

Synchronous primary lung cancers in a 51-year-old woman – a case report and literature review

Paweł Rogoziński¹, Marek Kucharzewski², Krzysztof Bruliński¹

¹Pulmonology and Thoracic Surgery Center in Bystra, Thoracic Surgery Department

²Chair and Institute of Descriptive and Topographic Anatomy, Medical University of Silesia



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Abstract

Synchronous primary lung cancers are two primary lung cancers diagnosed at the same time in one patient. The authors report the case of a 51-year-old woman who incidentally discovered tumors in both lungs. The patient underwent cytological diagnosis and PET-CT. There was no radiological evidence of lymph node involvement. On the left side, segmentectomy I was performed (large cell carcinoma), on the right side, upper lobectomy was performed (two foci of adenocarcinoma), and lymphadenectomy was performed on both sides – there was no histopathological evidence of mediastinal lymph node involvement. In view of the obtained results, the patient was diagnosed with synchronous primary lung cancers.

Subsequently, the authors conducted a systematic review of the literature on synchronous primary lung cancers published in the last decade. They point out that the classification of synchronous primary lung cancers still remains an open issue, as it is not taken into consideration by the current TNM classification (7th edition).

Key words: synchronous multiple primary lung cancer.

Streszczenie

Synchroniczne pierwotne raki płuc to sytuacja kliniczna, w której rozpoznaje się dwa pierwotne raki płuca w tym samym czasie u jednego chorego. Autorzy opisują przypadek 51-letniej kobiety, u której przypadkowo wykryto guzy w obu płucach. U chorej przeprowadzono diagnostykę cytologiczną oraz wykonano badanie PET-TK. Nie stwierdzono radiologicznych cech zajęcia węzłów chłonnych. W odstępie pięciu tygodni wykonano dwie torakotomie – po stronie lewej wykonano resekcję segmentu szczytowego, uzyskując rozpoznanie raka wielkokomórkowego, a po stronie prawej lobektomię górną, usuwając dwa ogniska raka gruczołowego. Obustronnie zabiegi zostały uzupełnione o limfadenektomię śródpiersia – histopatologicznie nie stwierdzono zajęcia węzłów chłonnych tego regionu. Wobec uzyskanych wyników rozpoznano u chorej synchroniczne pierwotne raki płuc.

W dalszej części autorzy dokonali systematycznego przeglądu piśmiennictwa opublikowanego w ostatnim dziesięcioleciu, dotyczącego synchronicznych pierwotnych raków płuca. Zwracają uwagę, że nadal otwarte pozostaje zagadnienie klasyfikacji synchronicznych pierwotnych raków płuca, która nie jest uwzględniona w obowiązującej klasyfikacji TNM (7 edycja).

Słowa kluczowe: synchroniczny pierwotny rak płuca.

Introduction

The simultaneous presence of two different lung cancers in the same patient was first recorded in a report by Beyreuther in 1924 [1]. Currently, synchronous multiple primary lung cancers (SMPLCs) are diagnosed with varying frequency, and the percentage of noted cases ranges from 0.2% to 20% [2]. This disparity results from the difficulties posed by evaluating and differentiating between synchronous cancers and primary cancers with intrapulmonary metastatic changes or metastatic changes in the lungs originating from primary cancers of various organs. SMPLC

is diagnosed relatively rarely, because such a diagnosis requires meeting certain clearly defined criteria.

In 1975, Martini and Melamed [3] proposed a set of diagnostic criteria designed to facilitate the diagnosis of SMPLC:

- I. Clearly separated tumors
- II. Histological type:
 - 1) different
 - 2) identical, but in another segment, lobe, or lung, if:
 - a) it originates from *in situ* cancer
 - b) there is no metastasis in the lymph nodes

Address for correspondence: Paweł Rogoziński, Pulmonology and Thoracic Surgery Center in Bystra, Thoracic Surgery Department, ul. J. Fałata 2, 43-360 Bystra, phone: +48 691 400 518, fax: +48 33 814 35 86, e-mail: progoszinski81@gmail.com

- c) there is no extrapulmonary metastasis at the time of diagnosis

In turn, in 1995, Antakli *et al.* [4] added DNA ploidy diagnostics to the criteria regarding histologically identical cancers and proposed the following criteria for the diagnosis of SMPLC:

- I. Different histological type
- II. Identical histological type and at least two of the following traits:
 - 1) anatomically separated
 - 2) originating from preneoplastic changes
 - 3) no distant metastasis
 - 4) no metastasis to mediastinal lymph nodes
 - 5) different DNA ploidy

Currently, the problem of synchronous lung cancers is encountered more often than in the past due to significant improvements in the area of diagnostic imaging (CT, PET-CT); as a result, more numerous pulmonary lesions are revealed more frequently. The proposed criteria are not always sufficient because of the difficulties in determining the etiology of a malignant lung neoplasm; molecular and genetic diagnostics are indispensable in situations in which the lung tumors have the same histological type [5].

Case study

A female patient, aged 51, was admitted to the Thoracic Surgery Department in September 2012 for the purpose of diagnosing and treating tumorous growths located in both her lungs. The tumors were revealed by chance on a chest X-ray (Fig. 1) performed in May 2012 on the request of the patient, who was quitting smoking at the time. During



Fig. 1. X-ray of the chest (PA projection). A round shadow in the upper field of the right lung and a round shadow in the upper field of the left lung

that time, the patient did not raise any complaints and was not treated due to other pathologies; in 2005, she underwent hysterectomy due to the presence of myomas. The patient had smoked approximately 20 pack-years. She was at risk due to family history, as her father died of diffuse neoplastic disease, and her mother suffered from leukemia.

After a month, a CT scan of the patient's chest was performed, which revealed a tumorous lesion in segment 1/2 of the left lung, 22 × 27 mm in size (Fig. 2), as well as a lesion in segment 2 of the right lung, 24 × 20 mm in size (Fig. 3) – both underwent contrast enhancement; the CT examination found no lesions in the remaining organs of the chest and epigastrium. The pulmonary diagnostics included a bronchofiberscopic examination, which did not reveal any endobronchial changes, and a cytological examination of the bronchial aspirate, whose results were negative. The results of additional tests, including spirometry (FEV₁ 2.5l 107%; FEV₁%VC 94%) and arterialized capillary blood gasometry (pH 7.498; pO₂ 64.9 mm Hg; pCO₂ 35.6 mm Hg; O₂sat 94.4%) were within normal ranges. During this period, a tumor biopsy was attempted; however,



Fig. 2. CT of the chest (axial view). A tumorous change in segment 1/2 of the left lung (size: 22 × 27 mm)

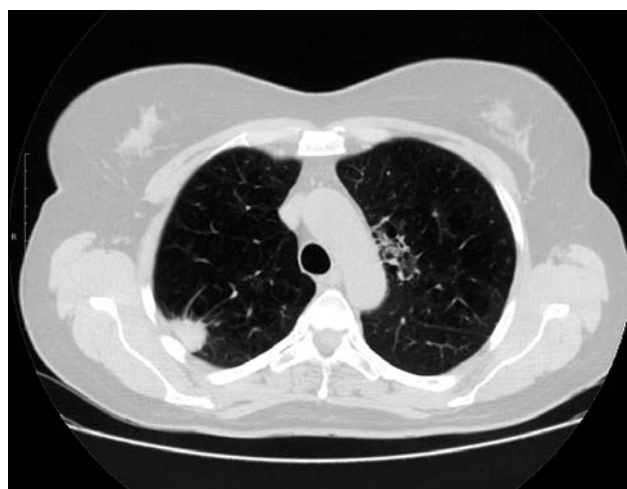


Fig. 3. CT of the chest (axial view). A tumorous lesion in segment 2 of the right lung (size 24 × 20 mm)

the attempt was aborted due to the proximity of emphysematous changes.

After three months, another tomographic examination of the chest revealed the progression of the lesions in both the left (36 × 47 mm) and the right lung (25 × 26 mm); furthermore, a satellite nodule (10 × 11 mm in size) appeared in the right superior lobe (Fig. 4). Additional ailments appeared in the form of wandering pains on the right side of

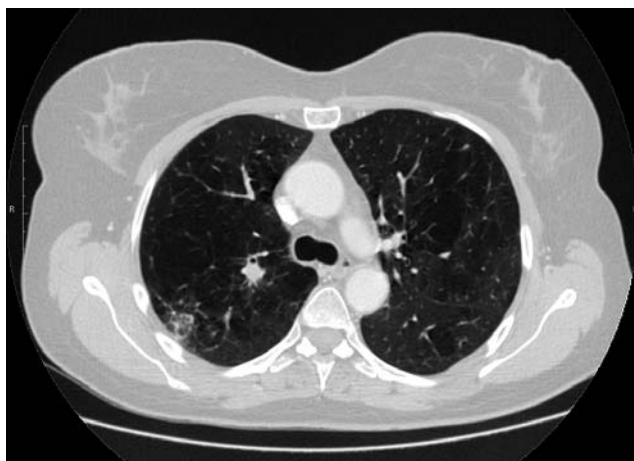


Fig. 4. CT of the chest (axial view). A satellite nodule in the superior lobe of the right lung (size: 10 × 11 mm)

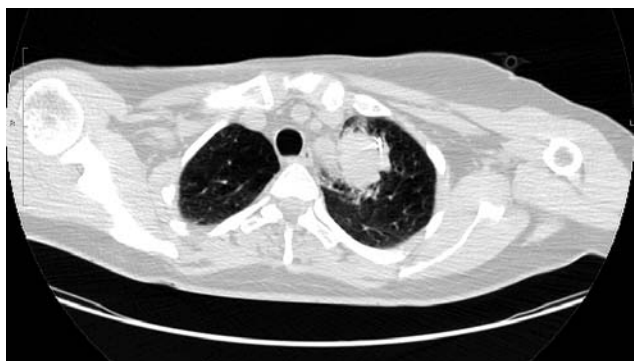


Fig. 5. CT of the chest (axial view). Fine-needle aspiration biopsy of the left lung tumor – the tip of the needle is in the tumor mass

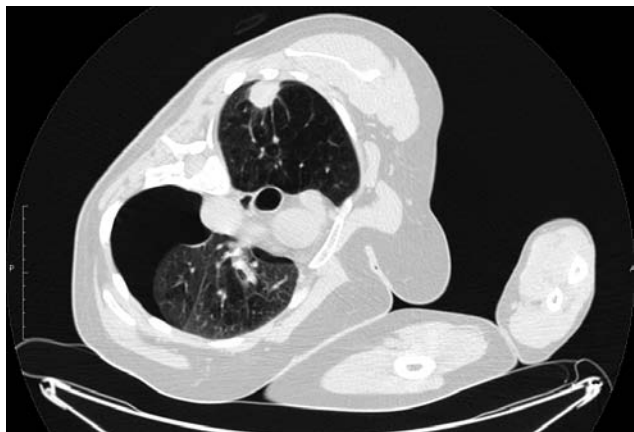


Fig. 6. CT of the chest (axial view). Tumor in the right lung, pneumothorax on the left side

the chest and in the neck area accompanied by cough with purulent sputum expectoration.

The patient was qualified for invasive diagnostics in the form of fine-needle aspiration biopsy (FNAB) of the lung tumors. FNAB was first performed on the tumor in the left lung because of its faster progression (one of its dimensions had increased by 20 mm). The examination was performed under CT control (Fig. 5), and its course was uneventful. Cytological diagnosis was obtained – non-small-cell lung carcinoma. On the next day, FNAB of the right lung tumor was attempted; however, iatrogenic pneumothorax was revealed on the left side (Fig. 6), and the biopsy was aborted. Lasting lung expansion was achieved after inserting a chest drain into the left pleural cavity.

In October, a PET-CT examination was performed; it revealed active metabolic tumorous changes in segment 1/2 of the left lung (size: 38 × 42 mm, SUVmax: 37.6) (Fig. 7) and in segment 2 of the right lung, located peripherally (size: 24 × 24 mm, SUVmax: 24.2) and below, more centrally (size: 10 × 11 mm, SUVmax: 17.7) (Fig. 8).

Based on the above imaging results, the lack of signs of mediastinal lymph node involvement, the potential operability of the lesions, the lack of contraindications for lung parenchyma resection, and the long-term outcomes of

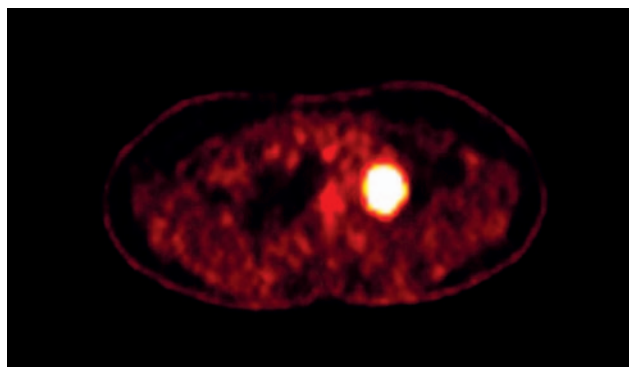


Fig. 7. PET-CT of the chest (axial view). Active metabolic tumorous changes in segment 1/2 of the left lung (size: 38 × 42 mm, SUVmax: 37.6)

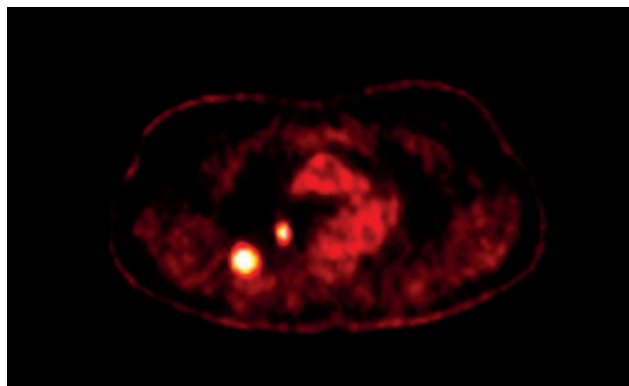


Fig. 8. PET-CT of the chest (axial view). Active metabolic tumorous changes in segment 2 of the right lung: peripheral (size: 24 × 24 mm, SUVmax: 24.2) and inferior, more central (size: 10 × 11 mm, SUVmax: 17.7)

surgical treatment of diagnosed synchronous cancers [2], the patient was qualified for a surgical procedure.

Before the end of October, an apical segment resection with lymphadenectomy was performed, enabling the achievement of a histopathological diagnosis: large-cell non-neuroendocrine carcinoma (stage: T2bN0). The procedure was complicated by the suppuration of the postoperative wound, which ultimately healed. Five weeks after the first procedure, a right upper lobectomy with lymphadenectomy was performed; histopathologically, the peripheral tumor turned out to be a G1 adenocarcinoma, while the satellite tumor was a G2 adenocarcinoma, resulting in a T3N0 stage, with the assumption that the satellite tumor was a metastatic lesion. The postoperative course was uneventful.

Both samples were verified histopathologically – the pathologist confirmed the initial diagnoses. After oncological consultation, the patient was not qualified for systemic treatment; the consulting oncologist recommended observation. Three months after the surgical treatment, a control CT of the chest and abdominal cavity was performed; it did not reveal any suspicious changes. The patient remains in good clinical condition; the pain and cough have subsided, and the patient does not require analgesic treatment due to the bilateral thoracotomies.

Discussion

The diagnosis of SMPLCs fits the discussed case study in accordance with both the criteria formulated by Martini and Melamed [3] and the criteria proposed by Antakli *et al.* [4]. The diagnosed histological types (large cell carcinoma and adenocarcinoma) indicate that the two neoplasms developed independently during the same time period. The microscopic image of the two tumors excludes their affinity, as one of the conditions for the diagnosis of large cell carcinoma is the lack of glandular differentiation [6].

Some uncertainty remains, however, with regard to the satellite tumor, as the two neoplasms in the right lung were both adenocarcinomas (with different levels of differentiation: G1 and G2). According to the aforementioned criteria, the presence of synchronous cancers in the right lung alone may be excluded (the same histological type, but both were located in segment 2). Similarly, Detterbeck *et al.* [7] argue that such cases should rather be diagnosed as metastatic changes, as corroborated by the longer survival times of patients.

The current 7th edition of the international TNM Classification, developed in cooperation with the International Association for the Study of Lung Cancer (IASLC) [8], does not classify synchronous primary cancers as separate units, but rather suggests treating one of the tumors as a metastasis. Therefore, a second primary lung cancer occurring on the same side but in another lobe should be classified as T4, while the presence of two primary cancers in two lungs is classified as M1a.

Detterbeck *et al.* [7] suggest that synchronous cancers should be *a priori* qualified for radical treatment in accordance with the generally accepted rules of treating lung can-

cer. Such an approach may be restricted by the respiratory reserve of the patient; however, in the discussed case, the reserve was sufficient for the performance of both procedures.

The four months which passed from revealing the tumors by the X-ray examination to obtaining a diagnosis allowed for the observation of the significant rate of disease progression; the tumor in the left lung increased in size, and a satellite lesion of the right lung tumor appeared. However, no radiological signs of metastasis to the mediastinal lymph nodes were found (as confirmed by the PET-CT examination and ultimately verified by the histopathological results). Based on the above imaging examination results, the authors of this study opted not to conduct mediastinoscopy and mediastinal verification, the results of which constitute important qualification criteria for the surgical treatment of synchronous lung tumors, both uni- and bilateral [5].

Taking into account the interview conducted with the patient, her young age, the lack of contraindications for lung parenchyma resection, and the suggestions found in the available literature [2, 5], oncological consultation was omitted (even though, in the view of the authors, an oncologist may be consulted in non-standard cases), and the patient was qualified for surgical treatment.

The decision to operate first on the tumor located in the left lung was based on its size, rate of expansion, proximity to large vessels, and previous cytological verification (vs. the results of PET-CT for the changes in the right lung) – similar criteria were proposed by Ferguson *et al.* [2]. In turn, Aziz *et al.* [9] suggest that, in the case of bilateral lesions, if only one tumor was diagnosed, the surgical treatment should first be applied to the non-diagnosed tumor.

The two thoracotomies were performed with an interval of five weeks, which falls within the range reported and suggested by other authors [7].

It is worth noting that the patient's smoking habit confirms the results of previous reports [10] suggesting that tobacco smokers are more susceptible to synchronous lung cancers.

The analysis of the discussed case allows one to conclude that SMPLCs are a nosological entity that can escape the notice of a diagnostician, who, observing multiple tumorous changes in the lungs and having diagnosed one of them as a malignant neoplasm, is prone to suspect metastasis. The authors underscore the significance of striving for the determination of diagnosis (FNAB) and the extent of the disease (PET-CT), as it offers a chance for successful treatment for patients with sufficient respiratory reserve. Of course, omitting invasive diagnostics of the mediastinum (mediastinoscopy) in spite of negative results of imaging examinations may be debatable; the authors underscore its significance in routine practice [5].

Based on the above case study, the authors performed a systematic review of the available literature. 637 publications were obtained. After limiting the search to studies published within the last ten years, 281 reports remained. The authors rejected studies that pertained to the molecular diagnostics of multiple lung cancers, publications on metachronous lung

cancers, and studies which reported additional extrapulmonary locations of synchronous malignant neoplasms.

The remaining 38 publications were concerned solely with cases of primary malignant neoplasms occurring within the lungs. The publications were divided into two groups: the first comprised original studies analyzing the practice employed in view of synchronous lung cancer diagnosis and the resulting long-term survival, while the second comprised case reports. In accordance with the assumed criteria, 20 original studies and 18 case reports from the last decade were found pertaining to synchronous lung cancers. Selected studies are presented in Tables I and II.

As mentioned above, SMPLCs are diagnosed relatively rarely. The analyses by individual authors presented in Ta-

ble I [5, 10-28] were based on sets of 3 [19] to 175 [17] case studies gathered over periods of time lasting from 4 [26] to 28 [28] years. The included authors conducted retrospective observations and confronted the employed treatment with the achieved long-term survival rates. Most of these studies [5, 10, 13, 15-25, 27, 28] describe results achieved using surgery, which was sometimes supplemented with oncological treatment; only a few of them [11, 12, 14, 26] pertain to radiation therapy. The fundamental aim of the above studies was to establish the optimal practice in the described cases, even though Ferguson *et al.* [2] pointed to promising results achieved by means of surgery as early as 1985.

Chang *et al.* [11] presented the long-term survival achieved in patients diagnosed with early-stage multiple

Table I. Summary of original works pertaining to synchronous lung cancer published in the years 2003-2013

Authors	Number of patients with synchronous multiple lung cancer	Treatment (number of patients)	Overall survival
Chang <i>et al.</i> [11]	101 (inoperable)	SABR	2-year OS 61.5% 4-year OS 39.7%
Griffioen <i>et al.</i> [12]	62	SABR (56) SABR and surgery (6)	2-year OS 56%
Xue <i>et al.</i> [10]	10 (2000-2010)	Surgery (3) Surgery + ChT/RT (4) Chemoradiation (3)	2-year OS 66% 2-year OS 50% 2-year OS 0%
Shah <i>et al.</i> [13]	47 (1997-2010)	Surgery (36) Surgery + ChT (11)	3-year OS 35%
Creach <i>et al.</i> [14]	15 (high risk of surgical resection)	SBRT	2-year OS 27.5%
Jung <i>et al.</i> [15]	32 (1995-2008)	Surgery	5-year OS 60.9%
Fabian <i>et al.</i> [16]	67 (1996-2009)	Surgery	3-year OS 64% 5-year OS 53%
Kocaturk <i>et al.</i> [5]	26 (2001-2008)	Surgery + ChT/RT	5-year OS 49.7%
Finley <i>et al.</i> [17]	175 (1995-2006)	Surgery	3-year OS 64%
Voltolini <i>et al.</i> [18]	43 (1990-2007)	Surgery	5-year OS 34% N1,2 – 0% N0 – 57%
Carretta <i>et al.</i> [19]	3 (1988-2005)	Surgery	5-year OS 66%
De Leyn <i>et al.</i> [20]	36 (1990-2007)	Surgery	5-year OS 38%
Rostad <i>et al.</i> [21]	94 (1993-2000)	Surgery	5-year OS 31.4% carcinoma planoepitheliale 5-year OS 23.2% adenocarcinoma 5-year OS 42.7% other cancers
Trousse <i>et al.</i> [22]	56 (1985-2006)	Surgery	5-year OS 48.2% 10-year OS 29.9%
Chang <i>et al.</i> [23]	92 (past 16 years)	Surgery	5-year OS 35.3% N1,2 – 15.5% N0 – 52.5%
Trousse <i>et al.</i> [24]	125 (1985-2006)	Surgery	2-year OS 61.6% 5-year OS 34%
Mun <i>et al.</i> [25]	19 (1999-2004)	Surgery	3-year OS 94.7% 5-year OS 75.8%
Sinha <i>et al.</i> [26]	10 (9 inoperable, 1 refused) (2001-2005)	SBRT	All alive in 2006
Feng <i>et al.</i> [27]	31 (1983-2004)	Surgery	1-year OS 52% 3-year OS 29% 5-year OS 20%
Tsunezuka <i>et al.</i> [28]	18 (1973-2001)	Surgery	5-year OS 69% 10-year OS 47%

OS – overall survival, SABR – stereotactic ablative radiotherapy, SBRT – stereotactic body radiation therapy, ChT – chemotherapy, RT – radiotherapy, N – nodes

Table II. Summary of case reports pertaining to synchronous lung cancer published in the years 2003-2013

Authors	Age (y), sex	Type of cancer (number of tumors)	Unilateral/bilateral	Comments	Treatment	Survival
Ito <i>et al.</i> [29]	78, F	Carcinoma planoepitheliale (1) Adenocarcinoma (2)	Unilateral	In one lobe	Lobectomy + lymphadenectomy	
Nagamatsu <i>et al.</i> [30]	67, F	Adenocarcinoma (1) Carcinoid (1)	Unilateral	In one tumor (cancer-in-cancer)	Lobectomy + lymphadenectomy	
Ohtsuka <i>et al.</i> [31]	63, M	Adenocarcinoma (2)	Unilateral	In two lobes	Segmentectomy + lymphadenectomy	
	67, M	Adenocarcinoma (2)	Unilateral	In two lobes		
Sepehrpour <i>et al.</i> [32]	70, M	Carcinoma planoepitheliale (1) Adenocarcinoma (1)	Unilateral	In one lobe	Lobectomy + lymphadenectomy	
Loo <i>et al.</i> [33]	74, M	Carcinoma planoepitheliale (2)	Bilateral	Inoperable	IMRT	Alive after 48 months
Yoshimoto <i>et al.</i> [34]	52, F	Adenocarcinoma (1) Bronchioloalveolar carcinoma (1)	Unilateral	In one lobe	Lobectomy + lymphadenectomy	
Okita <i>et al.</i> [35]	71, F	Carcinoma planoepitheliale (3)	Unilateral	In one lobe	Lobectomy	
Yazici <i>et al.</i> [36]	58, F	Typical carcinoid (2)	Bilateral		Wedge resection + lymphadenectomy	
Matsuoka <i>et al.</i> [37]	79, F	Adenocarcinoma (2)	Bilateral		Lobectomy + segmentectomy	
Hosaka <i>et al.</i> [38]	65, F	Adenocarcinoma (2)	Bilateral		Lobectomy + segmentectomy + lymphadenectomy via sternotomy	
Camargo <i>et al.</i> [39]	62, F	Carcinoid (3)	Bilateral		Sublobar resections	
Froio <i>et al.</i> [40]	59, M	Adenocarcinoma (1) Carcinoma planoepitheliale (1) Carcinoma microcellulare (1)	Unilateral		Lobectomy + segmentectomy	
Damas <i>et al.</i> [41]	50, F	Carcinoma microcellulare (1) Adenocarcinoma (1)	Bilateral	Hepatic metastasis	ChT + RT	Alive after 28 months
Ryoo <i>et al.</i> [42]	66, M	Bronchioloalveolar carcinoma (2) Carcinoma planoepitheliale (1)	Bilateral		ChT	
Kobashi <i>et al.</i> [43]	73, M	Carcinoma microcellulare (1) Adenocarcinoma (1)	Unilateral	In one lobe	ChT + lobectomy + lymphadenectomy	
Khan <i>et al.</i> [44]	75, M	Carcinoma non-microcellulare (2)	Unilateral		Wedge resection + segmentectomy	Alive after 6 months, relapse
Fujiwara <i>et al.</i> [45]	40, F	Carcinoma non-microcellulare (2)	Bilateral		Lobectomy + segmentectomy	
Mizuguchi <i>et al.</i> [46]	51, M	Large cell carcinoma (1) Adenocarcinoma (1)	Bilateral	Cancer in the walls of bullae	Lobectomy + bullectomy	Alive after 3 years

F – female, M – male, IMRT – intensity-modulated radiotherapy, ChT – chemotherapy, RT – radiotherapy

synchronous lung cancers, in whom there were contraindications for pulmonary parenchyma resection. Stereotactic ablative radiotherapy (SABR) was used in these patients; the achieved 2-year overall survival rate was 61.5%. Similarly, Griffioen *et al.* [12] promote this type of treatment in selected patients (no signs of lymph node involvement). The method's 2-year survival rate may be as high as 56%; the authors also point to its low toxicity and good local control after irradiation. Creach *et al.* [14] and Sinha *et al.* [26] conclude that using stereotactic body radiation therapy (SBRT) is a safe and efficacious method for patients in whom surgery is burdened with high risk and in patients not consenting to surgical procedures. They also observed that both progression-free survival (PFS) and overall survival

(OS) are better in the case of metachronous tumors than in the case of synchronous tumors [11, 14], and that local control of lesions after irradiation is beneficial in the case of synchronous tumors.

It is worth highlighting that topical treatment using only ionizing radiation is an efficacious low-risk method, which may be offered to patients who do not qualify for surgical intervention due to medical reasons or lack of consent [26]. Provided that the patients are properly qualified (no lymph node metastasis), the achieved long-term survival rates are comparable to those achieved after surgical intervention.

Xue *et al.* [10] present 10 case studies with different treatment regimens. All of the operated patients were negative for lymph node involvement. The best survival

rates were achieved in patients operated on for T1a and T1b tumors, in whom lobectomies and segmentectomies were performed. Patients in whom pneumonectomy was performed and supplemented with chemoradiotherapy (T1a-T3 tumors) had worse 2-year survival rates; the results were the worst among patients treated only with chemoradiotherapy (T2a tumors, one person with N1 lymph node involvement).

Kocaturk *et al.* [5] analyzed 26 patients operated on due to synchronous lung cancers, who received postoperative oncological treatment. Based on the obtained results, the authors concluded that surgical treatment is a low-risk option which offers a chance for a long survival. They suggest avoiding pneumonectomy in favor of lobectomy and segmentectomy, as the 5-year survival rate after lung removal was 27%, while after the other resections it was 71.1%. Long-term survival rates after resections less extensive than pneumonectomy did not differ between each other; therefore, the authors recommend performing resections which guarantee complete tumor removal, preferring segmentectomy in patients with low respiratory reserves. Like Trousse *et al.* [24], they also noted that postoperative chemotherapy may be of benefit to the patient's future health status.

Shah *et al.* [13] recommend aggressive surgery in patients with bilateral synchronous lung cancers. Most of the operated patients underwent pulmonary parenchyma resections (wedge resections, segmentectomies, lobectomies) using a videothoroscopic approach (96% lateral, 60% bilateral); in over 23% of them, adjuvant therapy was required. The 3-year overall survival rate was 35%. Feng *et al.* [27] also recommend aggressive surgical treatment; however, their results were less promising, as the 3-year survival rate was 29%. This may be a result of performing pneumonectomies in the study group. Tsunozuka *et al.* [28] advise employing aggressive surgical treatment as well; they report conducting parenchymal sparing procedures (sleeve resections), which directly influenced the long-term treatment outcomes (5-year survival was 69%).

Jung *et al.* [15] reported that female gender [17], younger age, not smoking, $FEV_1/FVC \geq 70\%$, small tumor size (pT1), and identical histological pattern of cancer tissue were associated with longer survival; PFS was influenced by tumor size and lymph node status (pT1N0), as well as by identical histological pattern. De Leyn *et al.* [20] did not find any significant differences in terms of long-term survival between patients with different histopathological types and patients with the same histopathological type of cancer. Trousse *et al.* [24] demonstrated that conducting pneumonectomies significantly deteriorates long-term survival.

Fabian *et al.* [16] highlight the survival rates achieved after the treatment of bilateral synchronous lung cancers with identical histological pattern (with the exception of bronchioloalveolar carcinoma) and negative N2 parameter. According to the current TNM classification, such patients should be considered as stage IV (Ma1 parameter), but the 5-year survival rates achieved by the authors of the said report, reaching 53%, are incongruent with survival

rates estimated for such an advanced stage of lung cancer [20, 22]. Additionally, Finley *et al.* [17] state that 5-year survival estimated for patients with SMPLCs is comparable to the survival of patients with single cancers in the same stages of advancement.

Voltolini *et al.* [18] clearly demonstrated that lymph node metastasis concomitant with two non-small-cell cancers in the lungs does not offer any chance for long-term survival (5-year survival: 0%); however, excluding lymph node metastasis [20] using a PET-CT examination and/or mediastinoscopy allows for the selection of patients with negative N parameters who may undergo efficacious surgical treatment (5-year survival: 57%). Chang *et al.* [23] achieved the following 5-year survival rates depending on lymph node status: 15.5% (metastasis present) and 52.5% (negative N parameter).

The analysis of synchronous lung adenocarcinomas by Carretta *et al.* [19] confirmed the validity of performing sublobar resections; the authors argued that the said procedures provide sufficient oncological radicality and offer a chance for long-term survival (5-year survival: 66%). Worse outcomes were reported by Rostad *et al.* [21], who evaluated 5-year survival in dependence on the histopathological diagnosis of concomitant primary cancers with identical pattern. In the case of adenocarcinoma, the 5-year survival rate was 23.2%, and in the case of squamous carcinoma it was 31.4%.

Mun *et al.* [25] presented the long-term outcomes of concurrent surgical treatments for synchronous cancers conducted in 19 patients (15 stage IA patients). In 14 patients, lung parenchyma resections were performed using a sternotomy approach, and in 5 patients via VATS (video-assisted thoracic surgery). Thirteen patients underwent lobectomy and wedge resection on the opposite side; bilateral wedge resection was performed in 5 patients, and one patient underwent segmentectomy and wedge resection. Adenocarcinomatous pattern was revealed in 84 of the removed lesions; the remaining lesions were identified as squamous carcinoma. The authors reported 5-year survival at the level of 75.8%, which correlates with the early stages of advancement of the patients qualified for surgery.

Within the last 10 years, 18 case reports have been published (Table II) [29-46]. Their authors described a total of 19 cases of SMPLCs: 10 of them in women and 9 in men. The mean age of the operated patients was 64.4 years, and the mean age of the patients undergoing oncological treatment was 63 years [33, 41, 42].

The most frequently diagnosed neoplasms included lung adenocarcinoma (12 cases), followed by squamous carcinoma (6 cases), small cell carcinoma and carcinoid tumors (3 cases each). Bronchioloalveolar carcinoma and non-small-cell carcinoma were diagnosed in two patients each, and large-cell carcinoma was found in one patient. In 10 patients, the tumors were located in one lung only, while in the remaining cases both lungs were involved. The most frequently conducted surgical procedure was lobectomy (11 patients); sublobar resections, i.e. segmentectomy and wedge

resection, were performed in 6 and 3 patients, respectively. Eight patients underwent mediastinal lymph node excision.

Oncological therapy was employed in three cases [33, 41, 42]. In one case, the tumors were inoperable (two synchronous squamous carcinoma tumors located in both lungs) [33] – the patient underwent intensity-modulated radiotherapy (IMRT) and was alive after 4 years. Another patient was diagnosed with adenocarcinoma in one lung and small-cell carcinoma in the other; metastases to the liver were also present [41]. Oncological combination therapy was employed (chemotherapy + radiation therapy), and the patient survived for over 2 years.

Nagamatsu *et al.* [30] describe the case of a 67-year-old woman, in whom non-small-cell carcinoma was diagnosed intraoperatively. The patient underwent lobectomy and lymphadenectomy. Postoperative slide examination revealed that within the main adenocarcinomatous tumor, there was a scar, in which a carcinoid developed (cancer-in-cancer). Hosaka *et al.* [38] present the case of a 65-year-old patient diagnosed with bilateral synchronous lung tumors. Intraoperatively, two adenocarcinomatous tumors were identified, and both lesions were excised concurrently via sternotomy. A right upper lobectomy and a left segmentectomy with lymphadenectomy were performed. The postoperative course was successful.

Finally, Mizuguchi *et al.* [46] analyzed the case of a 51-year-old man treated with lobectomy and bullectomy due to bilateral emphysematous bullae. Histopathological examination revealed the presence of large-cell carcinoma in the wall of one of the bullae as well as adenocarcinoma in the wall of another emphysematous bulla. No signs of recurrence were observed three years after the operation.

One of the conclusions drawn from this review of studies concerning synchronous multiple primary lung cancers published within the last ten years is that the status of this nosological entity is not yet fully determined, as it does not fit well into the current TNM classification of lung cancer (7th edition). The authors of the listed studies [5, 13, 15-20, 23-25, 27, 28] argue that surgery is an efficacious treatment for this disease and should be considered if no contraindications are present. They also demonstrated that, in spite of conducting sublobar resections, the prognosis for patients with at least two primary lung cancers with no lymph node involvement is comparable to the outcomes achieved in patients with similarly staged single lesions. Although the incidence of SMPLCs is very low, which may result from underdiagnosis and treating patients with multiple lung lesions as potential candidates for systemic treatment, the described treatment options should always be taken into consideration, because well-planned surgical treatment may offer a chance for long-term survival.

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