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**Case Report / Приказ болесника**

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**Multiple primary synchronous tumors in lungs – a case series**

Вишеструки примарни синхрони тумори плућа – прикази болесника

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## Multiple primary synchronous tumors in lungs – a case series

### Вишеструки примарни синхрони тумори плућа – прикази болесника

#### SUMMARY

**Introduction** The aim of this manuscript was to report a case series of three patients diagnosed with multiple primary synchronous cancers (MPSC) in the lungs who were treated multidisciplinary at a single-center institution.

**Outline of cases** Three male patients were referred to the Clinic for Chest Surgery, at the Military Medical Academy in Belgrade, Serbia for planned surgical treatment of previously detected lung cancers. During subsequent diagnostic procedures, second primary synchronous tumors were detected in all presented cases. All patients underwent surgical resection and chemotherapy or a combination of chemo- and radiotherapy. Two of three patients died with an average survival period of 32 months. One patient is still alive, with current disease-free interval of 21 months.

**Conclusion** MPSC is a rare condition. The final diagnosis should be based on clinical, radiological, histopathological, and genetic analyses. Treatment modalities of MPSC depend on the clinical staging of the disease, patient's general medical condition, and general assessment of tumor operability and resectability.

**Keywords:** lung cancer; multiple tumors; synchronous tumor; resection

#### САЖЕТАК

**Увод** Циљ овог рада је да се прикажу три случаја вишеструких примарних синхроних тумора плућа који су мутидисциплинарно лечени.

**Прикази болесника** Три пацијента мушког пола јавили су се на Клинику за грудну хирургију, Војномедицинске академије у Београду, Србија, ради планираног хируршког лечења раније дијагностикованог тумора плућа. Током дијагностичких порцедура, које су уследиле у сва три случаја детектовани су додатни синхрони тумори плућа. Сви пацијенти су хируршки лечени уз додатну хемиотерапију или комбинацију хемио и радио терапије. Два од три пацијента су преминула са временом преживљавања од 32 месеца. Трећи пацијент је и даље жив са периодом без болести од 21 месец.

**Закључак** Вишеструки примарни синхрони тумори плућа се ретко јављају. Дефинитивна дијагноза треба да се заснива на клиничким, радиолошким, хистопатолошким и генетичким анализама. Модалитет лечења наведених тумора зависи од клиничког стадијума болести, општег здравственог стања болесника и опште процене операбилности и ресектабилности.

**Кључне речи:** карцином плућа; вишеструки тумори; синхрони тумори; ресекција

#### INTRODUCTION

Epidemiological studies have reported the incidence of multiple primary lung cancers (MPLC) from 5.6% to 22% [1–4]. Genetic predisposition and environment exposure contribute to the development of MPLC [1]. The increased incidence of MPLC results from advances in screening and diagnostic procedures coupled with higher patient survival rates due to a more sophisticated treatment of the first primary lung cancer [1, 5].

Multiple primary tumors are tumors that arise in different sites and are of different histology and morphology characteristics [1]. The definition of MPLC has changed over time and differs according to different studies and guidelines. Last update of criteria for MPLC comes from American College of Chest Physicians (ACCP) in 2013 while the present most commonly used definitions of multiple primary tumors in general are the ones from the Surveillance Epidemiology and End Results (SEER) project and International Association of

Cancer Registries and International Agency for Research on Cancer (IACR/IARC) [4, 6, 7]. Nowadays, molecular analysis provides precise differentiation between multiple primaries and intrapulmonary metastasis [8, 9, 10]. Comprehensive histologic assessment is another proposed concept which may have advantages over molecular analyses, because it is more rapid and inexpensive [11, 12, 13].

MPLC can be synchronous or metachronous. Synchronous tumors are defined as two or more primary neoplasms detected simultaneously or within an interval of less than 6 months, while metachronous tumors are diagnosed if the interval of occurrence is longer than 6 months [6]. Synchronous primary lung cancers (SPLCs) occur less frequently with the incidence of 0.2% to 8%. It is important to make a distinction between MPLC and metastatic or recurrent primary tumors in order to provide optimal therapy.

The aim of this manuscript is to present a series of three patients diagnosed with MPLC and treated multidisciplinary at a single-center institution. Written informed consent was obtained from all patients or their family member in case of the deceased patients.

## CASE REPORTS

### Case 1

A 72-year-old male was admitted to the Military Medical Academy in Belgrade, Serbia for planned surgical treatment of adenocarcinoma located in the right lower lobe of the lung. The chest computed tomography (CT) showed a mass lesion of approximately 27mm in diameter in the right lower lobe and another mass lesion (21mm in diameter) of unknown etiology in the left lower lobe, without significant lymphadenopathy (Figure 1). Subsequent bronchoscopy revealed normal findings, while the cytological tests showed the presence of adenocarcinoma cells in the right lung. Due to the pathological change in the right lung, the patient underwent right lower lobectomy in February 2017 and histopathological findings confirmed a solid type of infiltrating adenocarcinoma. In June 2017 a control chest CT showed the remaining tumor in the left lung. Six months after the initial surgery the doctors' committee decided to perform atypical resection in the left lower lobe. The final diagnosis of synchronous primary lung typical carcinoid was made based on different morphological features of the tumors. Therefore, adjuvant oral chemotherapy (HT), Vepesida pills, was

combined with surgery. Less radical procedure with a delay of six months was chosen for second surgery due to patient's poor general condition. The patient is still alive, 21 months after the second surgery. The characteristics of the present case are given in Table 1.

## Case 2

A 56-year-old male was referred to our institution due to productive cough and fever in December 2010. CT of the thorax showed a larger mass (50 mm) in the right upper lobe and a smaller mass (33 mm) in the right lower lobe along with enlarged mediastinal bronchopulmonary lymph nodes (up to 15 mm in diameter) and diffuse bullae. Abdominal CT did not reveal the presence of any pathological changes. Bronchoscopy revealed normal findings, while the cytological tests showed the presence of planocellular malignant cells in the right lung, which was confirmed by needle biopsy and histological analysis of the tumor.

In January 2011 the patient underwent right pneumonectomy with systematic lymphadenectomy. Histopathological analysis revealed the diagnosis of planocellular carcinoma in the lesion located in the right upper lobe, and acinar type adenocarcinoma with a formed scar in the tumor in the right lower lobe. Following the decision of the doctors' committee, the patient underwent four cycles of Gemcitabine and Platinum adjuvant HT. In 2012, the patient was reevaluated and control X-ray and CT showed the new nodule in left lung (sized to 12 mm) (Figure 2). Consequently, patient continued with adjuvant HT (III cycles of Paclitaxel – Platinum protocol). Reevaluation in January 2013 showed the enlargement of pathological mass in left lung and patient underwent additional adjuvant therapy with two cycles of Docetaxel. In December 2013 patient presented with the pain under the right rib, loss of appetite and poor general condition. Control chest CT showed the presence of pathological mass in the left lung sized 50 x 50 mm and enlarged local lymph nodes up to 18 mm in diameter. Abdominal CT showed the presence of expansive mass in right liver lobe (70 mm) and nodes in both adrenal glands (up to 20 mm in diameter). The patient received Erlotinib therapy during next 4 months. After that therapy, the mass in left lung was unchanged and all pathological changes in abdomen were in regression. In February 2015 patient died with clinical manifestation of pulmonary thromboembolism (Table 1).

### Case 3

A 58-year-old male was referred to our institution for evaluation of non-microcellular carcinoma in the right lung. The initial chest CT revealed a mass lesion of 23x17 mm in the right upper lung lobe along with paratracheal lymphadenopathy ( $\leq 13$  mm) and another mass lesion in the left upper lobe (22 × 13 mm in size) (Figure 3). Subsequent bronchoscopy revealed normal findings. Transbronchial needle aspiration of lymph nodes showed no malignant cells, while the cytological analysis of the right bronchus revealed malignant cells of non-microcellular carcinoma. Believing that the change in the left lung might be a metastasis of the previously diagnosed primary carcinoma in the right lung, left atypical resection was performed in March 2016. Intraoperative findings revealed a subpleural tumor mass (22 mm in diameter) affecting the visceral pleura. No lymphovascular or perineural infiltration was observed. Final histopathological analysis confirmed infiltrating EGFR wild type adenocarcinoma. After the initial surgery, the patient underwent three cycles of Taxol and Cisplatin adjuvant therapy.

Follow-up CT showed the remaining pathological mass in the right lung. In August 2016 the patient underwent right upper lobectomy with systematic lymphadenectomy. Histology confirmed infiltrating squamocellular lung carcinoma. Subsequently, the patient received six more cycles of Gemcitabine and Cisplatin adjuvant therapy. The patient lived for 20 months after the second surgery and died in March 2018 due to liver metastasis. The characteristics of present case are given in Table 1.

### DISCUSSION

MPLC represents a significant challenge in everyday clinical practice, mostly due to difficulties in diagnosis and treatment of such conditions. To the best of our knowledge the only report of MPLC in Serbia was published by Kontic et al. [14] in 2011. Therefore, the present article is the largest addressing these tumors in Serbian population.

Adenocarcinoma was reported in all three patients as one of the tumors. Furthermore, typical carcinoid and squamocellular carcinoma, were identified as second primaries. Our findings corroborate the results of a previous study [4]. Namely, Bhaskarla et al. [4] analyzed data of 702,120 patients diagnosed with primary lung cancer and reported that a second

primary lung cancer had developed in 1.5% of the investigated population. Adenocarcinoma and squamous cell carcinomas were the most commonly diagnosed second primary lung cancers [4].

The differential diagnosis between MPLCs and a recurrence, metastatic, or satellite lesion arising from the original tumor is difficult. Distinguishing SPLCs and advanced disease is important because their prognosis and treatment are different and a surgical approach to SPLC may result in survival similar to solitary cancers [1, 15]. Sometimes, clinical or radiological evidence is not sufficient to undoubtedly differentiate these conditions. Apart from histopathological reports used as a golden standard, genetic analyses of the clonal origin of tumors are useful because these can help to determine whether MPLC have arisen from the same clone and therefore the same tumor [1, 16]. Song et al. [17] reported a patient with six synchronous invasive adenocarcinomas that were revealed due to whole-exome sequencing and analysis of nonsynonymous mutations. Previous studies have reported that mutations in the p53 tumor suppressor gene, mutation of EGFR and analysis of miRNA expression profiles represent reliable tools for diagnosing MPLC [10, 18, 19]. Therefore, these should be included in diagnosing MPLC [16]. A recent study demonstrated the more frequent disagreement of PD-L1 expression in patients with MPLC in comparison to patients with metastasis [9].

Although recommendations for the management of MPLCs have been published by three major lung cancer research institutes (Union for International Cancer Control, American Joint Committee on Cancer, and International Association for the Study of Lung Cancer), controversies still exist [5].

In general, the treatment of multiple primaries should cover all identified tumors and be conducted by a multidisciplinary team [1, 5]. According to the guidelines of the ACCP, surgical resection remains the treatment of choice for MPLCs whenever possible [6]. Namely, surgery may be performed if sufficient pulmonary reserve can be obtained after multiple lesions are resected [6]. Surgeons taking characteristics of the tumor and status of patients into consideration mainly decide the extent of resection [5]. For sMPLC, which occur in the same lung, anatomical resections (single, bilobectomy, or pneumonectomy) might be recommended [20]. We have included additional HT in all our cases. It was a decision after its presentation to the multidisciplinary team. Chang et al. demonstrated that anatomical resection of the first lesion and limited resection of the second might be safer

option for synchronous bilateral lesions [21]. The initial surgery should be performed on the side with the largest tumor [15]. In case of a resectable tumor, but the patient's intolerance to surgery due to impaired cardiopulmonary function, local therapy is an optional strategy. One of the options is stereotactic body radiation therapy (SBRT) [5]. Varlotto et al. [22] described that the overall survival rate, recurrence rate, and loco-regional control rate of SBRT treatment were acceptable compared with those obtained after surgical treatment. SBRT is limited by respiratory movements, and the complication of radiation pneumonitis. Patients who do not qualify for surgery may also receive percutaneous image-guided tumor radio frequent ablation (RFA) [5]. The advantage of RFA lies in the ability to locally heat tumors to a lethal temperature with minimal damage to surrounding normal lung tissue [23]. The limitations of CT-guided percutaneous RFA in lung tumor therapy is the high incidence of complications, such as pneumothorax, hemothorax, and bronchopleural fistula [24]. A novel option presented in a case report by Teng et al. is percutaneous RFA utilizing an electromagnetic navigation platform [25].

One of our patients is still alive, 21 months after the second surgery, while the other two died approximately 4 and 2 years after surgery. Disease-free interval reported by Bhaskarla et al. [4] was 3.3 years. Longer survival intervals were significantly associated with the lower stage of disease and complete resection of the second carcinoma [4]. Recent studies showed 5-year survival rates of 71.3% and 74% [10, 26].

In conclusion, MPLC is a rare condition. The final diagnosis should be based on clinical, radiological, histopathological and genetic analyses. Treatment of MPSC depends on the clinical staging of the disease, patient's general condition, and assessment of tumor operability and resectability.

**Conflict of interest:** None declared.

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**Table 1.** Characteristics of presented cases

Case number	Sex	Age	Smoker	Histopathological diagnosis	TNM classification	Localization	Diameter	Diagnostic procedure	Therapy	Disease-free survival
1	Male	72	Yes	Primary tumor: Adenocarcinoma	pT1cN0Mx	Right lower lobe	27 mm	Bronchoscopy CT Immunohistochemistry	Right lobectomy (02/2017)	Patient is still alive, 21 months after second surgery.
				*Secondary (synchronous) tumor: Typical carcinoid	T1cN0Mx	Left lower lobe	21 mm		Lower left atypical resection (08/2017)  Adjuvant oral therapy (Vipetid capsules)	
2	Male	56	Yes	Primary tumor: Non-small cell lung cancer (squamous cell carcinoma)	T2bN0M0	Right upper lobe	50 mm	Standard Chest X-Ray Bronchoscopy CT Needle biopsy Immunohistochemistry	Right pneumonectomy with systematic lymphadenectomy (01/2011)	Died in 02/2015 with clinical manifestation of pulmonary thromboembolism
				**Secondary (synchronous) tumor: Adenocarcinoma (acinar type)	T2aN0M0	Right lower lobe	33 mm		Postoperative radiotherapy  Four cycles of gemcitabine and platinum adjuvant therapy	
3	Male	58	Yes	Primary tumor: Non-small cell lung cancer (squamous cell carcinoma)	pT1cN2Mx	Right upper lobe	23x17 mm	Bronchoscopy Transbronchial needle aspiration CT Immunohistochemistry	Right upper lobectomy with systematic lymphadenectomy (08/2016) Six cycles of gemcitabine and cisplatin adjuvant therapy	Died in 03/2018 due to liver metastases
				*Secondary (synchronous) tumor: Adenocarcinoma	pT2NoMx	Left upper lobe	22 x 13 mm, tumor infiltrating visceral pleura		Atypical resection (03/2016) Three cycles of taxol and cisplatin adjuvant therapy	

TNM – tumor, lymph nodes, and metastasis;

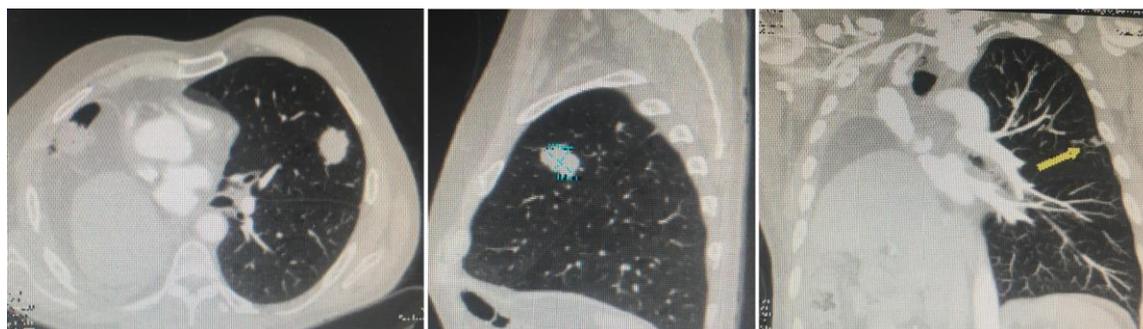
\*diagnosed at the same time;

\*\*diagnosed and operated on at the same time

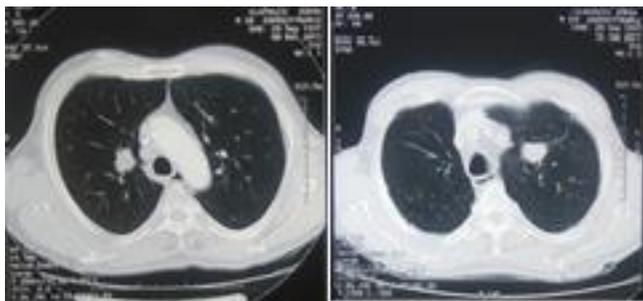


**Figure 1.** Multi-slice computed tomography findings of pathological masses in (A) right and (B) left lower lobes of lung

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**Figure 2.** Multi-slice computed tomography finding of secondary deposits in the left lung



**Figure 3.** Multi-slice computed tomography findings of pathological masses in the lungs

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