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Second Primary Lung Cancer: A Current Problem in Long-Survivor Cancer Patients

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Abstract

Background: Lung may be the site of synchronous or metachronous second primary malignancies (SPM) with an incidence between 0.8 and 14.5% of cases. Synchronous or metachronous SPM present, however, diagnostic and therapeutic challenges. The authors report their experience in the treatment of second primary lung tumors.

Methods: A retrospective study from 2008 to 2014 was conducted in patients with synchronous or metachronous second primary lung cancer.

Results: 30 patients (69.8%) underwent to pulmonary lobectomy, 4 (9,3%) to segmentectomy and 6 (14.0%) to wedge resections (Table n.1). Lung-sparing resections were referred to patients with unsuitable respiratory volumes for anatomical ones. The presence in the medical history of an intra- or extrathoracic primary cancer does not significantly influence survival, while the second primary malignancy's stage is crucial.

Conclusions: Lobectomy with hilar-mediastinal lymph node dissection should be offered to all suitable patient.

Keywords: Second Primary Lung Cancer; Martini and Melamed's Criteria; Lobectomy; Overall Survival.

Abbreviations

SPLC: Second Primary Lung Cancer;
SPM: Second Primary Malignancies;
DFI: Disease Free Interval

Introduction

Lung cancer is the leading cause of cancer-related death [1]. Non small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC) are the major histotypes, with the previous representing about 85% of cases [2,3]. The lung may be the site of synchronous or metachronous second primary malignancies (SPM) with an incidence between 0.8 and 14.5% of cases [4]. However, synchronous or metachronous SPMs present diagnostic and therapeutic challenges. In fact, occasionally, it is difficult to differentiate a SPM from a local recurrence or distant metastasis. Martini and Melamed's [5] and Antakli's [6] diagnostic criteria are universally accepted. The Authors report their experience in the treatment of second primary

lung tumors.

Material and Methods

This study involves 43 patients with a mean of 69.5 years of age, observed in our Institutions from 2008 to 2014 (Table n.1). Inclusion criterion was the presence of a diagnosed synchronous or metachronous second primary lung tumor (according to Martini and Melamed's and Antakli's diagnostic criteria); while exclusion one was the presence of a pulmonary metastases from extrathoracic or thoracic cancers. Aim of the study was to assess patients' outcome and to analyze risk factors (such as hystology, demographic datas) interfering with cumulative survival and with prognosis. All patients underwent total body CT and by PET-CT scans and were assessed for liver, kidney, bone marrow, heart (echocardiogram study with ejection fraction), and respiratory (PFR and blood gases) functions.

Table n.1. Second primary lung cancer patients.

	N	%
Demographics		
Sex		
Male	32	74,4
Female	11	25,6
Age	69,5±8,64 (48-84)	
Smoking history	13	30,2
No	14	32,6
Former	16	37,2
Previous chemotherapy	18	41,9
No	25	58,1
Death		
Yes	13	30,2
No	30	69,8
Disease Free Intervall	59,26±40,74 (3-228)	
Overall Survival	80,40±40,33 (10-231)	
Overall survival (Lung)	21,1±12,08 (3-49)	

13 patients (30.2%) were smokers, 16 (37.2%) former smokers and 14 (32.6%) had no history of smoking. Urological, colorectal, breast cancer and lung cancer were the prevalent first primary neoplasms, followed by laryngeal and upper gastrointestinal tract ones (Table n.2). 18 patients (41.9%) were previously treated with adjuvant chemotherapy for the first primary cancer. Right lung was the predominant site for second primary lung malignancies (n. 31 – 72.09%). Histologically, adenocarcinoma was the predominant histotype (n.25 – 46.5%), followed by squamous carcinoma and by lepidic or papillary adenocarcinoma (former BAC) (Table n.3).

Table n.2. First primary malignancies

		N	%
Site	*Colon-rectum*	8	18.6
	Upper GI tract (stomach, pancreas)	3	7.0
	Urological tract (kidney, bladder, prostate, adrenal gland, penis)	12	28.0
	Breast	5	11,6
	Larinx	3	7,0
	Lung	6	14,0
	Parathyroid	1	2,3
	Skin	2	4,7
	Eye	1	2,3
	Blood	1	2,3
	Uterus	1	2,3
Histology	*Adenocarcinoma*	19	44,1
	Epidermoid squamous carcinoma	6	14
	Lepidic adenocarcinoma	1	2,3
	Clear cell carcinoma	4	9,3
	Ductal carcinoma	5	11,6
	Melanoma	3	7,0
	Transitional cell carcinoma	4	9,3
	Lambda monoclonal gammopathy	1	2,3
Third primary cancer	*Yes*	7	16,3
	No	36	83,7

Table n.3. Second primary lung cancer: characteristics.

		N	%
Hystology	*Adenocarcinoma*	20	46,5
	Lepidic adenocarcinoma	7	16,3
	Papillary adenocarcinoma	3	7,0
	Epidermoid squamous carcinoma	11	25,6
	Large cell carcinoma	2	4,7
Lobe	*Right upper lobe*	17	39,5
	Middle lobe	2	4,7
	Right inferior lobe	12	27,9
	Left upper lobe	6	14,0
	Left inferior lobe	6	14,0
Occurrence	*Synchronous*	3	7,0
	Metachronous	40	93,0
Therapeutic strategy	*Surgery*	23	58,1
	Surgery + chemotherapy	16	32,6
	Chemotherapy	4	9,3

Occurrences reflect the current epidemiology of lung cancer. In fact, there has been a turnaround in incidence and prevalence between adenocarcinomas and squamous carcinomas [7-10]. Finally, 93% (n. 40) of patients had a metachronous tumor,

while 7% (n.3) a synchronous one.

Statistical Analysis

All data are presented as frequencies (N) and simple percentages (%). Bivariate analysis of some variables was accomplished and statistically significant results were defined as p less than or equal to 0,005. Patient overall survival was expressed according to the Kaplan and Meier's method. In particular, the survival function was adopted for the analysis of disease-free interval (DFI) or the histological correlation in relation to patients' outcome.

Results

31 (72.09%) patients presented with a right second primary lung carcer (SPLC), with a prevalence for the right upper lobe. All patients were staged according to the seventh edition of the TMN lung cancer staging system (Table n. 4).

Table n.4. Second primary lung cancer: staging.

		N	%
Stage	*IA*	13	30,2
	IB	4	9,3
	IIA	3	7,0
	IIB	5	11,6
	IIIA	12	27,9
	IIIB	1	2,3
	IV	5	11,6
N0* vs N+**	*N0*	26	60,5
	N+	17	39,5
Lymph node status	*NO*	26	60,5
	N1	3	7,0
	N2	14	32,6

*N0: no lymphnode metastasis

** N+: hilar or mediastinal (homolateral and controlateral) lymphnode metastasis

Interestingly, 46.5% presented with early stage disease, i.e. stage IA-IIA. In our opinion, this seems to be related to cancer follow-up programs (laboratory and radiology) allowing an early detection of second lung tumors in cancer patients.

3 patients, due to the presence of an advanced disease, underwent to fine-needle transthoracic lung biopsy. In the remainings, a pulmonary lobectomy was performed in 30 patients (69.8%), a segmentectomy in 4 (9.3%) and a wedge resections in 6 (14.0%) (Table n.3). Lung-sparing resections were referred to patients with unsuitable respiratory volumes or with severe comorbidities. Surgical strategy was confident with the guidelines of the European Society of Thoracic Surgeons (ESTS) and the American Society of Thoracic Surgery (AATS). A hilar-mediastinal lymphadenectomy has been always performed in order to assess the presence of tumoral lymphatic dissemination or skip metastasis, since lung cancer shows a lymphotropic behavior both in progression and dissemination. Referring to our data, previous chemotherapic protocols was a negative prognostic factor. In fact, patients who had undergone chemotherapy for the first primary tumor, showed a median survival of 84.9±6.5 months vs 149.0±26.9 months in patient with no history ($p < 0.005$). In the second part of the study, we analyzed the relationships between the Disease Free Interval (i.e. the time between the diagnosis of the primary tumor and second primary tumor) and the Overall Survival. In this regard, we proceeded by dividing the population into cohorts in order to have four independent braces: patients with early onset of secondary neoplasm (DFI: 0-36 months), patients with relative early onset of cancer (DFI: 37-72 months), patients with relative late onset of malignancy (DFI: 73-108 months), patients with late onset of malignancy (DFI> 108 months).

Compared to our results, it can be argued that patients with late or relatively late onset second primary lung cancer presented the highest survival rates (DFI>108: 180 months vs DFI0-36: 58.9 months) ($p<0.001$) (Figure n 1). Finally, the presence of a correlation between histological concordance between the first and the second tumor and overall survival was found ($p<0.001$) (Figure n 2). From the data it follows that the presence of a histological concordance between first and second neoplasm is a positive prognostically factor vis-a-vis collision forms.

Discussion

The prevalence of long survivor cancer patients has increased due to rising incidence and improving survival [11-13]. Second and higher-order malignancies now comprise about 18.0% in the USA [14]. Therefore, there is an increasing need to determine the risk of second primary cancer development providing an appropriate surveillance and behaviour advices (i.e. smoking cessation). Cancer patients have an increased risk for further primary tumors and this might be expected to be raised due to improvement of overall survival, on the one hand, and due to the persisting effects of genetic and behavioural risk factors (such as tobacco use, excessive alcohol intake, and obesity), genetic predisposition, environmental determinants, host effects and side-effects of medical therapies (chemo- and radiotherapy) [15].

An important theory often used to explain the occurrence fo multiple malignancies is the " Slaughter's concept of field cancerization". This latter states that exposure to the same carcinogenic agents increases the chance of multiple tumors

Figure n.1: Disease free interval (from the first primary tumor to lung cancer) vs overall survival.

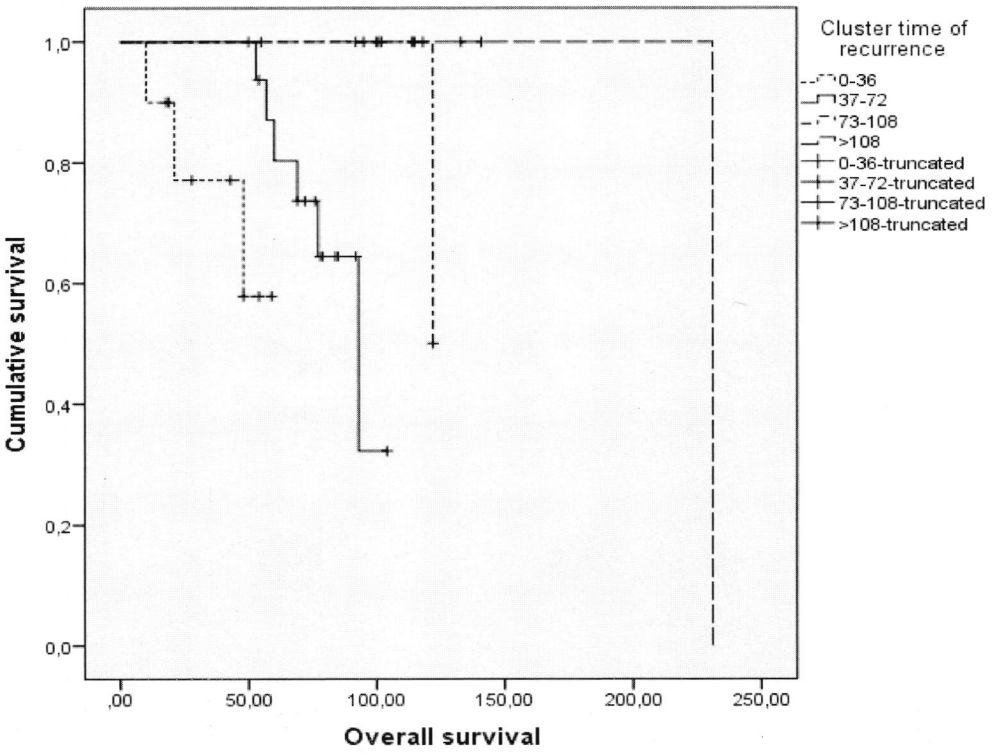
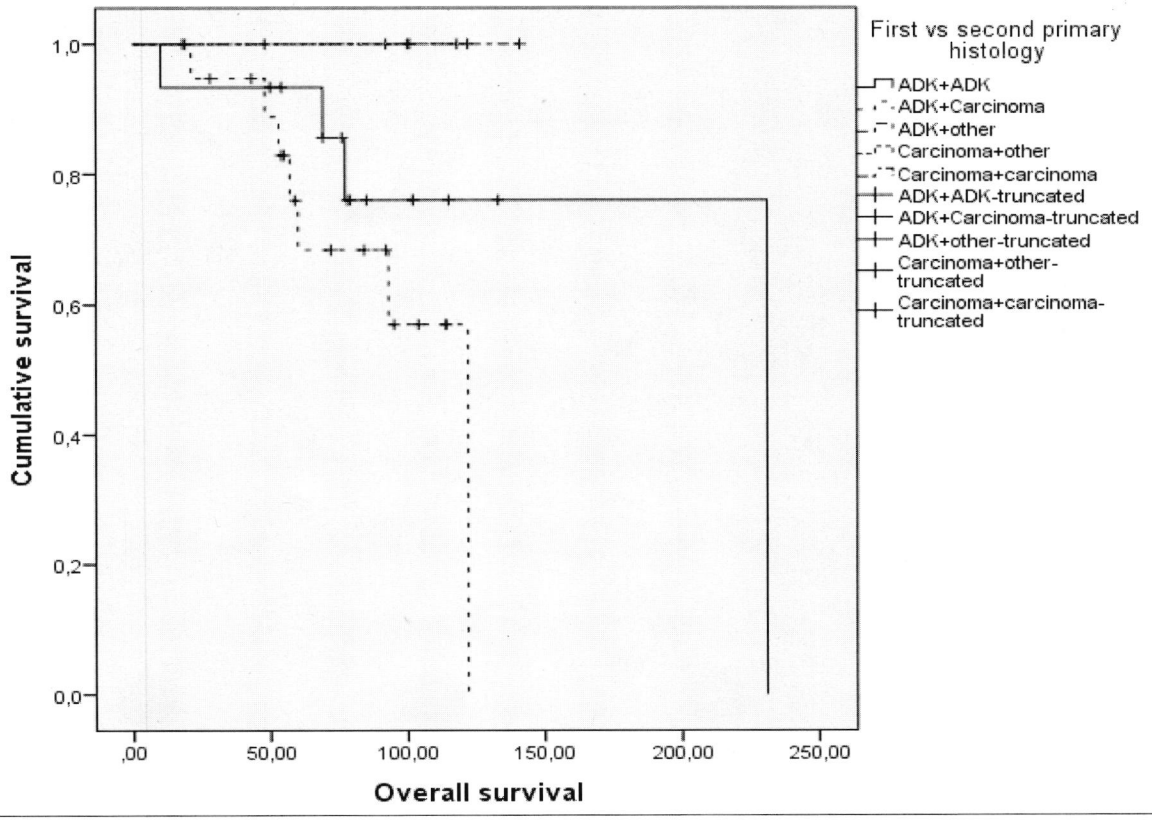


Figure n.2. Effect of histological concordance/discordance on overall.



[16]. Infact, after the treatment of a primary tumor, the risk of developing a second primary neoplasm increases [17] with a rate that varies from 4.2% to 28.4%. Second primary lung cancers (SPLCs) may present as synchronous and metachronous lesions, according to Martini and Melamed's criteria [5] or Antakli's ones [6]. The incidence of these lesions presents peculiarities: in fact, while for the previous ones has been observed a plateau phase in terms of incidence; for the latters, the trend appears increasing [18].

Synchronous tumors are significantly rarer than metachronous tumors [19]; as reported, the incidence of a synchronous second primary lung cancer varies from 0,26 to 1,33% [20,21]. The criteria for defining a second primary tumor have changed over time. Historically, Martini Melamed's criteria [5] and Antakli's ones [6] represent the first attempt to systematize and define a second primary tumor. Nowadays, two panels of rules are widely used: the rules of the Surveillance Epidemiology and End Results (SEER) Program [22] and those developed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) [23,24]. The SEER system takes account of histology, site, laterality and latency time from the first tumor; while, the second includes only a tumor to an organ. Diagnostic sensitivity has increased due to the adoption of worldwide screening programmes [25,26] and the improvement of medical imaging technologies [27].

Most patients with SPLC present an early-stage disease [28]. The reasons can be attributed, as reported by Shields et al [29], in a regular and systematic follow-up for cancer patients aiming not only in identifying a recurrence or a metastatic spread, but also the onset of a second primary lung cancer in its early stages.

In our study we reported the majority of patients with second primary lung tumors exhibits a 36-months survival rates comparable to patients with first primary lung cancer (Figure n.4); Therefore it would seem that the first neoplasm does not interfere with the patient outcomes, but this latter is subjected to independent factors as the clinical stage and the early onset of a second primary tumor ($p < 0.001$).

Koppe et al. [30] did not find any difference in survival between patients with first NSCLC and patients with a second primary tumor found in follow-up period. This circumstance suggests the prognosis of NSCLC patient with previous malignancies is more conditioned by the natural history of NSCLC rather than by the previous one.

Liu et al. [31] showed that the median survival of patients with a lung cancer as a second primary malignancy was better than the general lung cancer population. However, data are controversial. One explanation for the comparatively good survival, for example, is the greater proportion of patients in Stage I or early stages.

The prevalent sites of a first primary cancer in relation to NSCLC are clinically important in order to facilitate effective follow-up and to stay alert for second malignancies. In this study, the most frequent sites of the first primary cancer were colorectum, breast,lung and the urinary tract in order of frequency. Duchateau et al. [32], instead, reported the most frequently diagnosed double cancers were in the lungs, the head and neck region, and the urinary tract; while, Liu et al. [31] reported a closed association among lung cancer, upper airway tumors and colorectal cancer. Identification of the "risk period" as well as the prevalent site of relapsing malignancies could help physicians to define programs of surveillance for survivors. In the present study, 38,64% (n.17) of the second primary malignancies occurred within 5 years. Most SPLCs were diagnosed 5 years or later after diagnosis of the first primary cancer which is somewhat similar to two retrospective studies on surgical patients developing metachronous SPLC [33–35].

Histologically, we found the concordance between histological types present a better prognosis, although this evidence does not find acceptance in the case of double epidermoid tumors. As reported by Shen et al. [36] in this latter the highest rates of genetic recombination (microsatellite alterations, loss of heterozygosis) cause a sort of "synergic" biological resistance.

In Literature, excellent results in terms of survival are reported for patients undergoing resection of a SPLC [37]. Surgical treatment, whenever feasible, is considered the modality of choice for the management of patients with second primary lung cancers [38,39]. The type and extent of surgery are under discussion. Zuin et al [40] reported that lobectomy for metachronous and synchronous second primary lung cancer exhibited a statistically significant positive association with survival rate. By contrast, other surgical series reported that type of resection (sublobar vs. more extensive) for metachronous second primary lung cancer did not predict survival [35,41,42]. Zuin et al [40] observed no difference in recurrence rates between patients who underwent lobectomy (3.3%) and those who underwent sublobar resection (5%) for metachronous and synchronous second primary lung cancers.

Conclusions

Second primary malignancies are a common occurrence in long-survivor cancer patients. Epidemiological characteristics (high prevalence of early stage cancer) and the use of new technologies allow effective diagnostic classification. We believe that a second primary lung cancer should be treated as a first cancer, because it is a tumor with its own natural history. Therefore, surgery, whenever is possible, is the standard of treatment.

Compliance with ethical standards

Conflict of interest: The authors have no conflict of interest to be disclosed.

Ethical standard: The article is in accordance with ethical standards.

Research involving human participants and or animals: The article does not contain any research with human participants performed by the authors

Informed consent: For this type of study, no formal consent is not required. It is an anonymous one.

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