

## Pulmonary Metastasectomy For 29 Patients With Colorectal Carcinoma: A Single Center Experience

### Yirmidokuz Kolon Kanseri Hastada Akciğer Metastektomi: Tek Merkez Deneyimi

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#### ÖZET

**Amaç:** Kolorektal kanserli hastaların yaklaşık olarak %50-60'ında senkron veya metakron uzak metastazlar izlenmektedir. Kolorektal kanserlerin hepatik ve pulmoner metastazlarının cerrahi rezeksiyonu hastalıksız sağkalım (DFS) ve genel sağkalımı (OS) anlamlı düzeyde uzatmakta ve böylece son yıllarda yaygın olarak uygulanmaktadır.

**Yöntem:** Bu çalışmada, Dokuz Eylül Üniversitesi Tıp Fakültesi Hastanesi'nde tedavi gören ve kolorektal kanserlere bağlı akciğer metastazları nedeniyle metastazektomi uygulanan 29 hasta değerlendirildi. Hastalara ait bilgiler retrospektif olarak elde edildi.

**Bulgular:** Hastaların 24'ü (%82.8) izole akciğer metastazı, gerikalan 5'i (%17.2) ise hem akciğer hem karaciğer metastazına sahipti. Çalışmaya alınan hastaların tümüne akciğer metastazına yönelik rezeksiyon uygulanırken, 5 (%17.2) hastaya ise akciğer+karaciğer metastazektomisi uygulanmıştı. Tüm hasta grubunda ortalama OS 57 ay (SD± 4 ay), 1, 3 ve 5 yıllık sağkalım oranları sırasıyla %96, %92 ve %49 olarak tespit edildi. Metastazektomi operasyonu sonrası izlenen lezyonu olmayan hastalarda ortalama DFS 31 ay (SD± 3 ay), 1, 3 ve 5 yıllık DFS oranları sırasıyla %86, %42 ve %1 olarak saptandı. Metastazektominin şekline göre OS değerlendirildiğinde wedge rezeksiyon yapılanlarda ortalama OS 58 ay (SD± 5 ay), lobektomi yapılanlarda ise 50 ay (SD± 2 ay) olarak bulundu. Rezeksiyon türüne göre OS değerlendirildiğinde R0 rezeksiyon yapılanlarda ortalama OS 66 ay (SD± 5 ay), R1 rezeksiyon yapılanlarda ise ortalama OS 47 (SD± 7 ay) ay olarak bulundu.

**Sonuç:** Sonuçlarımız kolorektal kanser akciğer metastazlarının cerrahi rezeksiyonunun, özellikle R0 rezeksiyonun OS süresinin uzamasına katkı sağladığını göstermektedir.

**Anahtar Kelimeler:** Kolorektal kanser; Akciğer metastazektomi, Sağkalım

#### ABSTRACT

**Aim:** Synchronous or metachronous distant metastasis develops in approximately 50-60% of patients with colorectal cancer during the clinical course. Surgical resection of the hepatic and/or pulmonary metastasis of colorectal cancers significantly extends disease-free survival (DFS) and overall survival (OS) rates, and thus has been applied more broadly in recent years.

**Methods:** In this study, 29 patients who were treated at the Dokuz Eylül University Medical Faculty Hospital and who had received a metastasectomy due to a lung metastasis related to colorectal cancer were evaluated. Information on the patients was obtained retrospectively.

**Results:** Twenty-four (82.8%) patients had an isolated lung metastasis and 5 (17.2%) had both lung and liver metastasis. Resection was performed on all patients for lung metastasis, and a lung+liver metastasectomy was performed on 5 (17.2%). For the entire patient group, the median OS was 57 months (SD± 4 months), and 1, 3, and 5 year survival rates were 96%, 92% and 49%, respectively. In patients who received follow-up treatment after undergoing the metastasectomy operation and who did not have lesions, the median DFS was 31 months (SD± 3 months), and 1, 3, and 5 year DFS rates were 86.3%, 42% and 1%, respectively. In patients who received wedge resection treatment, the median OS was 58 months (SD± 5 months), and for the patients who received lobectomy treatment, the median OS was 50 months (SD± 2 months). In the evaluations made according to the resection type, median OS was 66 months (SD± 5 months) in patients who had R0 resection and 47 months (SD± 7 months) in patients who had R1 resection.

**Conclusion:** Our results show that surgical resection, particularly an R0 resection of lung metastasis in colorectal cancer patients contributes to extended patient OS time.

**Keywords:** Colorectal cancer; Pulmonary metastasectomy, Survival

## Introduction

Colorectal cancer is one of most common type of cancer (1). Metastasis is the primary cause of death in these patients, with the most common metastasis areas being the liver, lung and peritoneum. Distant metastasis is present in approximately 20-25% of patients with colorectal cancer at the time of diagnosis (2). Metachronous metastasis develops during the course of disease in approximately 40-50% of patients who received a resection and adjuvant therapies (3).

When patients with metastatic colorectal cancer are not treated, the prognosis is poor, with a median survival rate of approximately 5-9 months (4). The primary treatment for metastatic colorectal cancer is systemic; however, when metastasis is present in only the liver or the lung, a metastasectomy can also be performed. In systemic treatments, combinations of chemotherapeutic agents, such as 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, are typically used. With the recent addition of targeted agents that have been used, the level of efficiency has increased and due to their high response rates, they have become the agents of choice in induction treatments (5).

Among the colorectal cancer metastases, lung and liver metastases are particularly important, especially in terms of determining the treatment approach. In these patients, local ablative approaches are also commonly performed, in addition to systemic treatments. In liver metastases related to colorectal cancer, hepatic resection is the only curative treatment option, and 5-year survival rates are reported to have a ratio of 25-40%. Today, hepatic resection serves as the gold standard of treatment types (6, 7).

Patients with lung metastasis only are believed to have a more suitable biology in terms of local or systemic treatment options as compared to patients with multi-organ metastasis. In an autopsy study performed on patients who had died of metastatic lung disease, it was observed that the lungs were the single metastasis area in 20% of the patients. This lends strength to the idea that surgical

resection of lung metastases can extend survival time. Among all metastases, patients who are able to receive complete resection have a longer survival rate as compared to patients who unable to receive resection. It has been shown that time of survival of over 5 years can be obtained in about 20 to 40% of patients who have resectable lung metastasis (8). It has also been reported that synchronous or sequential resection of liver and lung metastases can extend survival (9).

In this study, the objective is to evaluate the effects on survival and prognosis of patients with colorectal-cancer-related lung metastasis who have undergone a metastasectomy.

## Methods

### *Patient Characteristics*

Evaluations were conducted on colorectal cancer patients who had received a metastasectomy due to lung metastasis and who were receiving follow-up treatment at Dokuz Eylül University Medical Faculty, Department of Internal Diseases, Medical Oncology between January 2001 and May 2013. The files of the patients, including information on their metastasectomy operation, the efficiency and toxicity of the treatments performed, as well as their demographical data, were retrospectively evaluated. The staging of the patients involved in the study was performed according to the American Joint Committee on Cancer's (AJCC) Cancer Staging, 6<sup>th</sup> edition, 2002 TNM staging system.

### *Treatment Characteristics*

In patients who had previously had stage II colon cancer or who have any of the high risk factors, the De Gramont regimen (Folinic acid 400 mg/m<sup>2</sup> + 5-FU 400 mg/m<sup>2</sup> bolus + 5-FU 2400 mg/m<sup>2</sup> 46-h infusion, fortnightly) was performed as the adjuvant chemotherapy, and for stage III patients, the mFOLFOX-4 (Folinic acid 400 mg/m<sup>2</sup> + 5-FU 400 mg/m<sup>2</sup> bolus + 5-FU 2400 mg/m<sup>2</sup> 46-h infusion+ Oxaliplatin 85 mg/m<sup>2</sup>, fortnightly) regimens were performed. For patients who had rectal cancer and were

undergoing chemoradiotherapy (CRT), radiotherapy was delivered 45 Gy in 25 fractions, at a dose of 1.8 Gy fraction a day, and 5-FU 225 mg/m<sup>2</sup>/day was administered in a continuous infusion. Chemotherapy regimens applied due to metastatic diseases were also grouped.

### *Efficiency Evaluation*

For patients receiving systemic treatment, a response evaluation was conducted once every 6 courses of treatments. The response evaluation was carried out according to the tumor response evaluation criteria of the World Health Organization (WHO). Complete disappearance of tumor and confirmation of this result in four weeks was considered a complete response (CR); a regression of 50% or above in the target lesion and a maximum progression of 25% in any lesion and confirmation of this result in four weeks was considered a partial response (PR); no change in the target lesion was considered a stable disease (SD); and a progression of 25% or above in the target lesion or determination of a new lesion was considered a progressive disease (PD). The sum of CR and PR was regarded as an objective response rate (ORR).

Patients' pre-metastectomy evaluations were carried out with thoracic, lower and upper abdominal computed tomography; PET-CT and colonoscopy were performed in the required cases. The lung metastasectomy process was grouped into wedge resection, segmentectomy, and lobectomy. The resection type was classified as R0, R1 or R2 resection.

### *Survival Analysis*

For patients who received follow-up after the metastasectomy operation and who did not have any lesions, the time between operation and recurrence was regarded as disease-free survival (DFS), and the time until death was considered as overall survival (OS).

### *Statistical Analysis*

The Statistical Package for Social Sciences (SPSS), Windows Version 15.0 was used to conduct statistical analysis of the data; the Chi-Square test and Fisher exact test were used for the comparison between the independent group

rates of two groups. For DFS and OS analyses, the Kaplan-Meier Method was used, and for the comparison of two survival curves, the Log rank Test was used. Statistical significance was set at  $p < 0.05$ .

## **Results**

### *Patient Characteristics*

Twenty-nine patients who were treated and received follow-up after being diagnosed with metastatic colorectal cancer and who had had a lung metastasectomy were involved in the study. A majority of the patients were female, and in a large portion of the female patients, the primary tumor was located in the colon. The tumor histology was adenocarcinoma in all patients. Six (20.7%) were metastatic at the time of diagnosis, while 23 (79.3%) became metastatic at a later period. Three of the 17 patients with a primary tumor location in the colon were metastatic at the time of diagnosis, and none of the 12 patients with a primary tumor location in the rectum were metastatic at the time of diagnosis. All the patients that were not metastatic at the time of diagnosis had a previous adjuvant history. Twenty-four (82.8%) patients had an isolated lung metastasis, and 5 (17.2%) had both lung and liver metastasis. Lung metastases were located mostly in the left lung's upper lobe and right lung's lower lobe. Wedge resection and R0 resection were the most commonly performed metastasectomy types. Resection was performed on all patients for lung metastasis, while additional liver metastasectomy was performed on 5 (17.2%). Patients' characteristics are shown in detail in Table 1. There were no operation related deaths.

### *Treatment regimens*

Neoadjuvant treatment was given to 18 (62.1%) patients before they had received a lung metastasectomy; on the remaining 11 (37.9%) patients, a lung metastasectomy was performed directly. Adjuvant treatment was performed on all patients after metastasectomy, with the most common treatment being the Folfiri- bevacizumab regimen. The chemotherapy characteristics of patients are shown in detail in Table 2.

<b>Variable</b>	<b>n (%)</b>
<b>Gender</b>	
Male	16 (55.2%)
Female	13 (44.8%)
<b>Primary Tumor localization</b>	
Colon	17 (58.6%)
Rectum	12 (41.4%)
<b>Location of tumor metastases during lung metastasectomy</b>	
Isolated lung	24 (82.8%)
Lung+liver	5 (17.2%)
<b>Metastasis location</b>	
Left lung's upper lobe	8 (27.5%)
Right lung's lower lobe	6 (20.6%)
Left lung's lower lobe	5 (17.2%)
Right lung's upper lobe	3 (10.2%)
Right lung's upper + left lung's lower lobe	2 (6.8%)
Right lung's upper and lower lobe	2 (6.8%)
Right lung's lower + left lung's upper lobe	1 (3.4%)
Left lung's upper and lower lobe	1 (3.4%)
Right lung's lower + left lung's lower lobe	1 (3.4%)
<b>Operation type</b>	
Solitary Lung metastasectomy	24 (82.8%)
Lung + liver metastasectomy	5 (17.2%)
<b>Type of Lung Metastasectomy</b>	
Wedge resection	24 (82.8%)
Lobectomy	5 (17.2%)
<b>Type of Resection in Lung Metastasectomy</b>	
R0	17 (58.6%)
R1	12 (41.4%)

**Table 2.** Chemotherapy characteristics and diagrams of patient

<b>Neoadjuvant chemotherapy</b>	
Performed	18 (62.1%)
Non-performed	11 (37.9%)
<b>Adjuvant chemotherapy type</b>	
Folfiri+bevacizumab	10 (34.5%)
Folfiri + cetuximab	4 (13.7%)
Folfox6	3 (10.3%)
Folfox4	3 (10.3%)
Folfiri	3 (10.3%)
Folfox + Bevacizumab	2 (6.9%)
Folfox7	1 (3.4%)
Raltitrexed + oxaliplatin	1 (3.4%)

**Table 3.** Recurrence pattern following metastasectomy

<b>Recurrence organ</b>	<b>n (%)</b>
Isolated lung	12 (41.3%)
Lung + liver	1 (3.4%)
Liver + peritoneum	2 (6.9%)
Lung + brain	4 (13.8%)
Spleen	1 (3.4%)
Rectum	1 (3.4%)
No recurrence	8 (27.6%)

### Survival

In the entire patient group, the median OS was 57 months (SD±4 months), and 1, 3, and 5 year survival rates were 96%, 92%, and 49%, respectively (Figure 1). In patients who received follow-up after undergoing the metastasectomy operation and who did not have lesions, the median DFS was 31 months (SD±3 months), and 1, 3, and 5 year DFS rates were 86.3%, 42%, and 1%, respectively (Figure 2). In patients who had received treatment at a prior time under the diagnosis of early stage colorectal cancer and then became metastatic, the median time between diagnosis and metastasis was 23 months. When the survival is evaluated according to the resection type, median OS was determined as 66 months (SD±5 months) in patients who had R0 resection and 47 months (SD±7 months) in patients who had R1 resection (Figure 3). When survival was evaluated according to the type of metastasectomy, the median OS was 58 months (SD±5 months) and 50 months (SD± 2 months) in patients that had wedge resection and lobectomy, respectively (Figure 4). When survival analyses were assessed according to the primary tumor location, the median OS was 45 months for those whose tumor was in the colon and 63 months for those whose tumor was in the rectum (Figure 5). In the patients that received chemotherapy as adjuvant treatment after metastasectomy, there was no significant difference in terms of survival according to CT regimen.

### Recurrence pattern after metastasectomy and treatment characteristics

Recurrence occurred in 21 (72.4%) patients after receiving a lung metastasectomy. Metastasis was present in a single organ in 14 of these patients and 7 had metastasis in two organs. Location and distribution of recurrences are shown in Table 3. A lung metastasectomy was repeated in 4 (19%) of the patients who had a recurrence; in 3 (15%) patients, a lung metastasectomy was performed after neoadjuvant chemotherapy; and palliative chemotherapy was performed on 14 (66%) patients. Of the 7 patients who had a second lung metastasectomy as a result of the recurrence, 6 were rectum derived and 1 colon derived.

### Conclusions

Colorectal cancers rank second among cancer related deaths. Lung metastasis occurs in 10-20% of colorectal cancers, whereas colorectal cancer metastasis accounts for only 2-4% of the lung metastases (10, 11, 12). The primary treatment for metastatic colorectal cancers is systemic treatment; however, additional metastasectomy treatment contributes to long-term survival in liver and lung metastases (9,13).

In our study, survival time following a lung metastasectomy in patients with a primary tumor location in the rectum was found to be longer than that in patients with a primary tumor location in the colon. In the literature, it is emphasized that survival time is typically

shorter for patients with a primary tumor in the rectum, and that this might be the result, to a large extent, of the rectum's lack of peritoneal protection (mean 5-year survival rate for colon and rectum is 35-65% and 30-53%, respectively) (12,14,-18). However, certain publications have suggested that the primary tumor's localization is not very effective in measuring mean survival rate (12). In the analysis performed on our patients, although there was no statistically significant difference between colon cancer and rectum cancer metastases in terms of survival after metastasectomy, the 5-year survival expectancy was 66% and 76%, respectively. The mean survival time was 45 months (SD±6 months) in patients with primary colon cancer and 63 months (SD±4 months) in patients with primary rectum cancer. We believe that the reason behind obtaining completely opposite results from the above mentioned study (14-18) can be attributed to the small number of patients with tumor location in rectum and the fact that most of the primary colon cancer cases were metastatic at the time of diagnosis.

Although chemotherapy is suitable in metastatic colon cancers that are unresectable and that show a systemic distribution, median OS time in these non-operable patients is 20-22 months, whereas the 5-year OS expectancy is only 5%. On the other hand, the mean 5-year OS time of colorectal cancer patients who had lung metastasectomy is reported to be 48% (varying between 41%-56%) (12). In our study, the median OS was 57 months (SD±4 months), and the 1, 3, and 5 year OS rates were 96%, 92%, and 49%, respectively, in the entire group. Published literature results are also similar to the results of the study conducted at our health center.

The report on disease free survival (DFS) published by the International Registry of Lung Metastases (IRLM) in 1997 suggested that a period of more than 36 months had a positive effect on prognosis; Pfannschmidt et al, however, reviewed many studies and stated that the DFS interval was effective on prognosis, independent of other factors, in only two of 20 case series (12,14, 17,19,20). Many of the publications with opposing views involve only predictions for lung metastases of colorectal cancers. The mean survival time in patients with <36 months of DFS was reported as 43.3 months, whereas the mean OS in

patients with >36 months of DFS was reported as 47.3 months (14). Similar to the studies seen in the literature, in our study, statistically significant data on the effect of median DFS time on mean OS time were not determined.

It has been reported that synchronous lung and liver metastases were found in approximately 5-10% of patients with primary colorectal cancer. Some studies suggest that systemic chemotherapy will provide better results than radical resection in primary colorectal cancers with synchronous lung and liver metastases (21,22), while some researchers indicate that complete resection of pulmonary metastasis and liver metastasis would have almost the same survival outcomes. Therefore, the performance of a complete resection on solitary liver and lung metastases in selected patients could lead to lasting palliation and encouraging results (14). In three other interesting studies found in the literature, the mean 5-year survival rate was reported as 31% in colorectal cancer diagnosed patients who had both a lung and a liver resection (23-25). Five of our patients had liver metastasis. While the mean 5-year OS was not measured in our study (because there were only 5 patients), the mean survival time for colorectal cancer diagnosed patients who had both a lung and a liver resection was 40 months. Moreover, the survival values of our patients were observed to be consistent with other studies, and the multiple metastases partially reduced mean survival time. However, it is difficult to assert more definite claims given that there are only a limited number of patients with primary colorectal cancer and multiple diagnoses..

In many multi-centered studies, the effects on mean survival of colorectal cancer patients who received R0 and R1/R2 metastasectomy resections for lung metastases were compared (12). Even though the results of these studies were not very clear, a significant effect on survival was not found for R0 and R1/R2 resections, but it was concluded that an R0 resection provided a partially better prognosis in comparison to an R1 resection. In our study, the mean OS time was 66 months (SD±5 months) and 47 months (SD±7 months) in patients that had R0 resection (n:17) and R1 resection (n:12), respectively; given these results, our study supports the view in the

literature that an R0 resection offers a better prognosis as compared to an R1 resection (12).

In most of the studies found in the literature, a wedge resection or segmentectomy (60-65%) was performed. A lobectomy was preferred in 35-40% of patients, while a pneumonectomy was performed in only 1-2% of patients (12). In a study conducted by Vogelsang et al, a wedge resection was performed on 52 patients and better results were obtained in terms of 5-year life expectancy as compared to an anatomic lung resection performed on 23 patients (5-year survival wedge resection: 39%, anatomic lung resection: 25%) (26). In other large studies conducted, it was found that resection type did not have a prognostic significance on life expectancy (11,24,27-29). In our study, a wedge resection was performed on 24 patients and a lobectomy on 5 patients. Mean OS following the wedge resection and lobectomy

surgeries were 58 months (SD±5 months) and 50 months (SD±2 months), respectively. Similar to many of the studies published in the literature, the results of our study support the view that the type of resection does not have a significant effect on prognosis.

Neoadjuvant treatment was given to 18 (62.1%) colorectal cancer patients who had a lung metastasectomy, while the remaining 11 (37.9%) had a direct lung metastasectomy operation; all patients received adjuvant chemotherapy following the operation. As the neoadjuvant chemotherapy and adjuvant chemotherapy types given in studies published in the literature are very different, it is quite difficult to examine the effect of chemotherapy on expected survival time (12). Adjuvant chemotherapy, however, was given after lung resection in 4 different studies, and no effect was reported on the prognosis or the expected survival time (26,27, 29, 30).

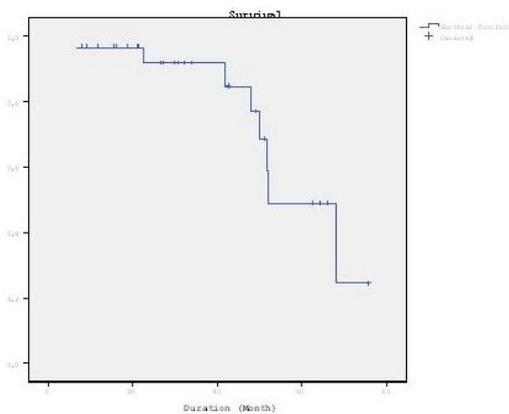


Figure 1

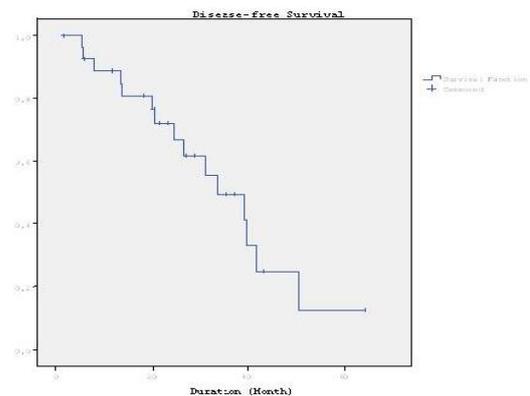


Figure 2

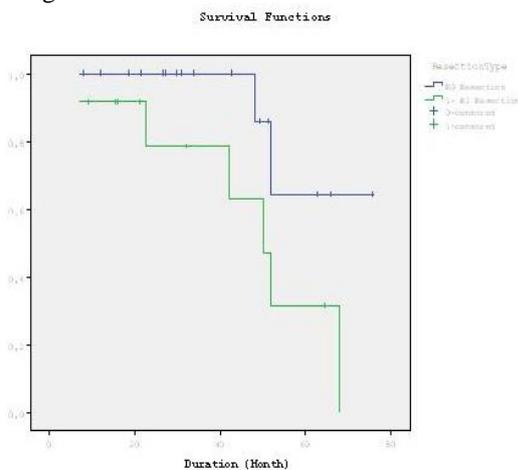


Figure 3

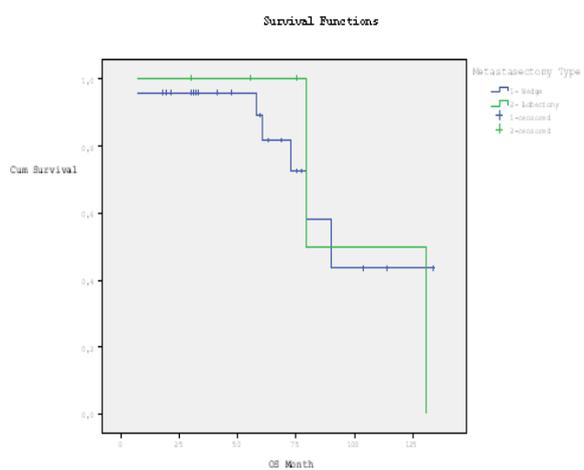


Figure 4

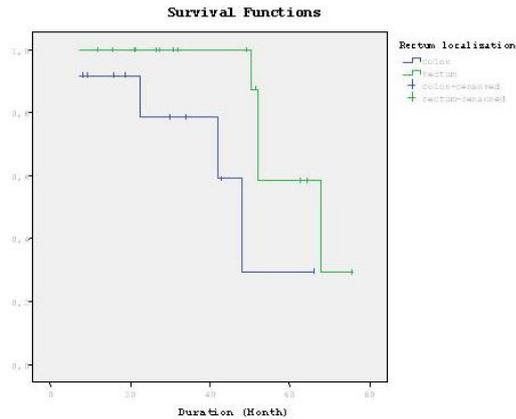


Figure 5

The mean value for isolated lung recurrence of colorectal cancers with lung metastasis following the lung resection was reported to be 36% (12) in the literature. In our study, recurrence was seen in a total of 21 patients, 12 of which (41%) had isolated lung recurrence, data similar to those seen in the published studies.

As a result of this study being performed on a limited number of patients with colorectal cancer, metastasectomy approaches on isolated metastases involving the lung generally provided

results similar to those seen in the literature. It is quite clear that the multidisciplinary approach in metastatic colorectal tumors, early diagnosis, newly developed and efficient chemotherapeutic agents and effective lung metastasectomies have reached quite significant and promising levels in terms of life expectancy compared to previous years. Complete resections (R0) performed following efficient neoadjuvant treatment, especially in metastases that emerge after a long disease-free survival period, provide significant improvements in the results of patients. Serial follow-up of patients is also very important, and serial metastasectomies performed in the event of recurrences contribute to survival. Therefore, a multidisciplinary approach plays a very important role in the follow-up of patients with colorectal cancer, just as it does in other cancer types.

**Conflict of interest:** None

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