



Reasoning about Ilo-Mediastinal Lymphectomy during Lung Metastasectomy for Colorectal Cancer: Appropriate or Unnecessary Effort?

Ferrari PA*

Unit of Thoracic Surgery, "A. Businco" Cancer Center, Azienda di Rilievo Nazionale ed Alta Specializzazione "G. Brotzu", Cagliari, Italy

*Corresponding authors: Paolo Albino Ferrari, Unit of Thoracic Surgery, "A. Businco" Cancer Center, Azienda di Rilievo Nazionale ed Alta Specializzazione "G. Brotzu", Cagliari, Italy, Tel: +3907052965470; Email: paolo.a.ferrari@aob.it; paoloalb.ferrari@gmail.com

Short Communication

Volume 7 Issue 2

Received Date: October 16, 2023

Published Date: November 02, 2023

DOI: 10.23880/ijst-16000193

Abstract

Lymph node dissection following lung metastasectomy is still debated, although it is considered necessary to achieve complete resection or at least gather prognostic information. When radical lymph node dissection is performed, the average rate of unexpected lymph node involvement in colorectal cancer is less than 20%. Lymph node co-involvement is an adverse prognostic factor, and preoperative mediastinal disease usually leads to patient exclusion from metastatic surgery. The authentic prognostic influence of systematic nodal dissection remains unclear. Unfortunately, many studies demonstrate no positive effect of lymphadenectomy during lung metastasectomy other than a pseudo-stage migration effect. Future studies should focus not only on survival but also on local and lymph node recurrence.

Keywords: Metastasectomy; Lymph Node; Lymphadenectomy; Colorectal Cancer

Abbreviations: LM: Lung Metastasectomy; CRC: Colorectal Cancer; OS: Overall Survival; LN: Lymph Node; CT: Computed Tomography; PET: Positron Emission Tomography.

Introduction

Lung metastasectomy (LM) is a well-established local treatment for lung-limited metastases of stage IV colorectal cancer (CRC) to increase overall survival (OS) or stop the further malignant spread from the lungs to other organs.

Though lymph node (LN) dissection is essential in primary lung cancer surgery and impacts patient prognosis [1,2], controversy exists regarding the need for lymphadenectomy during LM.

A survey among the European Society of Thoracic Surgery members revealed that only 13% perform systematic LN dissection during the removal of lung metastasis [3].

In the set of pulmonary metastatic CRC patients, the mediastinal LN positivity represents a well-documented unfavorable parameter, along with short disease-free interval, size and number of pulmonary metastases, elevated CEA, previous liver metastasis, and positive surgical margins [4].

The arguments for not performing the lymphadenectomy are partly related to the assumption that in a stage IV tumour disease, detecting any mediastinal LN positivity on pathological examination loses its significance. Even if

metastatic tumour cell dissemination in regional nodes is detected, this cannot be surgically controlled. On the contrary, LN dissection affects morbidity [5] without necessarily providing survival benefits.

In contrast to the previous belief that each new lung metastasis originates from the remaining cells of the primary tumour, it is now recognised that lung metastases can spread locally via lymphatic and hematogenous invasion. Therefore, in this case, radical resection of these metastases not only produces a significant reduction in the systemic tumour burden but can also lead to a cure [6,7].

Concurrent Thoracic Lymph Node Resection: An Overview

Approximately a half-century after the first report on the excision of two incidental lung nodules during the surgical resection of a chest wall sarcoma, Alexander and Haight in 1947 described the first series of solitary LM in 24 patients and the results of a 3-year follow-up [8,9]. Since then, many published studies have supported pulmonary

metastasectomy's safety and oncological benefits, depending on primary tumor histology [10].

Nowadays, LM is a generally accepted treatment for selected patients with CRC-related lung metastases. In many institutions, this procedure has been considered routine practice, supported mainly by the results of retrospective studies [10-12].

Interestingly, the criteria for LM were first proposed by Thomford, et al. [13]. The basic principle of surgery is to remove all possible metastatic lesions while preserving as much lung tissue as possible. Enucleation is the ideal surgical method for lung reserve and multiple metachronous lung metastases [10]. With the development of VATS surgery, wedge resection is usually performed, while lobectomy has mainly been used for patients with central tumours, large tumours, or multiple nodules within the same lobe [14]. According to this consensus, defined eligibility criteria for metastasectomy are now mandatory to provide a standardized surgical and oncological safety approach, as summarized in Table 1 [15-18].

I	Metastasectomy should only be performed in patients fit for lung resection
II	The primary tumor must be clinically controlled, with no evidence of active disease
III	If evidence of extra-thoracic disease is also suitable for resection or has already been successfully resected, the lung metastasectomy is not contraindicated
IV	The lung metastasis must be eligible for a guaranteed radical resection
V	There should be no better option for the treatment of metastasis, than surgery.

Table 1: Criteria of eligibility for surgical lung metastasectomy.

However, to better contextualise these assumptions, it is helpful to point out that only one randomised controlled trial concerning the effects of LM was undertaken, the PulMiCC trial, which was prematurely closed due to recruitment difficulties [19]. The results of this study revealed that patients in the control group, who received no local treatment for limited colorectal lung metastases, had better survival than previously assumed, with a five-year survival of 29.6% (95% CI: 15.3-45.7%). Patients randomised to surgical metastasectomy had a five-year survival of 36.4% (95% CI: 21.3-53.0%) [20]. Recently, the investigators published the results of the prospective observational cohort [21]. A total of 169 patients who did not undergo lung metastasectomy had a five-year survival of 21.9% (95% CI: 16-29%). Without

presenting the five-year absolute survival rate of patients undergoing pulmonary metastasectomy in this prospective cohort, the authors concluded that selection bias prevents a formal comparative analysis. According to literature screening where the OS of patients who underwent LM combined with lymphadenectomy were analyzed, the LN resection rate ranges from 12% to 100%.

As reported in Table 2, eleven studies described routine concurrent lymphadenectomy [22-26,28-33], and five specifically reserved this additional procedure only for central LM or lobectomy [27,34-37]. Other than the surgeon's preference, no indications were described for the combined lymphadenectomy in other twenty-four studies [38-61].

Patients (n)		Lymphadenectomy practice (%)	Nodal involvement (%)	Sub lobar resection (%)	Follow-up (months)	5-year survival NO (%)	5-year survival N+ (%)
Inoue, et al. [22]	25	100	36	N/S	108	49.5	14.3
Pfannschmidt, et al. [23]	167	100	19	65.5	59	38.7	0
Inoue, et al. [24]	89	100	28	N/S	85.9	50.8	19.3
Pfannschmidt, et al. [25]	114	100	28	N/S	N/S	N/S	N/S
Welter, et al. [26]	169	100	14	75.3	N/S	42	19.2
Kim, et al., [28]	27	100	7	100	39.5	N/S	N/S
Javed, et al., [29]	66	100	7	70.1	N/S	N/S	N/S
Bolukbas, et al., [30]	165	100	22	73.3	36	59	23
Renaud, et al. [31]	320	100	44	N/S	33	N/S	N/S
Balhareth, et al. [32]	11	100	30	N/S	60	87.5	12.5
Meimarakis, et al. [33]	89	100	18	N/S	35.2	39	18
Mean (95% CI)	112.9 (53-1173)	100%	23% (15-31%)	77.2% (52-102%)	57 (34-78)	52.3% (36-68%)	15.1% (8-22%)

Table 2: A selection of clinical trials and retrospective studies assessing the impact of routinary lymphadenectomy following colorectal lung metastasectomy on the overall survival.

Given the criterion of regional lymphadenectomy, according to the Naruke LN map [62], it was challenging to discriminate hilar lymph node metastasis from concurrent mediastinal involvement. However, we identified twelve studies in which a mean of 11.5% (95% CI: 7.2-15.8%) of patients had N1 metastasis without mediastinal lymph node involvement [22,51]. In comparison, in more studies, N2 involvement was described in a mean of 10.8% (95% CI: 8.3-13.3%) of patients without N1 metastasis [22,56].

Lung Metastasectomy and Concurrent Lymphadenectomy: 5-Year Overall Survival Rate

Twenty-seven studies Inoue M, et al. [22-27,61] provided details on 5-year OS rates after metastasectomy and LN dissection in lung metastatic CRC patients.

Only 18,5% of patients with lymph node metastases were alive at 5-year follow-up, while more than half (51,2%) of those without nodal disease were still alive at the same survival check.

In patients with metastatic lymph nodes, the 5-year OS of patients with N1 metastasis was 40.7% compared with

10.9% of patients with N2 lymph node metastasis.

Further fascinating insight should be made regarding the 5-year overall survival of patients without lymph node involvement after lymph node dissection (47.3%), compared with OS of patients undergoing lymph node sampling (53.2%).

Finally, the five-year OS for patients with lymph node involvement after lymph node dissection and sampling was 17.9% and 18.5%, respectively.

Prognostic Influence of Concurrent Thoracic Lymphadenectomy

Based on the data retrieved from a brief literature review, of all patients who underwent lymphadenectomy, either by sampling or lymph node dissection, 19.1% had lymph node involvement. Studies presenting the outcome of lymph node dissection had significantly more patients with lymph node involvement, and thus a higher rate of lymph node over-staging, than those that showed the outcome of lymph node sampling. However, lymph node dissection did not have a significantly different impact on the OS than lymph node

sampling.

Nevertheless, according to the selection criteria of each study, many patients with lymph node metastasis had unsuspected lymph node involvement. Patients with suspected or established mediastinal lymph node metastases in the preoperative workup are likely to have a poorer outcome. The results of this review highlight the worse oncologic outcome of patients with lung metastasis from CRC and simultaneous lymph node metastasis.

From the analysis of survival based on the anatomical location of the involved lymph node stations, differences were found: a five-year overall survival rate of 10.9% and a median survival of 23.2 months for N2 lymph node metastases, significantly lower than those found in patients with N1 lymph node metastases [11]. The next step will be to identify patients with mediastinal lymph node metastases better to select those most suitable for lung metastasectomy. Several studies have reported preoperative invasive mediastinal staging in CRC patients with LM by mediastinoscopy [63] or endobronchial-endoscopic ultrasound [64-66], the application of which, however, is limited. To date, there is no consensus on the contraindication for local radical therapy in cases of lymph node metastasis. Recently, Guerra, et al. [67] demonstrated the low sensitivity of both computed tomography (CT) and positron emission tomography (PET) in detecting lymph node metastasis in patients with lung metastasis from CRC (11% and 34%, respectively), concluding that PET-CT cannot adequately define an optimal treatment strategy. The main limitations of this review were the lack of detailed data description from individual studies and the lack of dispersion on the obtained survival data.

Currently, the retrospective studies available in the literature do not allow us to determine the potential therapeutic effect of lymphadenectomy in CRC lung metastasis. Despite attempts to objectify the impact of lymphadenectomy on survival [68], selection bias rules out generalizability.

Recommendations

Based on these assumptions, it is mandatory to exclude common confounders in order to identify the real benefit of lymphadenectomy during CRC lung metastasectomy. A prospective, randomized study of pulmonary metastasectomy has been unfeasible in the past and will be challenging to apply in the future for more detailed issues such as lymphadenectomy. Therefore, a multicenter or national enrollment of patients undergoing metastasectomy into a registry with prospectively collected data might be valuable. Based on a histologic entity with a single lesion, analysis of OS, disease-specific survival, and recurrence rate

(local, mediastinal, distant) can be stratified with or without systematic lymphadenectomy [33]. The type of resection (anatomic vs. nonanatomic), laser use, and lymph node metastatic involvement are other essential variables that must be considered.

Because of the suboptimal sensitivity of PET-CT in detecting thoracic lymph node metastases from CRC, a role should be defined for preoperative endosonographic staging of the mediastinum in selected patients or when extensive surgery may be indicated as radical intent.

Conclusion

In several retrospective studies, thoracic and mediastinal LN metastases are a significant and independent negative prognostic factor for survival after pulmonary metastasectomy for metastatic CRC. Either lymph node sampling or dissection (no significant difference in terms of detection) should be recommended to provide useful information on the presence of nodal metastasis for determining postoperative treatment.

However, because of the need for more evidence, its impact should be studied properly in further studies, possibly multicenter and with prospective data collection.

Conflict of Interest

Authors have no conflict of interest to declare.

Funding

No funding has been received for this study.

References

1. Liang W, He J, Shen Y, Shen J, He Q, et al. (2017) Impact of Examined Lymph Node Count on Precise Staging and Long-Term Survival of Resected Non-Small-Cell Lung Cancer: A Population Study of the US SEER Database and a Chinese Multi- Institutional Registry. *J Clin Oncol* 35: 1162-1170.
2. Wang W, Chen D, Xi K, Chen Y, Zhang X, et al. (2019) Impact of Different Types of Lymphadenectomy Combined With Different Extents of Tumor Resection on Survival Outcomes of Stage I Non-small-cell Lung Cancer: A Large-Cohort Real-World Study. *Front Oncol* 9: 642.
3. Internullo E, Cassivi SD, Van Raemdonck D, Friedel G, Treasure T, et al. (2008) Pulmonary metastasectomy: A survey of current practice amongst members of the European Society of Thoracic Surgeons. *J Thorac Oncol*

- 3(11): 1257-1266.
4. Pfannschmidt J, Dienemann H, Hoffmann H (2007) Surgical resection of pulmonary metastases from colorectal cancer: A systematic review of published series. *Ann Thorac Surg* 84(1): 324-338.
 5. Mokhles S, Macbeth F, Treasure T, Younes RN, Rintoul RC, et al. (2017) Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small-cell lung cancer: A systematic review of randomized trials and a meta-analysis. *Eur J Cardiothorac Surg* 51(6): 1149-1156.
 6. García-Yuste M, Cassivi S, Paleru C (2010) Thoracic Lymphatic Involvement in Patients Having Pulmonary Metastectomy. Incidence and the Effect on Prognosis. *J Thorac Oncol* 5 (6): S166-169.
 7. Welter S, Arfanis E, Christoph D, Hager T, Roesel C, et al. (2017) Growth patterns of pulmonary metastases: should we adjust resection techniques to primary histology and size? *Eur J Cardiothorac Surg* 52(1): 39-46.
 8. Weinlechner J (1882) Tumoren an der Brustwand und deren Behandlung. Resection der Rippeneröffnung der Brusthöhle und partielle Entfernung der Lunge. *Wien Med Wochenschr* 32: 589-591.
 9. Alexander J, Haight C (1947) Pulmonary resection for solitary metastatic sarcomas and carcinomas. *Surg Gynecol Obstet* 85(2): 129-146.
 10. Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, et al. (1997) Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 113(1): 37-49.
 11. Van Dorp M, Bousema JE, Torensma B, Dickhoff C, van den Broek FJC et al. (2022) Pulmonary metastasectomy with lymphadenectomy for colorectal pulmonary metastases: A systematic review. *Eur J Surg Oncol* 48(1): 253-260.
 12. Rena O, Casadio C, Viano F, Cristofori R, Ruffini E, et al. (2002) Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg* 21(5): 906-912.
 13. Thomford NR, Woolner LB, Clagett OT (1965) The surgical treatment of metastatic tumors in the lungs. *J Thorac Cardiovasc Surg* 49(3): 357-363.
 14. Shiono S, Matsutani N, Okumura S, Nakajima J, Horio H, et al. (2015) The prognostic impact of lymph-node dissection on lobectomy for pulmonary metastasis. *Eur J Cardiothorac Surg* 48(4): 616-621.
 15. Pastorino U (1997) Lung metastasectomy: why, when, how. *Crit Rev Oncol Hematol* 26(3): 137-145.
 16. Sudarshan M, Murthy SC (2020) Current indications for pulmonary metastasectomy. *Surg Oncol Clin N Am* 29(4): 673-683.
 17. Kondo H, Okumura T, Ohde Y, Nakagawa K (2005) Surgical treatment for metastatic malignancies. Pulmonary metastasis: indications and outcomes. *Int J Clin Oncol* 10(2): 81-85.
 18. Erhunmwunsee L, D'Amico TA (2009) Surgical management of pulmonary metastases. *Ann Thorac Surg* 88(6): 2052-2060.
 19. Treasure T, Farewell V, Macbeth F, Monson K, Williams NR et al. (2019) Pulmonary metastasectomy versus continued active monitoring in colorectal cancer (PulMiCC): A multicentre randomised clinical trial. *Trials* 20(1): 718.
 20. Milosevic M, Edwards J, Tsang D, Dunning J, Shackcloth M, et al. (2020) Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. *Colorectal Dis* 22(10): 1314-1324.
 21. Treasure T, Farewell V, Macbeth F, Batchelor T, Milošević M, et al. (2021) The Pulmonary Metastasectomy in Colorectal Cancer cohort study: Analysis of case selection, risk factors and survival in a prospective observational study of 512 patients. *Colorectal Dis* 23(7): 1793-1803.
 22. Inoue M, Kotake Y, Nakagawa K, Fujiwara K, Fukuhara K, et al. (2000) Surgery for pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 70(2): 380-383.
 23. Pfannschmidt J, Muley T, Hoffmann H, Dienemann H (2003) Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: Experiences in 167 patients. *J Thorac Cardiovasc Surg* 126(3): 732-739.
 24. Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K et al. (2004) Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 78(1): 238-244.
 25. Pfannschmidt J, Klode J, Muley T, Dienemann H, Hoffmann H (2006) Nodal involvement at the time of pulmonary metastasectomy: Experiences in 245 patients. *Ann Thorac Surg* 81(2): 448-454.
 26. Welter S, Jacobs J, Krbeek T, Poettgen C, Stamatis G (2007) Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. *Eur J Cardio Thorac Surg* 31(2): 167-172.
 27. Lin BR, Chang TC, Lee YC, Lee PH, Chang KJ, et al. (2009) Pulmonary resection for colorectal cancer metastases:

- Duration between cancer onset and lung metastasis as an important prognostic factor. *Ann Surg Oncol.* 16(4): 1026-1032.
28. Kim HJ, Kye BH, Lee JI, Lee SC, Lee YS, et al. (2010) Surgical resection for lung metastases from colorectal cancer. *J Korean Soc Coloproctol.* 26(5): 354-358.
 29. Javed MA, Sheel AR, Sheikh AA, Page RD, Rooney PS. (2014) Size of metastatic deposits affects prognosis in patients undergoing pulmonary metastectomy for colorectal cancer. *Ann R Coll Surg Engl.* 96(1): 32-36.
 30. Bolukbas S, Sponholz S, Kudelin N, Eberlein M, Schirren J (2014) Risk factors for lymph node metastases and prognosticators of survival in patients undergoing pulmonary metastasectomy for colorectal cancer. *Ann Thorac Surg* 97(6): 1926-1932.
 31. Renaud S, Alifano M, Falcoz PE, Magdeleinat P, Santelmo N, et al. (2014) Does nodal status influence survival? Results of a 19-year systematic lymphadenectomy experience during lung metastasectomy of colorectal cancer. *Interact Cardiovasc Thorac Surg* 18(4): 482-487.
 32. Balhareth AS, AlQattan AS, Alshaqaaq HM, Alkhalifa AM, Al Abdrabalnabi AA, et al. (2022) Survival and prognostic factors of isolated pulmonary metastases originating from colorectal cancer: An 8-year single-center experience. *Ann Med Surg (Lond)* 77: 103559.
 33. Meimarakis G, Spelsberg F, Angele M, Preissler G, Fertmann J, et al. (2014) Resection of pulmonary metastases from colon and rectal cancer: factors to predict survival differ regarding to the origin of the primary tumor. *Ann Surg Oncol* 21(8): 2563-2572.
 34. Ogata Y, Matono K, Hayashi A, Takamor S, Miwa K, et al. (2005) Repeat pulmonary resection for isolated recurrent lung metastases yields results comparable to those after first pulmonary resection in colorectal cancer. *World J Surg* 29(3): 363-368.
 35. Koga R, Yamamoto J, Saiura A, Yamaguchi T, Hata E, et al. (2006) Surgical resection of pulmonary metastases from colorectal cancer: Four favourable prognostic factors. *Jpn J Clin Oncol* 36(10): 643-648.
 36. Watanabe K, Nagai K, Kobayashi A, Sugito M, Saito N (2009) Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. *Br J Surg* 96(9): 1058-1065.
 37. Lo CK, Chu CSH, Zhu T, Chung C, Ming K, et al. (2007) Pulmonary resection for metastases from colorectal cancer. *Surg Pract* 11: 147-153.
 38. Carvajal C, Facundo H, Puerto P, Carreño J, Beltrán R, et al. (2022) Lung Metastasectomy from Colorectal Cancer, 10-year Experience in a South American Cancer Center. *Front Surg* 9: 913678.
 39. Chen F, Hanaoka N, Sato K, Fujinaga T, Sonobe M, et al. (2009) Prognostic factors of pulmonary metastasectomy for colorectal carcinomas. *World J Surg* 33(3): 505-511.
 40. Fukada M, Matsuhashi N, Takahashi T, Tanaka Y, Okumura N, et al. (2020) Prognostic factors in pulmonary metastasectomy and efficacy of repeat pulmonary metastasectomy from colorectal cancer. *World J Surg Oncol* 18(1): 314.
 41. Hamaji M, Cassivi SD, Shen KR, Allen MS, Nichols FC, et al. (2012) Is lymph node dissection required in pulmonary metastasectomy for colorectal adenocarcinoma? *Ann Thorac Surg* 94(6): 1796-1800.
 42. Hirosawa T, Itabashi M, Ohnuki T, Yamaguchi N, Sugihara K, et al. (2013) Prognostic factors in patients undergoing complete resection of pulmonary metastases of colorectal cancer: A multi-institutional cumulative follow-up study. *Surg Today* 43(5): 494-499.
 43. Hofmann HS, Doblinger C, Szoke T, Grosser C, Potzger T, et al. (2019) Influence of primary lymph node status of colorectal cancer on the development of pulmonary metastases and thoracic lymph node metastases. *Chirurg* 90(5): 403-410.
 44. Hwang MR, Park JW, Kim DY, Chang HJ, Kim SY, et al. (2010) Early intrapulmonary recurrence after pulmonary metastasectomy related to colorectal cancer. *Ann Thorac Surg* 90(2): 398-404.
 45. Ihn MH, Kim DW, Cho S, Oh HK, Jheon S, et al. (2017) Curative Resection for Metachronous Pulmonary Metastases from Colorectal Cancer: Analysis of Survival Rates and Prognostic Factors. *Cancer Res Treat* 49(1): 104-115.
 46. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, et al. (2013) Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: A retrospective analysis *Ann Surg* 257(6): 1059-1064.
 47. Iizasa T, Suzuki M, Yoshida S, Motohashi S, Yasufuku K, et al. (2006) Prediction of prognosis and surgical indications for pulmonary metastasectomy from colorectal cancer. *Ann Thorac Surg* 82(1): 254-260.
 48. Ike H, Shimada H, Ohki S, Togo S, Yamaguchi S, et al. (2002) Results of aggressive resection of lung metastases from colorectal carcinoma detected by intensive follow-up. *Dis Colon Rectum* 45(4): 468-473.

49. Jarabo JR, Fernandez E, Calatayud J, Gómez AM, Fernández C, et al. (2011) More than one pulmonary resections or combined lung-liver resection in 79 patients with metastatic colorectal carcinoma. *J Surg Oncol* 104(7): 781- 786.
50. Liu T, Chang W, Wang H, Lin Q, Wei Y, et al. (2021) Anatomical Resection Improves Disease-Free Survival After Lung Metastasectomy of Colorectal Cancer. *Cancer Manag Res* 13: 9429-9437.
51. Nanji S, Karim S, Tang E, Brennan K, McGuire A, et al. (2018) Pulmonary metastasectomy for colorectal cancer: predictors of survival in routine surgical practice. *Ann Thorac Surg* 05(6): 1605-1612.
52. Rapicetta C, Lococo F, Davini F, Carleo F, Kauppi J, et al. (2019) Is Adjuvant Chemotherapy Worthwhile After Radical Resection for Single Lung Metastasis From Colorectal Cancer? A Multicentric Analysis Evaluating the Risk of Recurrence. *Front Oncol* 9: 763.
53. Riquet M, Foucault C, Cazes A, Mitry E, Dujon A, et al. (2010) Pulmonary resection for metastases of colorectal adenocarcinoma. *Ann Thorac Surg* 89(2): 375-380.
54. Saito Y, Omiya H, Kohno K, Kobayashi T, Itoi K, et al. (2002) Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. *J Thorac Cardiovasc Surg* 124(5): 1007-1013.
55. Sclafani F, Incarbone M, Rimassa L, Personeni N, Giordano L, et al. (2013) The role of hepatic metastases and pulmonary tumor burden in predicting survival after complete pulmonary resection for colorectal cancer. *J Thorac Cardiovasc Surg* 145(1): 97-103.
56. Sun F, Chen L, Shi M, Yang X, Li M, et al. (2017) Prognosis of video-assisted thoracoscopic pulmonary metastasectomy in patients with colorectal cancer lung metastases: An analysis of 154 cases. *Int J Colorectal Dis*. 32(6): 897-905.
57. Tamura M, Oda M, Tsunozuka Y, Kawakami K, Watanabe G (2004) Vascular endothelial growth factor expression in metastatic pulmonary tumor from colorectal carcinoma: utility as a prognostic factor. *J Thorac Cardiovasc Surg* 128(4): 517-522.
58. Yang YH, Park SY, Kim HE, Park BJ, Lee CY, et al. (2021) Effects of mediastinal lymph node dissection in colorectal cancer-related pulmonary metastasectomy. *Thorac Cancer* 12: 3248-3254.
59. Yedibela S, Klein P, Feuchter K, Meyer T, Papadopoulos T, et al. (2006) Surgical management of pulmonary metastases from colorectal cancer in 153 patients. *Ann Surg Oncol* 13(11): 1538-1544.
60. Zampino MG, Maisonneuve P, Ravenda PS, Magni E, Casiraghi M, et al. (2014) Lung metastases from colorectal cancer: Analysis of prognostic factors in a single institution study. *Ann Thorac Surg* 98(4): 1238-1245.
61. Ziranu P, Ferrari PA, Guerrera F, Bertoglio P, Tamburrini A, et al. (2023) Clinical score for colorectal cancer patients with lung-limited metastases undergoing surgical resection: Meta-Lung Score. *Lung Cancer*. 184: 107342.
62. Naruke T, Suemasu K, Ishikawa S (1978) Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg* 76(6): 833-839.
63. Menon A, Milton R, Thorpe JA, Papagiannopoulos K (2007) The value of videoassisted mediastinoscopy in pulmonary metastasectomy. *Eur J Cardio Thorac Surg* 32(2): 351-354.
64. Dziejdz D, Peryt A, Szolkowska M, Langfort R, Orłowski T (2016) Evaluation of the diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration for metastatic mediastinal tumors. *Endosc ultrasound* 5(3): 173-177.
65. Tertemiz KC, Alpaydin AO, Karacam V (2017) The role of endobronchial ultrasonography for mediastinal lymphadenopathy in cases with extrathoracic malignancy. *Surg Endosc* 31(7): 2829-2836.
66. Khalid S, Hegde P (2022) Interventional Pulmonology and Esophagus: Combined Endobronchial Ultrasound and Endoscopic Ultrasound for Mediastinal Staging. *Semin Respir Crit Care Med* 43(4): 583-592.
67. Guerrera F, Renaud S, Schaeffer M, Nigra V, Solidoro P, et al. (2017) Low accuracy of computed tomography and positron emission tomography to detect lung and lymph node metastases of colorectal cancer. *Ann Thorac Surg* 104(4): 1194-1199.
68. Londero F, Morelli A, Parise O, Grossi W, Crestale S, et al. (2019) Lymphadenectomy during pulmonary metastasectomy: impact on survival and recurrence. *J Surg Oncol* 120(4): 768-778.

