Editorial

Personalized surgery for the management of pulmonary metastasis

Jean Yannis Perentes, Matthieu Zellweger, Michel Gonzalez

Service of Thoracic Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Correspondence to: Michel Gonzalez, MD. Division of Thoracic Surgery, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Email: Michel.Gonzalez@chuv.ch.

Provenance: This is an invited Editorial commissioned by the Section Editor Laura Chiara Guglielmetti (Cantonal Hospital Winterthur, Kantonsspital Winterthur, Switzerland).

Comment on: Welter S, Arfanis E, Christoph D, *et al.* Growth patterns of pulmonary metastases: should we adjust resection techniques to primary histology and size? Eur J Cardiothorac Surg 2017;52:39-46.

Submitted Nov 22, 2017. Accepted for publication Dec 04, 2017.
doi: 10.21037/jtd.2017.12.45
View this article at: http://dx.doi.org/10.21037/jtd.2017.12.45

Since the first report of pulmonary metastasectomy for colorectal cancer (CRC) by Blalock in 1946, many surgical adjustments have been suggested (1). Over the past years, growing evidence has shown that a subset of patients with pulmonary metastases (PMs) may benefit from a curative resection, provided some strict criteria are met (2,3). These included that all PMs are technically resectable; the patient can tolerate pulmonary resection; the primary tumor site is controlled; and no extra-thoracic lesion is detectable. Several retrospective studies have suggested an increased survival for patients who underwent complete resection of lung metastases in comparison to retrospective series of patients who did not benefit from surgery (4). Thus, surgical resection of PMs is nowadays widely offered to this group of patients, although the prospective randomized trial comparing pulmonary metastasectomy with chemotherapy or observation alone is currently ongoing and should provide a definitive answer (5).

The main goal of the surgical resection has traditionally been to obtain histological confirmation of metastatic disease while performing a complete resection of all detectable lesions to increase the patient's chance to survive and be cured. Recently, the development of personalized oncology has also redefined the role of surgery as a provider of metastatic tissue that can be analyzed and for which biomarker shifts or resistance patterns can be found. This ultimately can help tailor the treatment regimens such as targeted therapy or immunotherapy and offer better patient outcome (6). These patients are generally discussed in a multidisciplinary board? For best surgical and oncological management decision making.

Extension of the resection

The complete resection of all metastatic lesions has been described as the single most convincing prognostic factor of survival for patients with PMs (7). Based on the International Registry of Lung Metastases that includes 5,206 patients treated for PMs from various centers, complete resection could be achieved in 88% of patients, with 5-year survival rates at 36% in patients with complete resection compared to 13% in patients with incomplete resection (8). Similar results reported by other groups supported the idea that pulmonary metastasectomy offered a survival advantage when complete resection was achievable (9). This is especially convincing since these results collate reports from different clinics with different surgical approaches. Furthermore, the type of primary tumor was considered as an important prognostic factor with better survival in CRC than melanoma. Finally, surgical decision making is also based on the reports from several studies in CRC for example where four important prognostic factors of poorer survival where identified including (I) short disease-free interval between colonic tumor and lung metastasis occurrence; (II) elevated pre-thoracotomy carcinoma embryonic antigen (CEA) level; (III) metastatic hilar or mediastinal lymph node

involvement; (IV) multiple PMs (10).

PMs may have various origins, histological characteristics, local growth properties and size. The surgeon must also decide how to adjust the resection method and surgical technique to the type of PM. Furthermore, modern surgical techniques [video-assisted thoracoscopic surgery (VATS) approach, laser resection] offer new approaches to achieve resection with a proper safety margin.

In their recent study, Welter *et al.*, have studied the outcome of surgically managed PM patients according to their histology and invasive patters in the parenchyma (11). They found that PMs have local growth patterns that are associated with their histology. For example, PMs from sarcoma were associated with pleural infiltration but low incidence of lymphangitic spread and tended to grow along connective tissue borders. CRC metastases showed the highest rate of interstitial spread and the highest rate of aerogenous spread of floating cancer cell clusters. Melanoma metastases showed no pleural invasion, but an increased probability of perivascular growth and high incidence of lymphangitic spread. Renal carcinoma metastasis demonstrated mostly lymphangitic spread. In addition, the authors identify that aggressive patterns of growth were significantly associated with increased PM size. For example, local intrapulmonary recurrence was significantly more common in case of interstitial growth and pleural penetration as well as with metastasis of >5 mm and safety margins <7 mm. The authors recommend to linearly increase resection margins with increasing size of PMs; to resect CRC and epithelial PMs with a large circular resection margin; to use broad lateral margins and non-anatomical resection for sarcoma PMs; to use anatomical resections to remove PMs, lymphangitis and intrapulmonary lymph nodes in case of renal cell carcinoma PMs.

These results are of high interest in the context of achieving a complete resection of all PMs. Most of the PMs are generally located at the periphery of the lung and easily accessible to non-anatomical resections (considered the standard technique) (12). In this situation, wedge resection is generally performed using standard stapler, which gives clear surgical margins and efficient aerostasis. The drawback of the stapler technique is that more healthy lung tissue is sacrificed, especially when the metastasis lie farther towards the lung's center. Both the laser and the monopolar cutter allow removal of lung metastases by sparing as much healthy lung parenchyma as possible. In CRC patients, conflicting results have been reported for this type of resection: some authors report better prognosis in patients undergoing wedge resection than in those treated with anatomical resection (13). However Lin *et al.* reported better survival for patients undergoing major resection in CRC (14). Recently, the Spanish Group for Surgery of Lung Metastases from Colorectal Carcinoma (GECMP-CCR) reported results on 104 patients with CRC PMs treated with major anatomical resection and 418 (80.1%) with lesser resections (15). The overall DSS and DFS were 55 and 28.3 months in favor of major resection. These results suggest that anatomical resection is more likely to eliminate the spread of hidden hematogenous/lymphogenous metastasis of CRC in the same lobe and hilar lymph nodes. Shiono *et al.* have shown that the morphological features of aerogenous spread with floating cancer cell clusters and vascular invasion at the metastatic site are prognostic factors for CRC patients who have undergone pulmonary metastasectomy (16). In the light of these results, anatomical resection could be proposed in case of large, central metastatic lesions of CRC origin. However, for peripheral lesions, anatomic resection does not appear reasonable. Larger wedge safety margins could however be suggested in these cases.

Surgical approach

VATS in combination with pre-operative thin slice CT imaging is gaining progressive interest for pulmonary metastasectomy. Some of the advantages of the VATS approach are decreased post-operative pain, smaller incisions, better visualization of the pleural cavity less surgical morbidity, decreased length of hospitalization, fewer adhesion in cases of redo metastasectomy, shorter interval between surgery and adjuvant therapy with better treatment compliance (17). In addition, most PMs are generally located in the periphery of the lung, and can be easily resected by VATS (18). However, these advantages conflict with the inability to practice a bimanual palpation of the entire lung with the risk of missing detectable lesions not visible on pre-operative radiological exams.

Marron *et al.* reported the agreement between computed tomography and pathologic nodule counts in CRC PMs (19). They focused on patients who underwent thoracotomy and bimanual palpation. Solitary nodules were present in 73% of patients with radiological and pathological agreement of 95%, suggesting that the VATS approach was suitable for this group of patients. In spite of the absence of prospective randomized studies comparing thoracoscopic approach to open bimanual thoracotomy, several surgical

series have demonstrated comparable survival between the two approaches for patients with less than 3 lesions (17). We recently published a consecutive series of 77 patients undergoing VATS metastasectomy (20). Complete resection was obtained in all patients by wedge in 93% or anatomical resection in 7%. Overall survival (54% at 5 years) and pulmonary recurrence rate (30%) were comparable to those reported from traditional open surgical series. Interestingly, recurrent disease in the operated lung was not frequent (10%) and could be resected by a redo VATS procedure in the majority of patients. Thus, a less invasive approach seems superior to the traditional open approach in patients with solitary metastasis.

Mediastinal lymph node dissection

During pulmonary metastasectomy, a positive lymph node involvement affects survival. However, the real impact of systematic lymph node dissection during pulmonary metastasectomy has not been demonstrated. The incidence of mediastinal LN metastases with PMs has been reported to be between 12% and 32% among various tumor types. The study of Welter *et al.* emphasizes the role of lymph node dissection during lung metastasectomy, particularly in case of CRC or renal carcinoma as they present significantly more lymphangitic spread (11). Hamaji *et al.* reported on 518 patients operated for lung metastasectomy of CRC. Median survivals for the no lymph node dissection group, negative lymph node group, and positive lymph node group were 52, 58.5, and 34 months, respectively (21). In the Spanish prospective registry of CRC PM, lymph node dissection was realized in 48% of patients with 10% of lymph node involvement (22). The 5-year survival was best for patients with negative lymph node invasion, worst for those with positive lymph node invasion, and in-between for those with unknown lymph node status because they were not resected. These results suggest the important role of lymph node assessment during CRC metastasectomy for prognosis and possibly for increased survival rate. Seebacher *et al.* reported recently 256 procedure of pulmonary metastasectomy with lymph node sampling or complete dissection (23). Interestingly, unexpected LN involvement was found in 35% of patients with breast cancer, in 9.2% with CRC, and in 20.8% with renal cell carcinoma. In addition, they did not find statistical difference on 5-year survival between LN sampling *vs.* radical removal. Metastatic lymph node involvement in renal cancer has been reported in up to 46% of patients. Recently, Kudelin *et al.* reported a median OS of 72 months for pN0 patients, 51 months for pN1 and 36 months for pN2 patients without significant difference (P=0.2) (24). Central localization of PMs may also be associated with increase rate of lymph node involvement. Although survival benefit after lymph node dissection is unclear, most authors consider that complete mediastinal lymphadenectomy or sampling should be recommended during pulmonary metastasectomy to achieve accurate staging and guide additional chemotherapy.

Perspective

The paper from Welter *et al.* offers a new view on the management of PMs by surgery. To our mind, it first emphasizes the need to discuss the management of PMs on an individual basis in an interdisciplinary context, in order to offer the best possible oncological and surgical approach. This paper also reinforces the notion of personalization of surgery that should be tailored to the tumor type in terms of technique (VATS *vs.* thoracotomy) and resection extension (wedge *vs.* anatomical resection; size of safety margin; lymph node dissection and localization). These various elements are also correlated to the histological profile of the primary tumor offering a useful, albeit rough, framework for initial decision-making: VATS for solitary metastasis, wedge resection and larger safety margin with lymph node dissection for PMs with a renal or colorectal origin; thoracotomy for multiple PMs, especially if their origin is a sarcoma; anatomical resection and lymph node dissection for large, central PMs. Of course, such a framework is tentative at best and needs to be supported by more studies, but the trend towards more evidence-based personalized surgery will without a doubt highly benefit patients. A specific TNM classification for PMs could be an adjunct to better characterize the profile of the metastatic patients and simplify the decision algorithm (25). In both instances, this promises exciting improvements in surgical management of PMs.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Gonzalez M, Ris HB, Krueger T, et al. Colorectal cancer and thoracic surgeons: close encounters of the third kind. Expert Rev Anticancer Ther 2012;12:495-503.
2. Rusch VW. Pulmonary metastasectomy. Current indications. Chest 1995;107:322S-31S.
3. Pastorino U. Lung metastasectomy: why, when, how. Crit Rev Oncol Hematol 1997;26:137-45.
4. Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". J Thorac Oncol 2011;6:1373-8.
5. Treasure T, Fallowfield L, Lees B, et al. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. Thorax 2012;67:185-7.
6. Moorcraft SY, Jones T, Walker BA, et al. Molecular profiling of colorectal pulmonary metastases and primary tumours: implications for targeted treatment. Oncotarget 2017;8:64999-5008.
7. Schirren J, Schirren M, Lampl L, et al. Surgery for pulmonary metastases: quo vadis? Eur J Cardiothorac Surg 2017;51:408-10.
8. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37-49.
9. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg 2007;84:324-38.
10. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2013;20:572-9.
11. Welter S, Arfanis E, Christoph D, et al. Growth patterns of pulmonary metastases: should we adjust resection techniques to primary histology and size? Eur J Cardiothorac Surg 2017;52:39-46.
12. Erhunmwunsee L, D'Amico TA. Surgical management of pulmonary metastases. Ann Thorac Surg 2009;88:2052-60.
13. Vogelsang H, Haas S, Hierholzer C, et al. Factors influencing survival after resection of pulmonary metastases from colorectal cancer. Br J Surg 2004;91:1066-71.
14. Lin BR, Chang TC, Lee YC, et al. Pulmonary resection for colorectal cancer metastases: duration between cancer onset and lung metastasis as an important prognostic factor. Ann Surg Oncol 2009;16:1026-32.
15. Hernández J, Molins L, Fibla JJ, et al. Role of major resection in pulmonary metastasectomy for colorectal cancer in the Spanish prospective multicenter study (GECMP-CCR). Ann Oncol 2016;27:850-5.
16. Shiono S, Ishii G, Nagai K, et al. Predictive factors for local recurrence of resected colorectal lung metastases. Ann Thorac Surg 2005;80:1040-5.
17. Perentes JY, Krueger T, Lovis A, et al. Thoracoscopic resection of pulmonary metastasis: current practice and results. Crit Rev Oncol Hematol 2015;95:105-13.
18. Bellier J, Perentes JY, Abdelnour-Berchtold E, et al. A plea for thoracoscopic resection of solitary pulmonary nodule in cancer patients. Surg Endosc 2017;31:4705-10.
19. Marron MC, Lora D, Gamez P, et al. Agreement Between Computed Tomography and Pathologic Nodule Counts in Colorectal Lung Metastases. Ann Thorac Surg 2016;101:259-65.
20. Abdelnour-Berchtold E, Perentes JY, Ris HB, et al. Survival and Local Recurrence After Video-Assisted Thoracoscopic Lung Metastasectomy. World J Surg 2016;40:373-9.
21. Hamaji M, Cassivi SD, Shen KR, et al. Is lymph node dissection required in pulmonary metastasectomy for colorectal adenocarcinoma? Ann Thorac Surg 2012;94:1796-800.
22. Call S, Rami-Porta R, Embun R, et al. Impact of inappropriate lymphadenectomy on lung metastasectomy for patients with metastatic colorectal cancer. Surg Today 2016;46:471-8.
23. Seebacher G, Decker S, Fischer JR, et al. Unexpected lymph node disease in resections for pulmonary metastases. Ann Thorac Surg 2015;99:231-6.
24. Kudelin N, Bolukbas S, Eberlein M, et al. Metastasectomy with standardized lymph node dissection for metastatic renal cell carcinoma: an 11-year single-center experience. Ann Thorac Surg 2013;96:265-70; discussion 70-1.
25. Migliore M, Gonzalez M. Looking forward lung metastasectomy-do we need a staging system for lung metastases? Ann Transl Med 2016;4:124.

Cite this article as: Perentes JY, Zellweger M, Gonzalez M. Personalized surgery for the management of pulmonary metastasis. J Thorac Dis 2018;10(1):52-55. doi: 10.21037/jtd.2017.12.45

