Review
Article

Pulmonary Metastasectomy for Germ Cell Tumors

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Germ cell tumors (GCTs) are the most common malignancy among young men in the United States. Although prognosis is favorable and response to cisplatin-based chemotherapy regimens is good, 10%–20% of patients with thoracic metastases require surgical management following completion of chemotherapy. Pulmonary metastasectomy (PM) has been employed for GCT patients with lung metastases for several decades. Outcomes have been excellent thus far. However, there have been no randomized controlled trials of PM in GCT and, as new surgical techniques are developed, there is variability in management. This article reviews the existing data on current management of pulmonary metastases in GCT, with attention paid to timing of surgery, surgical approaches, and complications.

Keywords: pulmonary metastasectomy, metastatic germ cell tumor, germ cell tumor, lung metastases, secondary lung cancer

Introduction

Although rare in the general population, germ cell tumors (GCTs) are the most common malignancy in men in the United States between the ages of 15 and 44 years.[1] Despite excellent response to cisplatin-based chemotherapy regimens, 10%–20% of patients with thoracic metastases will require either pulmonary metastasectomy

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(PM), mediastinal lymph node dissection, or both.[2] PM has been employed for such patients with excellent results and has become increasingly popular since the 1980s.

As is the case with PM for other primary cancers, no randomized controlled trials have been conducted for PM in metastatic GCT because of the small series of patients at any single site and the difficulty in conducting large clinical trials in this field. Consequently, surgical planning and decision-making rely on data collected from retrospective reviews. Given the possibility of achieving excellent outcomes for GCT patients with successful metastasectomy, it is important to evaluate the existing data. The purpose of this review is to examine the current surgical practice for PM in GCT, with special attention paid to the timing of metastasectomy, type of incision and resection most commonly used, and directions for future improvement.

Methods

Studies were identified by searching the PubMed, Cochrane, Scopus, and Embase databases using the keywords "germ cell tumor," "metastasectomy," and "pulmonary metastasectomy." To reflect the most contemporary practices, studies published before 1990 were

Table 1 Indications and contraindications for pulmonary metastasectomy in GCT patients

Indications	Contraindications
Completion of cisplatin-based chemotherapy + stabilization of tumor markers with residual thoracic disease	Rapidly progressive disease with increasing tumor marker levels
Lack of disease response or only partial response to standard chemotherapy	Clinical status prohibiting surgery
Need for identification of tumor histology (i.e., viable tumor vs. necrosis/fibrosis)	
Palliation of rapidly enlarging mass	

GCT: germ cell tumors

excluded, as were those with fewer than 10 GCT patients. Studies with a pediatric population were excluded to assess a representative adult GCT population, which consists primarily of young adult men. All other English-language studies relevant to our topic were included.

Indications for PM

International guidelines currently recommend PM in patients with metastatic testicular GCTs who have completed standard cisplatin-based chemotherapy and have normalization of serum tumor markers with residual thoracic disease.[3] Other indications include disease that does not respond to chemotherapy, partial response to chemotherapy or recurrence while on chemotherapy, need for identification of viable tumor versus fibrosis/necrosis, and palliative resection of enlarging masses (**Table 1**).[4] Studies have concluded that multiple pulmonary lesions and persistently elevated tumor markers should not preclude surgery, and repeat PM is a viable option.[5,6]

Surgical Approach

Surgical considerations for PM in GCT often mirror those for metastasectomy in general. Multiple studies have demonstrated the safety and efficacy of the procedure in GCT patients, with mortality ranging from 0.0% to 2.0%.[7–15] Metastasectomy is very beneficial for GCT patients with residual thoracic disease and survival is among the highest in the general metastasectomy population, with the 5-year survival ranging from 42% to 95%.[7–15]

Improved prognosis for GCT patients post-metastasectomy is associated with complete (R0) resection, lower tumor markers prior to surgery, lack of extrapulmonary metastases, fibrosis or mature teratoma found on pathology from resected lesions (as opposed to viable tumor), and longer disease-free interval (DFI).[7,10,12–19] Many studies have shown that complete resection is the best positive prognostic indicator, and repeat metastasectomies are a safe and viable option.[7,10,13–18,20,21] Additionally, it has been shown that patients with viable malignant cells found on pathology have a worse prognosis than those with fibrosis, necrosis, or mature teratoma, although active metastases are less commonly found.[15,18] Interestingly, in bilateral metastases, the histology of tumors in one lung do not necessarily predict the histology of tumors in the other, indicating that bilateral disease requires bilateral resection.[14,22] Thus, evidence for complete resection is strong. However, specific recommendations regarding timing of metastasectomy, type of incision, best type of resection, and appropriate margins are less clearly defined. Here, we review the available data.

Timing of metastasectomy after initial diagnosis

There are no definitive guidelines regarding when metastasectomy should be undertaken in patients with GCT. In the general metastasectomy population, most studies favor operating as soon as possible after diagnosis of thoracic disease.[23–27] In the GCT population, PM is most often done following completion of chemotherapy with control of the primary tumor and extrathoracic disease. It is generally recommended to wait 3–6 weeks after the last cycle of chemotherapy to best optimize patients for surgery and reduce wound healing complications.[14,20,28] For patients with recurrent disease, multiple studies have shown that repeat PM can prolong survival.[6,29]

Type of incision

With the growing popularity of minimally invasive surgery such as video-assisted thoracic surgery (VATS) since the 1990s and now robotic surgery, the best surgical approach for PM has been debated. Minimally

Table 2 Summary of selected series

Author, year	No. of GCT patients	Type of incision	Type of resection	Survival	Perioperative mortality
Kulkarni, 1991[11]	67	Thor: 15	Wedge: 13 Lobectomy: 1 Pneumonectomy: 1	N/A	4.0% (for all procedures)
Tóth, 1993[28]	42	Uni thor: 27 Clamshell: 1 Bilat thor: 1 Sternotomy: 15	Wedge: 30 Lobectomy: 7	60% at 5 years	N/A
Gels, 1997[8]	31	Thor: 31 Sternotomy: 6 Clamshell: 1	Minimal resection: 6 Wedge: 24 Lobectomy: 1 Wedge + lobectomy: 1	86.8% at 5 years	0.0%
Cagini, 1998[7]	141	Uni thor: 66 Bilat thor: 15 Sternotomy: 13 Thoracoscopy: 1	Wedge: 86 Segmentectomy: 3 Lobectomy: 8 Pneumonectomy: 3	77% at 5 years,	2.0%
Liu, 1998[12]	157	Uni thor: 104 Sternotomy: 20 Clamshell: 22 Staged bilat thor: 11	Wedge: 141 Lobectomy: 14 Pneumonectomy: 2	68% at 5 years	0.6%
McGuire, 2003[18]	105	Thor: 130	N/A	Fibrosis: 96% at 2 years Teratoma: 82% Viable cancer: 25%	N/A
Kesler, 2005[9]	85	N/A	Wedge: 65 Segment/lobe: 24 Pneumonectomy: 14	42.3% at 5 years	3.7%
Pfannschmidt, 2006[13]	52	Thor: 69	Wedge: 53 Segmentectomy: 1 Lobectomy: 7 Pneumonectomy: 2 Other (laser, enucleation): 15	75.8% at 5 years	0.0%
Schnorrer, 2009[15]	63	Thor: 55 Sternotomy: 24	Wedge: 53 Lobectomy: 8 Bilobe: 1 Pneumonectomy: 1	67% at 8.88 years	1.2%
Besse, 2009[22]	71	Uni thor: 36 Bilat thor: 34 Sternotomy: 4	N/A	94% at 5 years	N/A
Schirren, 2011[14]	124	Thor: 144 Sternotomy: 33	Wedge: 173 Segmentectomy: 30 Laser: 29 Lobectomy: 8 Sleeve: 1	87% at 5 years	0.5%
Kikuchi, 2017[10]	32	N/A	Wedge: 23 Segment/lobe: 9	73% at 5 years	0.0%
Totals	970	Thoracotomy: 738 (84%) Sternotomy: 115 (13%) Clamshell: 24 (3%) VATS: 1 (0.1%)	Wedge: 661 (77%) Lobe/segment: 123 (14%) Pneumonectomy: 23 (3%) Other (laser, sleeve): 51 (6%)	42.3–94.0% at 5 years	0.0–2.0% 878

bilat: bilateral; GCT: germ cell tumor; Thor: thoracotomy; Uni: unilateral; VATS: video-assisted thoracic surgery

invasive surgery has the advantage of improved post-operative pain and pulmonary function.[30] However, there is concern that a minimally invasive approach results in incomplete resection of small lesions, as manual palpation of lung parenchyma is not possible with this method.[20,31–34] Some studies have shown that minimally invasive approach may be a viable option for patients with single, peripheral lesions and other-wise good prognosis.[35–37] As preoperative imaging techniques improve, smaller lesions may be detected and manual palpation may become less necessary. However, in the work of Margaritora et al., helical computed tomography (HCT) was more sensitive in detection of LM than high-resolution CT, but still missed lesions smaller than 6 mm in diameter.[31] For this reason, most surgeons still prefer to use an open approach. It should be noted that most of the afore-mentioned studies were conducted in the general metastasectomy population but are assumed to be applicable to GCT.

A summary of the most common surgical approaches used in PM for GCT is shown in **Table 2**. We identified 12 retrospective studies specifically focused on PM in GCT patients published between 1990 and 2018, with a total of 970 patients.[7–15,18,22,28] In that population, 84% of the metastasectomies performed were thoracotomies, 13% were median sternotomies, and 3% were done using the "clamshell" approach. Only 1% of patients under-went VATS. The decision of which approach to use is made based on tumor laterality, number, size, and anat-omy. In metastatic GCT, lung lesions are typically small and peripheral, and can be unilateral or bilateral.[20] Although minimally invasive approach is an attractive option, thoracotomy remains the most common approach by far.

Type of resection

In PM for GCT, as in the general population, wedge resection is the most commonly employed technique, accounting for 77% of the cases listed in **Table 2**. Wedge resection is ideal, given the ability to spare parenchyma, particularly in patients with numerous lesions. When dic-tated by anatomy, segmentectomy, lobectomy, and pneu-monectomy can be performed. In the case series published by Kesler et al., 16.5% of the metastasectomies done for GCT lung metastases were pneumonectomies.[9] This rate was higher than the overall rate of pneumonectomy in **Table 2** (3%). More extensive resections were neces-sary in this population due to more aggressive, high-risk

disease, with 19.4% of patients requiring removal of malignant disease from both the lung and mediastinum. Indications for pneumonectomy in this cohort included large extent of disease, or anatomically compromising location (i.e. involvement of great vessels or main stem bronchus).[9,38] Several studies have demonstrated no relationship between survival and the type of resection, but prognosis is impacted by high-risk disease factors such as greater than four intrathoracic metastases.[9,36]

Extent of resection

Complete resection of all detectable lung metastases is associated with better survival rates in both the GCT and general populations.[5,7,13,17,21,39–41] In the work of Pfannschmidt and colleagues, survival in GCT patients with incomplete resection was 28.6% versus 80.9% in those with complete resection. Several authors recom-mend removing nodules as small as 0.3–0.6 cm.[28,31,33] Prognosis is strongly associated with the histology of the resected masses. A finding of necrosis and fibrosis or mature teratoma is favorable while viable malignant cells on histopathology are associated with worse out-comes.[12,15,18,22] Besse and colleagues found a 95% con-cordance in pathologic findings between lungs in patients with bilateral metastases, suggesting that, if necrosis is found in one lung, small lesions in the contralateral lung may be monitored, rather than resected.[22]

For those patients with larger pulmonary lesions, or lesions in an anatomically compromising location, a more extensive resection can be warranted, with the goal of complete resection remaining paramount.[9,16,42] Although no randomized studies have been performed, there is evidence that extended resections, defined as pulmonary resection with *en bloc* resection of chest wall and/or other major structures, may be a viable approach for patients with large burden of disease, with 5-year survival of 25.4%–42.0%.[9,16,42] There has been no conclusive evidence to indicate that large nodules are associated with worse prognosis, although a higher number of metastases does seem to negatively impact survival.[19,43,44]

Margins

Recommendations for appropriate surgical margins in PM for GCT are not clearly defined. For metastasectomy in general, Rusch recommends a cone-shaped resection with 0.5–1.0 cm of normal lung tissue surrounding the lesion in all directions.[40] Others recommend a 1.0–2.0 cm margin.[19,45] These guiding principles also apply to PM in

patients with GCT; surgeons should aim for complete resection while preserving as much of the lung parenchyma as possible. However, there is not sufficient data to definitively define what is an adequate margin.

Postoperative complications

Although perioperative morbidity and mortality are low overall, complications do occur. Reported pulmonary complications include acute respiratory distress syndrome (ARDS), pneumonia, prolonged air and chyle leaks, atelectasis requiring bronchoscopy, and prolonged respiratory failure requiring mechanical ventilation.[9,46] Non-pulmonary complications include atrial fibrillation, non-pulmonary sepsis, and acute kidney injury.[46]

Patients treated with chemotherapeutic regimens containing bleomycin seem to comprise a population at higher risk of postoperative complications. Bleomycin, etoposide, and cisplatin (BEP) has historically been the standard treatment for those patients with high-risk GCT,[47] though recently, etoposide, ifosfamide and cisplatin (VIP) has become more common.[48] Exposure to bleomycin is independently associated with an increased risk of pulmonary toxicity.[46,47,49] Although a smaller study with short follow-up demonstrated equivalent survival after PM between patients treated with VIP versus those treated with BEP,[50] Ranganath et al. found that those who had been treated with bleomycin had higher rates of postoperative complications following metastasectomy, including ARDS and prolonged requirement for mechanical ventilation.[48] This is an important consideration in an already higher-risk subgroup and supports the preference for use of VIP.

Conclusion

Patients with GCTs achieve excellent survival. In patients with residual intrathoracic disease after completion of chemotherapy, metastasectomy is safe and effective and can improve long-term outcomes,[1,2,7,9–12,15,17–19,22,28,29,43,51] with survival rates approaching 90% at 5 years in some studies.[22] Although there are currently no randomized control studies on the subject, the studies we reviewed demonstrated certain trends in the community. PM should be done promptly after completion of chemotherapy, with an appropriate window of approximately 4 weeks for patient optimization. Those with multiple nodules and other poor prognostic indicators should not be excluded, as they may still benefit from PM.

The most common surgical approach remains thoracotomy, despite increasing use of minimally invasive surgery. Given the small size of most GCT lung metastases, the lack of ability to manually palpate lung parenchyma with a minimally invasive approach remains problematic. Complete resection is important for survival, as is sparing of lung parenchyma. For these reasons, wedge resection remains the most commonly employed type of resection in PM for GCT. When indicated, lobectomy, segmentectomy, and pneumonectomy can also be done. It is generally agreed that margins should be in the 0.5–2.0 cm range. For patients with residual or recurrent disease, repeat metastasectomy may be of utility.

In summary, PM for patients with GCTs achieves better survival than PM for almost all other primary tumor histologies. Due to the nature of the disease and relatively small patient population, much of the data that exist is extrapolated from the general PM population or based on retrospective chart reviews. Large, randomized control trials are needed to more clearly elucidate best surgical practices for this unique group of patients; however, they are unlikely given the small number of patients at any single institution to gather traction for meaningful data.

Disclosure Statement

References

1) Ghazarian AA, Trabert B, Devesa SS, et al. Recent trends in the incidence of testicular germ cell tumors in the United States. Andrology 2015; **3**: 13-8.
2) Kesler KA, Donohue JP. Combined urologic and thoracic approaches for advanced or disseminated testis cancer. Atlas of Urol Clin N Am 1999; **7**:79-94.
3) Krege S, Beyer J, Souchon R, et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. Eur Urol 2008; **53**: 497-513.
4) Johnston MDPM. Treatment of metastatic cancer. In: Devita VHS Jr, Rosenberg SA eds. Cancer, Principles and Practice of Oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2005; pp 2337-51.
5) Robert JH, Ambrogi V, Mermillod B, et al. Factors influencing long-term survival after lung metastasectomy. Ann Thorac Surg 1997; **63**: 777-84.

6) Stewart JR, Carey JA, Merrill WH, et al. Twenty years' experience with pulmonary metastasectomy. Am Surg 1992; **58**: 100-3.

7) Cagini L, Nicholson AG, Horwich A, et al. Thoracic metastasectomy for germ cell tumours: long term survival and prognostic factors. Ann Oncol 1998; **9**: 1185-91.

8) Gels ME, Hoekstra HJ, Sleijfer DT, et al. Thoracotomy for postchemotherapy resection of pulmonary residual tumor mass in patients with nonseminomatous testicular germ cell tumors: aggressive surgical resection is justified. Chest 1997; **112**: 967-73.

9) Kesler KA, Wilson JL, Cosgrove JA, et al. Surgical salvage therapy for malignant intrathoracic metastases from nonseminomatous germ cell cancer of testicular origin: analysis of a single-institution experience. J Thorac Cardiovasc Surg 2005; **130**: 408-15.

10) Kikuchi S, Sekine Y, Sugai K, et al. Salvage surgery for pulmonary metastases in patients with testicular germ cell tumors. J Thorac Oncol 2017; **12**: S2200.

11) Kulkarni RP, Reynolds KW, Newlands ES, et al. Cytoreductive surgery in disseminated non-seminomatous germ cell tumours of testis. Br J Surg 1991; **78**: 226-9.

12) Liu D, Abolhoda A, Burt ME, et al. Pulmonary metastasectomy for testicular germ cell tumors: a 28-year experience. Ann Thorac Surg 1998; **66**: 1709-14.

13) Pfannschmidt J, Zabeck H, Muley T, et al. Pulmonary metastasectomy following chemotherapy in patients with testicular tumors: experience in 52 patients. Thorac Cardiovasc Surg 2006; **54**: 484-8.

14) Schirren J, Trainer S, Eberlein M, et al. The role of residual tumor resection in the management of nonseminomatous germ cell cancer of testicular origin. Thorac Cardiovasc Surg 2012; **60**: 405-12.

15) Schnorrer M, Ondrus D, Vichova B, et al. Surgical treatment of pulmonary metastases in germ-cell testicular cancer patients–long-term results. Bratisl Lek Listy 2009; **110**: 620-2.

16) Casiraghi M, Maisonneuve P, Brambilla D, et al. The role of extended pulmonary metastasectomy. J Thorac Oncol 2015; **10**: 924-9.

17) Hendriks JM, Romijn S, Van Putte B, et al. Long-term results of surgical resection of lung metastases. Acta Chir Belg 2001; **101**: 267-72.

18) McGuire MS, Rabbani F, Mohseni H, et al. The role of thoracotomy in managing postchemotherapy residual thoracic masses in patients with nonseminomatous germ cell tumours. BJU Int 2003; **91**: 469-73.

19) 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.

20) Boffa DJ, Rusch VW. Surgical techniques for nonseminomatous germ cell tumors metastatic to the lung. Chest Surg Clin N Am 2002; **12**: 739-48.

21) Pfannschmidt J, Hoffmann H, Dienemann H. Thoracic metastasectomy for nonseminomatous germ cell tumors. J Thorac Oncol 2010; **5**: S182-S6.

22) Besse B, Grunenwald D, Fléchon A, et al. Nonseminomatous germ cell tumors: assessing the need for postchemotherapy contralateral pulmonary resection in patients with ipsilateral complete necrosis. J Thorac Cardiovasc Surg 2009; **137**: 448-52.

23) Detterbeck FC, Grodzki T, Gleeson F, et al. Imaging requirements in the practice of pulmonary metastasectomy. J Thorac Oncol 2010; **5**: S134-S9.

24) Krüger M, Schmitto JD, Wiegmann B, et al. Optimal timing of pulmonary metastasectomy–is a delayed operation beneficial or counterproductive? Eur J Surg Oncol 2014; **40**: 1049-55.

25) Kuijer A, Furnée EJ, Smakman N. Combined surgery for primary colorectal cancer and synchronous pulmonary metastasis: a pilot experience in two patients. Eur J Gastroenterol Hepatol 2016; **28**: 15-9.

26) Mountain CF, McMurtrey MJ, Hermes KE. Surgery for pulmonary metastasis: a 20-year experience. Ann Thorac Surg 1984; **38**: 323-30.

27) van Halteren HK, van Geel AN, Hart AA, et al. Pulmonary resection for metastases of colorectal origin. Chest 1995; **107**: 1526-31.

28) Tóth L, Bodrogi I, Baki M, et al. Thoracic surgery of testicular cancer patients. Eur J Surg Oncol 1993; **19**: 609-13.

29) Mizuno T, Taniguchi T, Usami N, et al. Histological impact of primary tumor on indication of repeated pulmonary metastasectomy. J Thorac Oncol 2013; **8**: S651.

30) Landreneau RJ, Hazelrigg SR, Mack MJ, et al. Postoperative pain-related morbidity: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 1993; **56**: 1285-9.

31) Margaritora S, Porziella V, D'Andrilli A, et al. Pulmonary metastases: Can accurate radiological evaluation avoid thoracotomic approach? Eur J Cardio-thorac Surg 2002; **21**: 1111-4.

32) McCormack PM, Bains MS, Begg CB, et al. Role of video-assisted thoracic surgery in the treatment of pulmonary metastases: results of a prospective trial. Ann Thorac Surg 1996; **62**: 213-6; discussion 6-7.

33) Saisho S, Nakata M, Sawada S, et al. Evaluation of video-assisted thoracoscopic surgery for pulmonary metastases: 11-years of experience. Surg Endosc 2009; **23**: 55-61.

34) Eckardt J, Licht PB. Thoracoscopic versus open pulmonary metastasectomy: a prospective, sequentially controlled study. Chest 2012; **142**: 1598-602.

35) Lin JC, Wiechmann RJ, Szwerc MF, et al. Diagnostic and therapeutic video-assisted thoracic surgery resection of pulmonary metastases. Surgery 1999; **126**: 636-41; discussion 41-2.

36) Lo Faso F, Solaini L, Lembo R, et al. Thoracoscopic lung metastasectomies: a 10-year, single-center experience. Surg Endosc 2013; **27**: 1938-44.

37) Mutsaerts EL, Zoetmulder FA, Meijer S, et al. Outcome of thoracoscopic pulmonary metastasectomy evaluated by confirmatory thoracotomy. Ann Thorac Surg 2001; **72**: 230-3.

38) Kesler KA. Surgical techniques for testicular nonseminomatous germ cell tumors metastatic to the mediastinum. Chest Surg Clin N Am 2002; **12**: 749-68.

39) 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.

40) Rusch VW. Pulmonary metastasectomy. Current indications. Chest 1995; **107**: 322S-331S.

41) Rusch VW. Surgical techniques for pulmonary metastasectomy. Semin Thorac Cardiovasc Surg 2002; **14**: 4-9.

42) Putnam JB, Suell DM, Natarajan G, et al. Extended resection of pulmonary metastases: is the risk justified? Ann Thorac Surg 1993; **55**: 1440-6.

43) Corona-Cruz JF, Domínguez-Parra LM, Saavedra-Pérez D, et al. Lung metastasectomy: long-term outcomes in an 18-year cohort from a single center. Surg Oncol 2012; **21**: 237-44.

44) Friedel G, Pastorino U, Buyse M, et al. Resection of lung metastases: Long-term results and prognostic analysis based on 5206 cases—The International Registry of Lung Metastases. Zentralbl Chir 1999; **124**: 96-103.

45) Martini N, McCormack PM. Evolution of the surgical management of pulmonary metastases. Chest Surg Clin N Am 1998; **8**: 13-27.

46) Andrade RS, Kesler KA, Wilson JL, et al. Short- and long-term outcomes after large pulmonary resection for germ cell tumors after bleomycin-combination chemotherapy. Ann Thorac Surg 2004; **78**: 1224-8; discussion 8-9.

47) Loehrer PJ, Johnson D, Elson P, et al. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern cooperative oncology group trial. J Clin Oncol 1995; **13**: 470-6.

48) Ranganath P, Kesler KA, Einhorn LH. Perioperative morbidity and mortality associated with bleomycin in primary mediastinal nonseminomatous germ cell tumor. J Clin Oncol 2016; **34**: 4445-6.

49) O'Sullivan JM, Huddart RA, Norman AR, et al. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol 2003; **14**: 91-6.

50) Hinton S, Catalano PJ, Einhorn LH, et al. Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. Cancer 2003; **97**: 1869-75.

51) Yaftian N, Antippa P, Cheung F, et al. Long-term outcomes of pulmonary metastasectomy: a 12-year dual centre experience. J Thorac Oncol 2018; **13**: S990-S1.