Synchronous primary lung cancer.
Critical review of diagnostic criteria

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QUESTION OF THE STUDY: *Synchronous primary lung cancers (SPLCs) may pose a radiologic-pathologic and therapeutic dilemma in according to recent WHO classification.*
PATIENTS AND METHODS: *Two cases of surgically treated SPLCs are reported.*
RESULTS: *In the first case two nodules were detected by Computed Tomography (CT) in the upper right lobe. The patient underwent lobectomy and histological diagnosis was adenocarcinoma and squamous cell carcinoma. The second patient presented at CT one nodule in the upper left lobe and another nodule in the upper right lobe. Sternotomic access was chosen for bilateral removal of the lesions. The diagnosis was sarcomatoid carcinoma and large cell neuroendocrine adenocarcinoma.*
DISCUSSION: *The criteria of Martini and Melamed are inadequate for the diagnosis of SPLCs. The use of TTF-1 (thyroid transcription factor-1) is necessary to establish the diagnosis of SPLC in patients with adenocarcinoma of other sites. Bronchioloalveolar carcinomas must be excluded because of their multicentricity. When histology of two tumors found in the same lobe is identical and histotype is adenocarcinoma, large cell carcinoma or sarcomatoid carcinoma, the diagnosis of SPLCs must be excluded and those lesions must be considered as metastatic disease. The prognosis and treatment of SPLCs are discussed after critical review of the literature.*

KEY WORDS: Large cell neuroendocrine cancers, Sarcomatoid carcinoma, Synchronous primary lung cancers.

Introduction

Multiple lung cancers are subdivided into synchronous and metachronous. Synchronous cancers are defined as two or more tumors present or detected at the same time, whereas metachronous are defined as tumors detected with an interval. The distinction between synchronous and metachronous cancers is arbitrary: the majority of metachronous cancers may have existed for a long period as minute radiologically non-detectable cancers, consequently they could be considered as synchronous. The diagnosis of synchronous primary lung cancers (SPLCs) with same histology may be difficult because of the possibility of metastatic disease. Radiologic-pathologic standards and treatment strategies still need improvement.

TABLE I - *Incidence of synchronous primary lung cancer*

Author	Total cases	Synchronous lung cancer (nr)	Synchronous lung cancer (%)
Martini et al [9]	5163	12	(0.23)
Mathisen et al [25]	2041	10	(0.49)
Ferguson et al [26]	2100	28	(1.33)
Wu et al [27]	3815	10	(0.26)
Sugimura et al [28]	2647	46	(1.74)
Deschamps et al [5]	9111	36	(0.8)
Verhangen et al [6]	1287	15	(1.16)
Ribet et al [7]	1980	24	(1.21)
Okada et al [8]	908	28	(3.1)
Hiraki et al [10]	668	4	(0.60)
Feng et al [11]	4649	31	(0.67)
Bisenkov et al [12]	896	43	(4.8%)
Nonami et al [13]	363	7	(1.9)
Total	**35628**	**294**	**(0.825)**

Surgical management of SPLCs implies various controversial issues, such as timing and surgical access in bilateral SPLCs, and finding the right balance between adequate oncological margins and functional preservation when deciding the extension of the resection.

After the first description by Beyreuther in 1924 [1] several studies have been published regarding the frequency of SPLCs (Table I).

In this paper we describe two cases of SPLCs. The histology of tumors in one case was large cell neuroendocrine carcinoma and sarcomatoid carcinoma. To the best of our knowledge this is the first histological combination reported in literature, since these histotypes have only been described in the current lung cancer classification of WHO (2004) [2].

In the past two decades the management of SPLCs has been complicated by substantial changes in lung cancer classification, diagnostic criteria and surgical approach. A critical review of the literature was performed with the purpose of establishing correct and complete clinicopathological criteria for accurate diagnosis of the disease.

Material and Methods

From the pathology archives of two institutions, we retrospectively reviewed two synchronous primary lung cancers (SPLCs) in two patients who underwent resection for primary lung cancer between 1998 and 2008. We describe two cases of SPLCs using the criteria reported in the discussion.

Case 1

A 72-year-old man, heavy smoker, was admitted on September 2006 with diagnosis of double synchronous lung cancer. A routine roentgenogram of the chest, performed to check a severe restrictive breathing disorder, revealed two tumoral shadows, 2.5 x 2 cm and 1.5 x 1 cm respectively, in the upper right lung lobe. This finding was confirmed by CT-scan (Fig. 1 A, B).

Case 2

A 70-year-old man, heavy smoker, was admitted on November 2006 for laparoscopic cholecystectomy. The preoperative chest radiograph showed two nodules located bilaterally in the superior fields of the lungs. CT-scan revealed a nodule (3 x 2.5 cm in diameter) in the apical segment of the upper left lobe and another lesion, with ill-defined margins, (2 x 1.5 cm in diameter) in the apical segment of the upper right lobe. (Fig. 2 A, B).

Results

Case 1

Bronchoscopy, bronchial brushing, cytology and sputum were negative. High risk of pneumothorax in diffuse bollous emphysema precluded transthoracic biopsy in this patient. Abdominal CT, bone scintigraphy and magnetic resonance imaging of the brain revealed no evidence of distant metastasis.

Lobectomy of the upper right lung lobe with lymphadenectomy of paratracheal nodes was performed through right thoracotomy. Since preoperative diagnosis of the two lesions was not possible, intraoperative frozen section was made with diagnosis of malignancy excluding small cell carcinoma. The neoplastic lesions were localized in the apical and posterior segments. The two tumors displayed different proliferative patterns. The 1.5
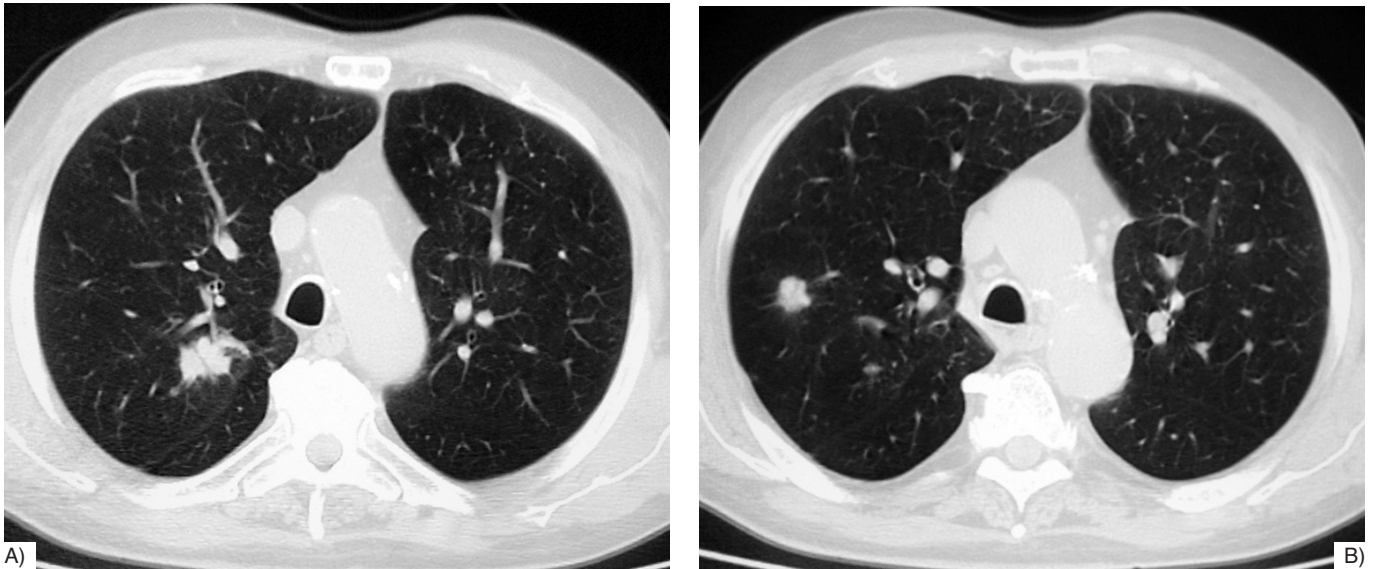
Fig. 1: (A) CT scan shows in the posterior segment of the upper right lobe near to the scissure the bigger (25-mm in diameter) of the two nodules, polilobate, near to the scissure. (B) The smaller 15-mm in diameter) of the two nodules in the lateral segment of the upper right lobe is spiculated.
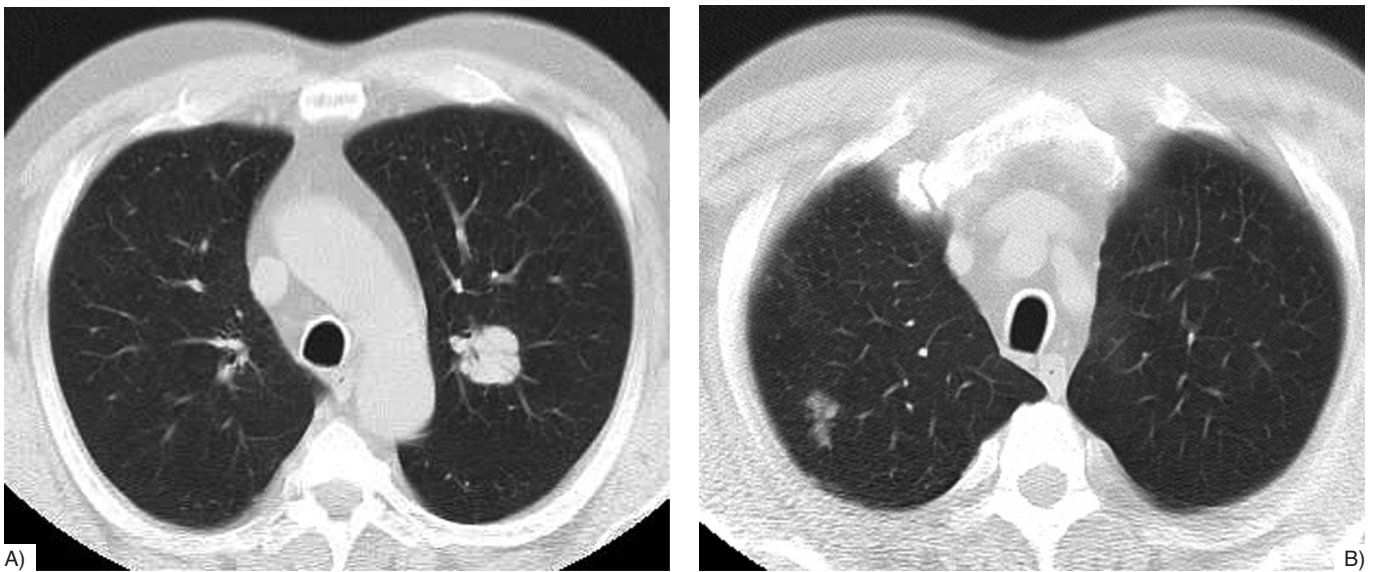

Fig 2: (A) CT scan shows in the apical segment of the left lobe, near to a sub-segmental bronchus, a nodule (3-cm in diameter), polilobate. (B) CT scan shows another nodule (2-cm in diameter) in the apical segment of the right lobe.

cm nodule was identified as squamous cell carcinoma. The 2 cm lesion had the histological features of an adenocarcinoma. Immunohistochemistry revealed expression of epithelial markers (AE1/AE3, CAM 5.2 epithelial membrane antigen) and TTF-1 (thyroid transcription factor-1). Nodal metastases were absent (pT1aN0M0). At present the patient is alive and free of disease.

CASE 2

Bronchoscopy, sputum, and brushing cytology were negative. The respiratory function test revealed a slightly restrictive breathing disorder. The CT-scan of the abdomen, PET, MRI of the brain, and a bone scintigraphy revealed no distant metastasis. Given the retroscapular and paramediastinic location of the two lesions, transthoracic biopsy was not viable. Upper segmental resection of the left lung and apical "wedge resection" of the right lung were performed simultaneously through median sternotomy. The tumor located in the upper left lobe showed histological features suggesting neuroendocrine differentiation (Fig. 3). The diagnosis of large cell neuroendocrine carcinoma was confirmed by immunohistochemical positivity for chromogranin, synaptophysin, NCAM (CD56) and TTF-1. Nodal
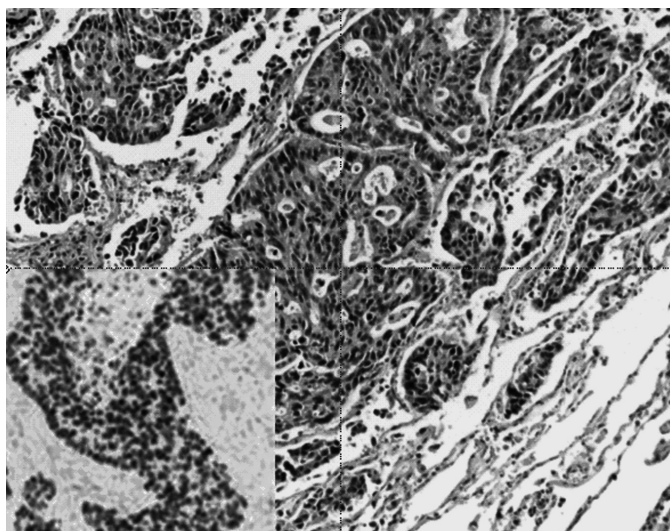
Fig. 3: Large cell neuroendocrine carcinoma. Trabecular growth and organoid nesting is present with extensive necrosis (H&E 10x). In the inset is evident NCAM (CD56) staining.
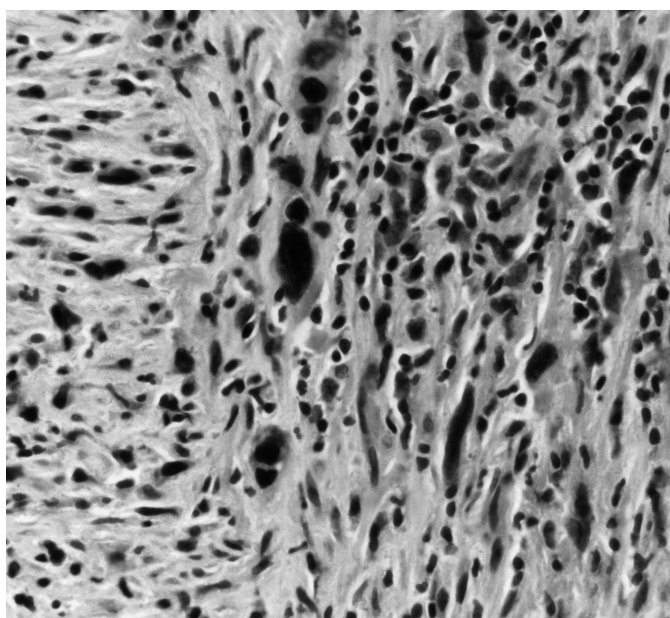

Fig. 4: Sarcomatoid carcinoma: 30% of the tumor was formed by proliferation spindle and giant cells. (H&E 10x).

metastases were absent (pT1bN0M0). The neoplastic nodule of the upper right lobe revealed a histological pattern of sarcomatoid carcinoma, according to the criteria of the current WHO classification [2]. (Fig. 4). Expression of epithelial markers (AE/1AE3, CAM 5.2, CK7) was diffusely found in the neoplastic glands and focally in the sarcomatoid proliferative pattern (pT1aN0M0). The patient is alive and free of disease.

Discussion

In most of the reported series of SPLCs, lung cancer is described according either to the 1982 [3] or to the 1999 [4] WHO classification. Therefore, sarcomatoid carcinoma and large cell adenocarcinoma with neuroendocrine features were not described, since the criteria have been established only in the 2004 WHO classification [2]. Our case is the first report of this combination of neoplasms.

The incidence of SPLC has increased over the last years due to diagnostic improvements in detecting small lesions, but most series report long period data. Moreover some reports of SPLCs include bronchioloalveolar histotype, which must be excluded; other series include patients in which a metastatic disease can not be ruled out. Therefore it is hard to establish the actual SPLC incidence.

Deschamps et al. [5] reported 117 out of 9611 patients (1.2%) with multiple primary lung cancer diagnosis. Thirty-seven of these patients were excluded from further analysis because they received noncurative therapy for at least one of the primary cancers. Forty-four patients had metachronous cancers and the remaining 36 had SPLCs. Similar cell types occurred in 12 patients with SPLCs (squamous cell carcinoma in 5, adenocarcinoma in 3, and bronchoalveolar cell carcinoma in 4).

In 1287 patients subject to resection for primary lung cancer, Verhagen et al. (6) found 55 (4.3%) multiple primary lung cancers, of which 15 cases (1.2%) were synchronous. Double tumors showed the same cell types in 12 cases (8 epidermoid carcinoma, 3 adenocarcinoma and 1 undifferentiated large-cell carcinoma).

Ribet et al. (7) described 75 cases of multiple primary lung cancers. SPLCs were found in 24 patients. In the group of synchronous cancers, the tumors had identical histology in 14 patients: 11 squamous carcinomas and 3 adenocarcinomas. In ten (41.6%) they had different histotype. Nine synchronous lesions were unilateral and 15 were bilateral.

Of 908 patients who underwent operation for primary lung cancer Okada e coll. (8) considered 57 (6.3%) to have a second primary lung cancer which was synchronous in 28 cases (3.1%) and metachronous in 29 cases (3.2%). Squamous cell carcinoma was found in 14 out of 28 (50%) of the first group and 12 out of 28 (43%) of the second. Adenocarcinoma was seen in 11 out of 28 (39%) of the first group and 15 out of 28 (54%) of the second group.

In the above mentioned reports of SPLCs, the diagnostic criteria of Martini and Melamed (9) were used. However, these criteria could be improved. Appropriate diagnosis has a prognostic and therapeutic impact. In fact, patients with SPLCs have a more favorable prognosis than patients with locally recurrent or metastatic disease (2-8; 10-14). Therefore, appropriate identification of SPLCs is crucial.

In our experience other criteria must be considered in order to establish the correct diagnosis of the SPLCs

excluding metastatic disease. A different histotype in each of the multiple lung tumors, as in our cases, is generally considered conclusive of SPLCs. In clinical studies, distinguishing with absolute certainty multicentric primary lung cancers from either a single primary lung cancer with pulmonary metastases or from a cancer originating in a non-pulmonary site with lung metastases can be extremely difficult. The highest incidence of SPLCs (4.8%) is reported in the study by Bisenkov et al [12]. But out of 43 patients with SPLCs, 10 showed a simultaneous tumor of the gastro-intestinal tract and 13 of the urinary tract. Only 20 patients could be considered as having SPLCs, since a pulmonary metastatic disease cannot be excluded in the other cases. Consequently, the 4.8% incidence in Bisenkov's series is overestimated. Presently, thyroid transcription factor-1 (TTF-1) can determine the primary pulmonary origin of a neoplasm in patients with adenocarcinoma in other sites [15]. TTF-1 was not used in previous reports of SPLCs in patients with adenocarcinoma of other sites. These cases should be excluded from the total number of reported SPLCs. All cases of bronchioloalveolar carcinoma should be excluded because of their multicentricity. When two tumors are found in the same lobe and the histology is identical with histotype of adenocarcinoma, large cell carcinoma or sarcomatoid carcinoma, the diagnosis of SPLCs must be excluded and the diagnosis of "metastatic disease" should be made. Since these histotypes do not have an "in situ" malignant component, Martini and Melamed's criteria [9] cannot be applied.

In 2004, the World Health Organization (WHO) [2] proposed the histopathologic diagnostic criteria for large cell neuroendocrine carcinoma (LCNAC).

Reports of SPLCs with LCNAC and other histological types are very rare and their clinical behavior or prognosis are not clear. Yamada et al [16] described a case of synchronous primary lung carcinoma consisting of large cell neuroendocrine carcinoma and squamous cell carcinoma. The histology and immunohistochemical marker of large cell neuroendocrine carcinoma, according to the current WHO classification, is not reported and metastases cannot be excluded. Niho et al. [17] described SPLCs with neuroendocrine features, but the diagnosis was not based upon the criteria for LCNAC proposed by the recent WHO classification. According to these criteria, sarcomatoid carcinomas are a group of poorly differentiated non-small cell lung carcinomas containing a component (at least 10%) of sarcoma or sarcoma-like (spindle and/or giant cell) differentiation.

In many of these patients, difficulty in establishing a precise preoperative diagnosis presents remarkable problems: when a patient has several lung nodules, differential diagnosis between primitive lung cancer with intrapulmonary metastases, SPLCs and lung metastases of other cancers is to be considered. Moreover, surgery is not always indicated for these patients. A citologic or histologic diagnosis through transthoracic or broncho-

scopic procedures is not always available. Therefore in most series percentages of "preoperative diagnosis" include, a part from histopathological characterization, also simply radiologic diagnosis of multiple lesions.

In literature the incidence of preoperative diagnosis of SPCLs vary greatly. In 15 patients (41.7%) with SPCLs, examined by Deschamps at al. [5] a synchronous tumor was not suspected preoperatively and it was discovered during pulmonary resection for the known cancer. Of the 15 patients with SPLCs reported by Verhagen et al. [6] synchronous lesions were evident on preoperative chest radiographs in 11 cases. In 2 patients the second lesion was discovered by histological examination of the resected lung tissue. In one case a synchronous tumor appeared at the time of operation and in the remaining patient a carcinoma in situ was diagnosed by bronchoscopy one week after the initial operation.

In Ribet's article [7] a synchronous cancer was not immediately diagnosed in one third of 75 cases.

In Okada et al. [8] sixteen (57%) out of 28 synchronous tumors were detected on preoperative radiography or bronchoscopy and 11 (39%) at the time of operation. In the remaining patients, the second tumor was diagnosed accidentally at histological examination. Despite the latest advances of diagnostic technologies, SPLC diagnosis is often only a hypothesis preoperatively, while, in a high percentage of cases, SPLCs are discovered only intraoperatively or accidentally during the histological examination.

Serial sections of resected carcinomatous lobes have shown totally ignored tumors of 1 to 2 mm in diameter in 19% of the cases [18].

Among the reasons hindering an improvement in SPLC's diagnosis we emphasize their proximity and/or bilateral tumors: in the first case is often impossible to obtain two separate bronchoscopic biopsies, in the second case a bilateral transthoracic biopsy can be unfeasible.

In both cases transthoracic biopsy was not carried out, in the first patient because of bollous emphysema, in the second because of the tumors' location. Therefore diagnosis was based on intraoperative frozen examination.

Controversies exist on surgical treatment of SPLCs.

The lobectomy on both lungs is not recommended because of high mortality rate (10%) and a limited resection under thoracoscopic surgery should be considered to treat the other contra lateral cancer [19].

Feng at al. [11] think that aggressive and reasonable surgical approach can achieve satisfactory outcomes in patients with synchronous SPLCs since the postoperative morbidity is low and some patients might obtain long-term survival.

Based on a series of 27 patients with SPLCs, Pommier at al. [20] conclude that the prognosis for patients with synchronous NSCLC may not be dismal if both tumors are resectable and stage I or II. Wedge resections are an alternative for patients who cannot tolerate lobectomies or pneumonectomy.

We believe that in SPLCs, the two tumors can be removed through lobectomy, bi-lobectomy, "sleeve lobectomy" or multiple wedge resections, preserving the best possible respiratory function with "tissue-sparing" resections.

"Tissue-sparing" resections do not worsen prognosis and give a better chance of long term survival [8,19,21]. In the event of recurrence, a second resection can be considered. In bilateral SPLCs the timing of surgery must be assessed. Most of the authors perform delayed thoracotomies with 4-6 weeks intervals, firstly attacking the apparently most advanced lesion [7-8]. Recent studies demonstrate similar results with bilateral video-assisted thoracoscopy (VATS) [22-23]. The median sternotomy approach, which we applied in the second case, is considered effective for cancers located in the upper lobes and present the advantage of lower drawbacks on the respiratory function [22-23]. In our opinion, median sternotomy represents a valid approach also for SPLCs located in other lobes.

The prognosis of SPLCs is generally considered to be poor and worse than metachronous.

Deschamps et al. [5] reported two 30-day operative deaths in 36 patients with SPLCs (mortality rate, 5.6%). Actuarial overall 5 - and 10 – year survival rates after pulmonary resection are 15.7% and 13.8%.

Verhagen at al. [6] described 15 patients with SPLCs treated surgically: ten submitted to a two-stage resection whereas 5 patients underwent a one-stage intervention. There were 3 postoperative deaths (20%). The 3-and 5-year actuarial survival rates were 26% and 15%. This study asserts that survival is positively influenced by: differing histological type between both cancers, an interval of more than 3 years, a bilateral localization, and a stage I or II cancer.

In the 24 SPLCs examined by Ribet et al [7] thirteen of 15 patients with bifocal resections were alive at 1 year, seven at 2 years, one at 3 years, and none at 5 years. The survivors at 2 years had stage I tumors from a total of 9 stage I, 4 stage II and 2 stage III tumors which had been completely resected. No patient with unifocal resection survived 2 years. Stage I appeared as a favorable prognostic factor, but the figure is too small to be appreciable. There is no difference whether the two tumors are of identical or different structures, and unilateral or bilateral.

To define prognostic parameters for patients with synchronous non-small cell lung cancer (NSCLC) Van Rens et al. [24] examined 2764 patients with single and 85 with synchronous NSCLC. Five-year survival was 41% for single NSCLC and 19% for synchronous. The relative risk of death was 1.75 higher in patient with synchronous lung cancer than in patients with single lung cancer, irrespective of the stage of the disease. When the stage of the disease was taken into account, the relative risk of death ranged from 1.73 to 1.93. The most advanced tumor in synchronous NSCLC was a significant predictor of survival (p < 0.005). This study confirms the poorer survival of patients with synchronous NSCLC.

The five-year survival for 19 patients with SPLCs surgically treated by Rea et al. [21] from the time of initial diagnosis of cancer was 20% and 10-year survival was 0%. In the study of Feng et al. [11] the postoperative morbidity of 31 patients surgically treated for SPLCs was 29%. No death occurred during operation or within 30 days postoperatively. The postoperative 1-, 3-, and 5-year survival rates were 52%, 29%, and 20% respectively.

Pommier et al. (20) examined prognostic factors for 27 patients (0.8%) with synchronous NSCLCs of 3034 lung cancers patients. Fourteen were completely resected with a 5-year survival rate of 45%. The 5-year survival rate for patients whose highest stage tumor was stage I or II was 38%, versus 0% for patients with stage III tumors (P = 0.01). The 5-year survival rate for patients with two stage I tumors was 41% versus 0% for patients with two stage III tumors (P = 0.03). The 5-years survival rate was similar for patients treated either with wedge resection or with lobectomy or pneumonectomy.

Another aspect to be considered is the type of follow-up that patients must undergo. It is widely accepted that it should be a life-long follow-up, even if the time-schedule of the checks is not specified. The best diagnostic method is spiral CT.

In conclusion, in our experience the criteria of Martini and Melamed are inadequate for the diagnosis of SPLCs. The use of TTF-1 is necessary to establish the diagnosis of SPLC in patients with adenocarcinoma of other sites. Bronchioloalveolar carcinomas must be excluded because of their multicentricity. When histology of two tumors found in the same lobe is identical and histotype is adenocarcinoma, large cell carcinoma or sarcomatoid carcinoma, the diagnosis of SPLCs must be excluded and those lesions must be considered as metastatic disease (pT4).

Even if it is not common, SPLCs diagnosis must be taken into consideration when two or more lung lesions are found. Despite technological advances in diagnostic imaging, SPLCs diagnosis often represents a dilemma and at times it can be established only intraoperatively or during histological examination.

Early diagnosis (stage I-II) and subsequent resection contribute to long-term survival.

Aggressive surgical approach is justified, adopting when possible "tissue-sparing" resections to safeguard the postoperative respiratory function. In bilateral locations, iterative interventions or, alternatively, mediam sternotomy to simultaneously remove bilateral tumors are safe and effective. Thoracoscoy is a valid alternative which can be applied bilaterally during the same intervention.

Riassunto

I cancri polmonari sincroni e primitivi (SPLCs) possono determinare problematiche radiologiche, di valutazione patologica e terapeutiche in rapporto alla recente classificazione della WHO.

Si prendono in considerazione due casi di cancri polmonari sincroni e primitivi trattati chirurgicamente. Nel primo dei due vennero individuati con la TAC nel lobo superiore di destra due noduli. Il paziente venne sottoposto a lobectomia e la diagnosi istologica fu di adenocarcinoma e di carcinoma a cellule squamose. Nel secondo paziente con la TAC venne individuato un nodulo nel lobo superiore di sinistra ed un altro nodulo nel lobo superiore di destra. Per la loro asportazione venne scelto un accesso sternotomico e la diagnosi fu rispettivamente di carcinoma sarcomatoide e di carcinoma neuroendocrino a grandi cellule.

I criteri di Martini e Melamed sono inadeguati per la diagnosi di cancri polmonari sincroni e primitivi. L'uso del TTF-1 (thyroid transcription factor-1) è necessario per stabilire la diagnosi di SPLC in pazienti con adenocarcinomi di sedi diverse. I carcinomi bronchioalveolari devono essere esclusi per la loro intrinseca multicentricità. Quando l'esame istologico di due tumori localizzati nello stesso lobo è identico e l'istotipo è quello di un adenocarcinoma, di carcinoma a grandi cellule o carcinoma sarcomatoide, la diagnosi di SPLC deve essere esclusa e quelle lesioni vanno considerate come malattia metastatica.

A conclusione vengono discussi la prognosi ed il trattamento dei SPLC dopo una revisione critica della letteratura.

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