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Survival outcome of pulmonary metastasectomy among the patients with colorectal cancers

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SUMMARY

OBJECTIVE: Pulmonary metastasectomy for the treatment of metastatic colorectal cancer is essential, but high ranked evidence of survival benefit is lacking. Here, we aimed to examine the prognostic factors after pulmonary metastasectomy in patients with colorectal cancer.

METHODS: This is a single-center, retrospective hospital-based observational case series study. We reviewed data for 607 patients with metastatic colorectal cancer (mCRC) who were treated and observed from 2012 to 2019. Of the 607 patients with mCRC, 87 were with solitary lung metastases. Of the 87 patients, 39 were not appropriate for metastasectomy, while 15 patients recognized as suitable candidates by the multidisciplinary thoracic tumor board rejected metastasectomy. Consequently, only 33 patients were included in the final analysis.

RESULTS: Rectum was detected as the primary site in 16 (48.5%) patients. Over 80% of patients had metachronous lung metastases, with a median of 29.0 months from initial diagnosis. Video-assisted thoracic surgery with wedge resection was performed in 20 (60.6%) patients. Over 90% of patients had solitary metastasis resected, with 97% of R0 resection. Median tumor size was 23.0 mm (min: 10; max: 90). Adjuvant treatment was given to 31 (93.9%) patients, while neoadjuvant treatment was given only to 8 (25%) patients. Of the 33 patients, there were 25 (75.7%) relapses. The most frequent site of relapse was lung in 15 (45.5%) patients. Interestingly, there were only 4 (12.2%) patients who had a relapse in the liver after lung metastasectomy. We found that median disease-free survival (DFS) and overall survival (OS) were 43.0 (13.0–73.0) and 55.0 (31.6–78.4) months, respectively.

CONCLUSIONS: Pulmonary metastasectomy was associated with significantly long-time survival rates in mCRC (43 months of DFS and 55 months of OS). The second relapse occurred in 25 (75.7%) patients, with isolated lung metastases in nearly half of the patients (45.5%). Therefore, lung metastases in mCRC were unique and a multidisciplinary team including a thoracic surgeon should manage these patients.

KEYWORDS: Colorectal cancer. Pulmonary metastasectomy. Second relapse. Surgical resection. Oligometastases.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common and third deadly cancer diagnosed with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database[1]. Twenty-five percent of newly diagnosed colorectal cancer cases had distant metastases. The recurrence rate of the curatively resected colorectal cancer was reported as 30%[2]. Therefore, over 50% of CRC eventually become metastatic, and similar to other solid tumors, metastases are the principal cause of death in these patients with CRC. Distant metastases, notably the liver, lung, and peritoneum, are virtually the most significant prognostic factors for CRC.

The lung is the second common metastatic site in CRC, and approximately 10–20% of patients with CRC develop pulmonary metastases[3]. However, the resection rate in lung metastases was far lower than that in liver metastases. Yedibela

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et al. reported that four percent of all mCRC patients had isolated lung metastases but only half of them (2% of mCRC) were candidate for curative resection[4]. Nonetheless, respectable studies have shown that 40–60% of 5-year survival rate can be reached in curatively resected lung metastases from mCRC[5]. However, there is a paucity of evidence from clinical trials that prove a survival benefit of lung metastasectomy in mCRC. The PulMicc trial, which is the only single randomized trial, showed nonsignificant benefit in 5-year survival rate (38 versus 29%) for metastasectomy over non-metastasectomy but had extremely low accrual rate (only 10% of the planned subjects were recruited)[6]. Despite lack of high-quality evidence, there is a strong rationale. So, European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend for the evaluation of lung similar to liver metastases by the multidisciplinary team for possible resection.

In the current study, we conducted a retrospective hospital-based observational study of lung metastasectomy for patients with mCRC. The primary aim of this study was to explore the outcomes of the patients with lung metastasectomy in mCRC. Secondary aims were to examine the rate of lung metastasectomy in patients with mCRC and define clinicopathological characteristics of these patients, which may stratify outcomes after metastasectomy.

METHODS

Patients

The current retrospective hospital-based observational case series study was conducted with 607 patients with mCRC treated and observed at Baskent University Faculty of Medicine, Adana Dr Turgut Noyan Research and Treatment Centre, between 2012 and 2019. Of the 607 patients with mCRC, 87 were with lung metastases. Of the 87 patients, 39 were found to be ineligible for metastasectomy, while 15 of them rejected pulmonary metastasectomy although they were evaluated as suitable candidates by multidisciplinary thoracic tumor board. Therefore, 33 patients were included in the final analysis (Figure 1).

Main demographic and clinicopathological characteristics including age, sex, primary site, European Cooperative Oncology Group (ECOG) performance, primary tumor stage, time to relapse, type of surgery, the number of metastases, size of metastases, surgical outcome, and whether treated with adjuvant versus neoadjuvant chemotherapy are summarized in Table 1.

Statistical analysis

We present all the results as the rate for categorical values or mean/median for continuous variables. Overall survival (OS) was defined as the time from lung metastasectomy to death or

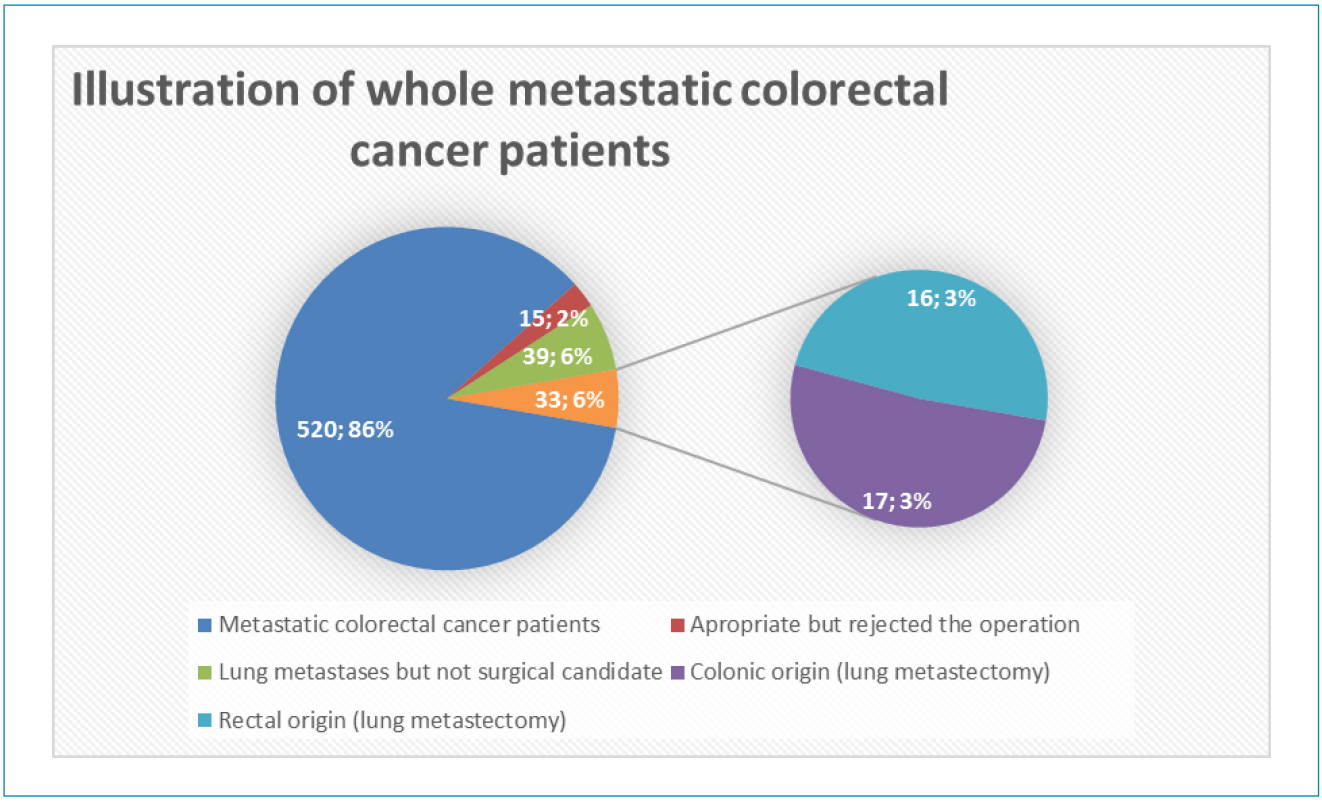

Figure 1. Illustration of whole metastatic colorectal cancer patients.

Table 1. Demographic and clinical characteristics of the study cohort.

Number of patients (n)	Whole group
	33
Sex: female, n (%)	13 (39.4)
Age (mean)	60.4 (SD:12.13)
ECOG 0, n (%)	33 (100)
Rectal origin, n (%)	16 (48,5)
Stage at diagnosis, n=20 (missing in 13 patients), n (%)	
II	5 (25)
III	11 (55)
IV	4 (20)
Time to relapse, months, n=33, median (range)	29.0 (0–67)
Type of surgery, n (%)	
VATS wedge	20 (60.6)
Open lobectomy	9 (27.3)
VATS lobectomy	2 (6.1)
Segmentectomy	1 (3.0)
Thoracotomy wedge	1 (3.0)
Metastatic site(s), right lung, n (%)	18 (54.5)
Number of metastases, n (%)	
Solitary	30 (90.9)
<3	3 (9.1)
Size of tumor, mm, (median)	23.0 (min: 10; max: 90)
The surgical outcome with R0, n (%)	32 (97.0)
Neoadjuvant treatment, n=31, n (%)	8 (25.0)
Adjuvant treatment after surgery, n=33, n (%)	31 (93.9)
Presence of relapse after lung surgery, n (%)	25 (75.7)
Sites of relapse, n=25, n (%)	
Lung	15 (45.5)
Liver	2 (6.1)
Lung plus liver	2 (6.1)
Other organs	6 (18.1)
Median follow-up period, months, median (range)	30.0 (2.0–79.0)
DFS, months, median (range), 95% CI	43.0 (13.0–73.0)
OS, months, median (range), 95% CI	55.0 (31.6–78.4)

ECOG: Eastern Cooperative Oncology Group; VATS: video-assisted thoracic surgery; DFS: disease-free survival; OS: overall survival.

last control date and was reported in terms of months. Disease-free survival (DFS) was defined as the time to relapse or time between the resection of the primary tumor and the first diagnosis of pulmonary lesions and was reported in months. Survival was estimated using Kaplan-Meier curve, and log-rank tests were used for univariate statistical comparisons. Adjusted hazard ratio (HR) and 95% confidence interval (95%CI) were used for estimation. All statistical data were analyzed using the SPSS version 25.0, and a $p<0.05$ was considered statistically significant. Recurrence-free survival (RFS) was defined as the time between pulmonary metastasectomy and metastatic recurrence and was reported in terms of months.

RESULTS

Patients characteristics

Thirty-three patients with mCRC who had undergone pulmonary metastasectomy were included in the final analysis. Most of the patients were male (20, 60.6%), and the mean age of the participants was 60.4 years (SD 12.1). All patients had an ECOG performance score of 0 at the time of surgery. In all, 16 patients had rectum and 17 had colon as the primary site, with 11 at stage III, 5 at stage II, and 4 at stage IV at the time of diagnosis. Data about the initial stage of the tumor were missing for 13 patients.

Thirty patients had solitary metastasis, while three had multiple metastases (1–3) to the lung. Lung metastases were commonly located in the right lung, 18 (54.5%). Resection was performed on all patients for lung metastasis, and the type of surgery was based on the size and location of the tumor. The median size of the tumor was 23.0 mm (min: 10; max: 90).

Treatments and outcomes

Video-assisted thoracic surgery (VATS) wedge resection with R0 surgical outcome was the principal surgical method performed in our patients. Wedge resection was performed in 20 patients, open lobectomy in 9, VATs lobectomy in 2, segmentectomy in 1, and wedge thoracotomy in 1. There was no surgery-related mortality.

Thirty-one patients received neoadjuvant treatment, and all patients received (33) adjuvant treatment after surgery. Chemotherapy was given to patients depending on the perceived benefits based on the characteristics and their ECOG status to withstand the treatment.

Survival analysis was done using Kaplan-Meier curves; the median DFS was 43.0 months (95%CI 13.0–73.0) and OS was 55.0 months (95%CI 31.6–78.4). Recurrence occurred in 25 (75.7%) patients after pulmonary metastasectomy, with

the lung being the major site of relapse. In all, 15 (45.5%) patients had a recurrence in the lung, 2 (6.1%) in the liver, and 2 (6.1%) in the lung and liver, while 6 (18.1%) patients had relapsed at other organs.

Univariate statistical analysis failed to demonstrate significant effect of the number of metastases, size and site of the tumor, stage at diagnosis, and types of surgery on DFS or OS (p>0.05) (Table 2). Multivariate analysis was not done because all univariate analysis had p value below 0.2.

DISCUSSION

Although most of the CRC is diagnosed at the local stage, 30% and 70% of patients at stages II and III CRC become metastatic in 24–36 months of initial diagnosis[7]. At the metastatic stage, if patient's metastatic sites could be resected with R0, 30% of these patients can be potentially cured[8]. Most frequent sites of metastases of the CRCs were the liver and lung in 70% and 15% of the patients, respectively. Unfortunately, in patients with CRC, metastatic sites could be resected in only 15% of metastatic patients[9].

In our study, only 5% (33/607) of patients with mCRC underwent curative lung metastasectomy. Rectum was detected as the primary site in 16 (48.5%) patients. Over 80% of patients became metastatic after initial primary treatment with curative resection and adjuvant treatments, with median of 29.0 months (0–67). VATS with wedge resection was performed in 20 (60.6%) patients. Over 90% of patients had solitary metastasis resected with 97% R0 resection. Median tumor size was 23.0 mm (min: 10; max: 90). Adjuvant treatment was given to 31 (93.9%) patients, while neoadjuvant treatment was given only to 8 (25%) patients. Of the 33 patients, there were 25 (75.7%) relapses. The most frequent site of relapse was the lung in 15 (45.5%) patients. Interestingly, there were only 4 (12.2%) patients who had relapsed in the liver after lung metastasectomy. The median DFS and OS were found to be 43.0 (13.0–73.0) and 55.0 (31.6–78.4) months, respectively.

In the literature, Zhang et al. evaluated over 80,000 patients with cCRC and reported that isolated lung metastases and resection rate were 8.2% and 3.6%, respectively. In our results, over 600 patients with mCRC, 14% (n=87) of the patients had isolated lung metastases, 8% (n=42) of them were suitable for the lung metastasectomy, and 6% (n=33) were resected[8]. These numbers showed a smaller group of patients compared to liver metastasectomy and, therefore, could easily be overlooked in daily practice and patients can lose the chance of curative metastasectomy. We found that 80% of patients developed metachronous lung metastasis, and

Table 2. Univariate analysis of disease-free survival and overall survival

Variable	Univariate analysis, median time, months (95%CI)	p
Number of metastases, n=33		
Solitary, n=30	43.0 (15.0–71.0)	0.73
1–3, n=3	Not reached	
Size of the tumor, n=33		
≤2.5 cm, n=20	43.0 (19.9–35.6)	0.89
>2.5, n=13	Not reached	
Site of the tumor, n=33		
Right, n=18	43.0 (12.9–73.3)	0.94
Left, n=15	28.0 (26.1–54.3)	
The stage at diagnosis, n=20		
Stages II and III, n=16	22.0 (14.4–29.6)	0.66
Stage IV: n=4	21.1 (17.5–24.7)	
Origin of the tumor, n=33		
Colon, n=17	43.0 (15.0–71.0)	0.43
Rectum, n=16	Not reached	
Type of surgery		
VATS, n=22	28.0 (NA)	0.27
Open, n=11	43.0 (NA)	
Number of metastases, n=33		
Solitary, n=30	55.0 (26.8–83.2)	0.56
1–3, n=3	48.0 (NA)	
Size of the tumor, n=33		
≤2.5 cm, n=20	65.0 (31.7–98.2)	0.55
>2.5, n=13	48.0 (27.2–68.7)	
Site of the tumor, n=33		
Right, n=18	41.0 (16.7–65.3)	0.21
Left, n=15	65.0 (45.7–84.3)	
Stage at diagnosis, n=20		
Stages II and III, n=16	65.0 (17.7–112.3)	0.49
Stage IV: n=4	28.0 (NA–66.9)	
Origin of the tumor, n=33		
Colon, n=17	48.0 (24.6–71.4)	0.33
Rectum, n=16	Not reached	
Type of surgery		
VATS, n=22	55.0 (25.0–85.0)	0.95
Open, n=11	48.0 (13.9–78.4)	

VATS: video-assisted thoracic surgery. Any of the variables had no p-value below 0.2; therefore, no multivariate analysis was made.

rectum was the primary site in 16 (80%) patients. Also, our data showed that median RFS was 29 months. Our results were compatible with the literature by Sadahiro et al. reporting that the development of the distant metastasis from rectal cancer required significantly longer times (26 months versus 17 months) compared to colon cancer. In addition, they showed that the development of the lung metastasis appeared significantly later in comparison with colon cancer (p=004)[7]. With these results, the inclusion of the appropriate imaging of the thorax in surveillance of the patients with CRC beyond 24 months could be appropriate.

In our center, a limited number of lung metastases were resected along with the decision of the tumor board. Therefore, of the 33 patients, 30 (90%) were solitary, and accordingly, 67% of our operation were performed by the VATS technique. Though we know the prognostic effect of the mediastinal lymph node positivity of the lung metastases, routine lymph node dissection with lung metastasectomy was not done in our center. Ihn et al.[10] reported that involvement of mediastinal lymph nodes showed poor prognosis, but making routine lymph node dissection did not improve RFS in CRC. In the literature, new studies also reported a high rate of solitary metastases and wedge resection with VATS and no benefit of the segmentectomy or lobectomy was shown with respect to wedge resection[11-13]. There are no phase III randomized data that show the significant benefit of adjuvant treatment after curatively resected mCRC. However, NCCN and ESMO guidelines suggested that 6 months of adjuvant chemotherapy may be given perioperatively. If neoadjuvant treatment included biological agents like bevacizumab and anti-EFGR, we can also include these agents in the regimen after the curative surgical resection[7,8]. In the current study, 31 (93.9%) patients were treated with the neoadjuvant treatment and 33 (100%) patients with adjuvant 6 months of systemic chemotherapy. We did not use a biological agent in the adjuvant setting, but if we started a biological agent at neoadjuvant setting, we must complete the 6-month systemic chemotherapy with the same regimen.

Although lung metastasectomy was made by curative intent, 75.7% (n=25) of the whole group relapsed, with a median RFS of 43 months. Median RFS in this study was better than those reported in previous multi-center trials[13]. We found out that over 90% of patients in our study had solitary metastasis with a median size of 23 mm and R0 resection rate of 97% (n=32). Most of the studies showed that solitary metastases with R0 resection and relatively small size were good prognostic factors in these patients[7-13,15]. Interestingly, after initial lung metastasectomy, the second relapse site of these patients was isolated lung metastases in 45.5% of the cases. Whereas isolated liver relapse and synchronous lung and liver relapse were detected in 6.1% and 6.1% of the entire group, consecutively. In the literature, most of the studies reported a higher rate of lung recurrence after lung metastasectomy[7,9,11,13]. Therefore, we have to make a vigilant follow-up for the second lung relapse to seize an opportunity for the second metastasectomy, which was shown to increase survival in retrospective analysis[13].

Our results provide relevant data about mCRC with lung metastasectomy with curative intent. However, some limitations are worth noting. The retrospective nature of the present study and the small size of the main cohort represent limitations that prevented us from drawing general conclusions. In addition, our study had limited data for the type of adjuvant chemotherapy and biological agent used and details about some important prognostic genomic characteristics like KRAS, NRAS, and B-RAF mutation status. Finally, our study also lacks chemotherapy toxicity and postoperative complication data. However, the information was retrospectively retrieved from hospital records and filtered from 607 patients with mCRC, of which 87 of them had isolated lung metastases but only 33 of them underwent curative lung metastasectomy, which is somehow cumbersome.

CONCLUSIONS

Our findings showed that isolated lung metastases occurred in significantly fewer patients and at a later time compared to liver metastases. Surgical resection of the lung metastases from mCRC is associated with unexpectedly high long-time survival rates (43 months of DFS and 55 months of OS). The second relapse occurred in 25 (75.7%) patients and isolated lung metastases in near half of the patients with CRC (45.5%). Therefore, lung metastases in mCRC were unique and these patients have to be managed by a multidisciplinary team including a thoracic surgeon along with a medical and surgical oncologist.

AUTHORS' CONTRIBUTIONS

OY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SAD:** Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. **AF:** Data curation, Formal analysis, Resources, Supervision. **FK:** Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Sharma R. An examination of colorectal cancer burden by socioeconomic status: evidence from GLOBOCAN 2018. EPMA J. 2019;11(1):95-117. https://doi.org/10.1007/s13167-019-00185-y
2. Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire swedish population. Dis Colon Rectum. 2018;61(9):1016-25. https://doi.org/10.1097/DCR.0000000000001158
3. Mitry E, Guiu B, Cosconea S, Jooste V, Faivre J, Bouvier AM. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut. 2010;59(10):1383-8. https://doi.org/10.1136/gut.2010.211557
4. Yedibela S, Klein P, Feuchter K, Hoffmann M, Meyer T, Papadopoulos T, et al. Surgical management of pulmonary metastases from colorectal cancer in 153 patients. Ann Surg Oncol. 2006;13(11):1538-44. https://doi.org/10.1245/s10434-006-9100-2
5. Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, Yasumitsu T, et al. Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. Ann Thorac Surg. 2004;78(1):238-44. https://doi.org/10.1016/j.athoracsur.2004.02.017
6. Treasure T, Farewell V, Macbeth F, Monson K, Williams NR, Brew-Graves C, et al. Pulmonary metastasectomy versus continued active monitoring in colorectal cancer (PulMiCC): a multicentre randomised clinical trial. Trials. 2019;20(1):718. https://doi.org/10.1186/s13063-019-3837-y
7. Sadahiro S, Suzuki T, Ishikawa K, Nakamura T, Tanaka Y, Masuda T, et al. Recurrence patterns after curative resection of colorectal cancer in patients followed for a minimum of ten years. Hepatogastroenterology. 2003;50(53):1362-6. PMID: 14571738
8. Zhang GQ, Taylor JP, Stem M, Almaazmi H, Efron JE, Atallah C, et al. Aggressive multimodal treatment and metastatic colorectal cancer survival. J Am Coll Surg. 2020;230(4):689-98. https://doi.org/10.1016/j.jamcollsurg.2019.12.024
9. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii1-9. https://doi.org/10.1093/annonc/mdu260
10. Ihn MH, Kim DW, Cho S, Oh HK, Jheon S, Kim K, et al. Curative resection for metachronous pulmonary metastases from colorectal cancer: analysis of survival rates and prognostic factors. Cancer Res Treat. 2017;49(1):104-15. https://doi.org/10.4143/crt.2015.367
11. Saito H, Kikuchi T, Matsunaga Y, Kikkawa H. Surgical resection of pulmonary metastases from colorectal cancer. Kyobu Geka. 1996;49(11):909-11. PMID: 8913063
12. Koga R, Yamamoto J, Saiura A, Yamaguchi T, Hata E, Sakamoto M, et al. Surgical resection of pulmonary metastases from colorectal cancer: four favourable prognostic factors. Jpn J Clin Oncol. 2006;36(10):643-8. https://doi.org/10.1093/jjco/hyl076
13. Okumura T, Boku N, Hishida T, Ohde Y, Sakao Y, Yoshiya K, et al. Surgical outcome and prognostic stratification for pulmonary metastasis from colorectal cancer. Ann Thorac Surg. 2017;104:979-87. https://doi.org/10.1016/j.athoracsur.2017.03.021
14. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, et al. NCCN Guidelines Insights: colon cancer, Version 2.2018. J natl Compr Canc Netw. 2018;16(4):359-69. https://doi.org/10.6004/jnccn.2018.0021
15. Cao G, Cheng D, Ye L, Pan Y, Yang F, Lyu S. Surgical resection of pulmonary metastases from colorectal cancer: 11 years of experiences. PLoS One. 2017;12(4):e0175284. https://doi.org/10.1371/journal.pone.0175284