39 (90.7)	
Female	2 (6.3)	18 (11.8)	4 (9.3)	0.765
Age				
mean [SD]	66.7 [8.3]	68.7 [8.4]	67.8 [9.7]	0.428
Tobacco smoking habit				
Smoker	24 (100.0)	133 (95.7)	33 (97.1)	
Non-smoker	0 (0.0)	6 (4.3)	1 (2.9)	0.840
Unknown	8	14	9	
Histology (lung cancer)				
Small-cell carcinoma	3 (9.4)	17 (11.1)	4 (9.3)	
Undifferentiated-cell carcinoma	3 (9.4)	20 (13.1)	6 (14.0)	
Squamous-cell carcinoma	16 (50.0)	71 (46.4)	20 (46.5)	
Adenocarcinoma	5 (15.6)	43 (28.1)	12 (27.9)	
Others	5 (15.6)	2 (1.3)	1 (2.3)	0.105
Stage (lung cancer)				
I	16 (61.5)	17 (13.2)	6 (17.1)	
II	2 (7.7)	9 (7.0)	7 (20.0)	
III	5 (19.2)	40 (31.0)	5 (14.3)	
IV	3 (11.5)	63 (48.8)	17 (48.6)	<0.001
Unknown	6	24	8	
Curative surgery				
Yes	18 (58.3)	25 (16.3)	6 (14.0)	
No	14 (43.8)	128 (83.7)	37 (86.0)	<0.001

[*] Fisher's exact test; ANOVA.

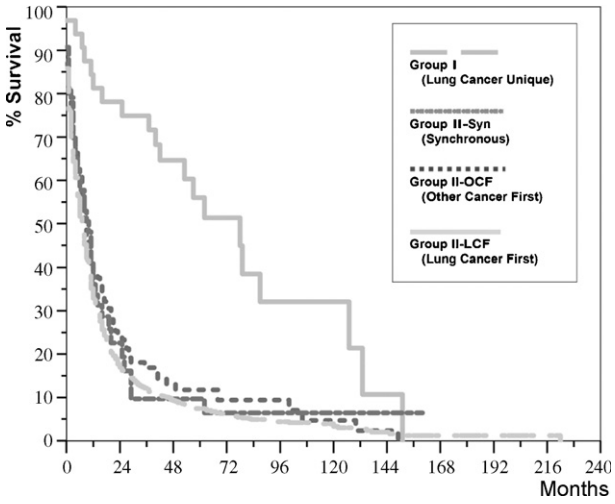

Fig. 1. Survival curves of patient groups with observed survival time calculated from the date of lung cancer diagnosis.
Median (95% CI) observed survival in months (mo), and observed 5-year survival (5-ys)—Group I: 7 (6—8) mo; 5-ys: 7.3%. Group II-synchronous: 10 (6—14) mo; 5-ys: 6.4%. Group II-lung cancer first: 78 (39—117) mo; 5-ys: 51.5%. Group II-other cancer first: 9 (7—11) mo; 5-ys: 9.4%. Log-rank test: 42.4; $p < 0.001$.

first it was more than 20% higher (HR: 0.80; $p = 0.024$), and in the group of patients with a synchronous other cancer it did not differ significantly (always, with respect to group I). Model C also showed that females and younger patients, as well as patients with tumors in earlier stages had higher chances of survival.

4. Discussion

The main findings of our study were that the percentage of patients with MIP involving a lung cancer has increased substantially in recent years; that independent risk factors of cancer multiplicity were smoking, lung cancer diagnosed at stages I and II, and age older than 60 years; and that prognosis was not worse for patients with multiple cancers, as the main determinant of survival was not cancer multiplicity but lung cancer stage. These findings imply that any patient treated for a first primary cancer with curative intention should be closely followed-up. Furthermore, if a second independent cancer is diagnosed, treatment with curative intention should again be considered the first option.

In our series, the 228 patients with MIP represented 11.9% of the total 1914 lung cancer patients analyzed. Similar percentages were reported by other studies that also used hospital cancer registries [14—17]. To our knowledge, this is the first study based on a hospital tumor registry that compares a consecutive series of patients with lung cancer as unique primary and patients with lung cancer plus any another independent primary cancer, the survival of the latter analyzed by three subgroups: lung cancer first, lung cancer plus a synchronous other cancer, and other cancer first. While a study based on a hospital tumor registry cannot be assumed to be fully representative of the general population, it often can analyze a spectrum of clinical information (e.g., stage, histology) that is clinically more relevant than data included in most population-based cancer registries [18]. Using population registries, Buiatti et al. reported that 2.4% second primary cancers occurred among 19,252 cancer patients [2], and Levi et al. reported a significant excess of second lung cancers and other tobacco-related cancers in lung cancer patients [3], whereas Teppo et al. concluded that the relative risk of new primary cancers among patients diagnosed of lung cancer was higher in recent times [5].

Several mechanisms may underlie the growing incidence of MIP involving lung cancer, including better results in recent decades in the treatment of cancer and other diseases, the effect of common carcinogens, and genetically related susceptibility to carcinogens [2—5,7—9]. Among characteristics analyzed in our study, smoking emerged as the most

Table 5
Relative risk of death by group and selected variables

	Model A, HR (95% CI)	Model B, HR (95% CI)	Model C, HR (95% CI)
Group			
I-Primary unique	1[a]	1[a]	1[a]
II-LCF	0.28 (0.18—0.44)	0.27 (0.17—0.42)	0.44 (0.24—0.80)
II-OCF	0.84 (0.70—1.01)	0.81 (0.68—0.98)	0.80 (0.65—0.99)
II-Synchronous	0.84 (0.60—1.16)	0.83 (0.60—1.15)	0.77 (0.52—1.15)
Sex			
Male	—	1[a]	1[a]
Female	—	0.86 (0.73—1.01)	0.80 (0.66—0.98)
Age (years)			
<60	—	1[a]	1[a]
60—69	—	1.04 (0.91—1.18)	1.11 (0.95—1.29)
70—79	—	1.22 (1.07—1.39)	1.39 (1.19—1.63)
>80	—	1.70 (1.40—2.06)	2.00 (1.59—2.54)
Stage (lung cancer)			
I	—	—	1[a]
II	—	—	1.41 (0.96—2.07)
III	—	—	2.04 (1.65—2.52)
IV	—	—	4.22 (3.41—5.21)

Cox proportional hazards regression. Values are hazard ratio (HR) with 95% confidence intervals (CI) given in parentheses.
[a] Reference category (hazard ratio = 1).

important independent risk factor of cancer multiplicity. We also identified age, and lung cancer stages I and II as independent risk factors of presenting MIP. This result links survival and multiplicity, as lung cancer stages I and II are well established survival factors [19]. Certainly, as already noted by Rheingold, the probability of developing a second cancer depends on surviving a first cancer [4]. So, our patients with a prior lung cancer and a second other cancer (group II-lung cancer first) probably represent a select subgroup of lung cancer patients: they showed a much higher chance of survival than all the other groups, as 69% had their diagnosis of lung cancer at stage I or II. Interestingly, curative surgery lost its statistical significance in multivariate analyses, probably because it largely covariates with stage.

The incidence of MIP involving a lung cancer may continue to increase in the future, aided by improved diagnostic tools (high-resolution scan, positron emission tomography, endoscopic ultrasonography), and by molecular biology techniques for the differential diagnosis of tumors [20]. Establishing the prognostic significance of cancer multiplicity is especially important in terms of treatment, as in most cases, the clinical management of a second primary must be decided without being certain whether the first primary is cured (in our series, 67.6% second cancers were diagnosed within 5 year from the diagnosis of the first primary). Importantly, then, results showed that cancer multiplicity does not carry a worse prognosis. The observation that lung cancer survival is associated with lung cancer stage rather than to cancer multiplicity has previously been reported [15,17,21—23]. In their studies on patients with a lung cancer as second primary, Massard et al. reported that lung cancer survival varied according to lung cancer stage, and that no higher risk of death was related to multiplicity [22]. Koppe et al. observed that a history of previous malignancy was a favorable prognostic factor in the univariate analysis, although not so in the multivariate analysis [23]. Particularly outstanding is our group of patients with a lung cancer and a synchronous other cancer (group II-synchronous), which showed no significant difference in survival compared to patients with a unique lung cancer. Thus, it seems that both cancers barely interact, and that it is the cancer with worst prognosis that is the one which ultimately determines the outcome.

Along with other available evidence, results strongly suggest that a second independent cancer should be approached as a separate entity in terms of prognosis and treatment: if the first primary was treated with curative intention, a thorough surveillance addressed to diagnose as early as possible the second cancer should be a part of the follow-up [24,25]. Results also emphasize the importance of distinguishing a recurrence from a second primary, in order to offer the patient the most appropriate management option.

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