



Preoperative evaluation and indications for pulmonary metastasectomy

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Abstract: Pulmonary metastasectomy (PM) is an established treatment that can provide improved long-term survival for patients with metastatic tumor(s) in the lung. In the current era, where treatment options other than PM such as stereotactic body radiation therapy (SBRT), immunotherapy, and molecular-targeted therapy are available, thoracic surgeons should review the approach to the preoperative evaluation and the indications. Preoperative evaluation consists of history and physical examinations, physiological tests, and radiological examinations. Radiological examinations serve to identify the differential diagnosis of the pulmonary nodules, evaluate their precise number, location, and features, and search for extra thoracic metastases. The indication of PM should be considered from both physiological and oncological points of view. The general criteria for PM are as follows; (I) the patient has a good general condition, (II) the primary malignancy is controlled, (III) there is no other extrapulmonary metastases, and (IV) the pulmonary lesion(s) are thought to be completely resectable. In addition to the general eligibility criteria of PM, prognostic factors of each tumor type should be considered when deciding the indication for PM. When patients have multiple poor prognostic factors and/or a short disease-free interval (DFI), thoracic surgeons should not hesitate to observe the patient for a certain period before deciding on the indication for PM. A multidisciplinary discussion is needed in order to decide the indication for PM.

Keywords: Pulmonary metastasectomy (PM); indication; radiological examinations; prognostic factor

Submitted Nov 22, 2019. Accepted for publication Dec 04, 2020.

doi: 10.21037/jtd-19-3791

View this article at: <http://dx.doi.org/10.21037/jtd-19-3791>

Introduction

Ever since Barney and Churchill described the first successful pulmonary metastasectomy (PM) case in 1939, PM has become established as a viable treatment that provides improved long-term survival (1,2). However, there has been no evidence based on randomized trials to indicate that PM is indeed the best treatment for patients with pulmonary metastases. Although many observational studies have presented favorable results with PM, these studies

were limited by bias, such as patient selection bias (3).

Over the past two decades, remarkable advancements in drug therapy for various cancers have been made (4). In terms of local control of pulmonary metastases, stereotactic body radiation therapy (SBRT) has recently become widely performed as it was found to provide a favorable local control rate (5).

With this, thoracic surgeons are recommended to review their approach to the preoperative evaluation and the indications.

Preoperative evaluation

History and physical examinations

The basics of preoperative evaluation include taking a patient's medical history and performing a physical examination. Detailed information on the treatment history for primary tumors, including the treatment mode, tumor stage and histologic type, time interval between the treatment for primary tumor and the detection of pulmonary metastases, presence of other metastatic sites, and the regimen and timing of chemotherapy, is necessary, as these can indicate important prognostic factors (6). Determining any past or present comorbidities, such as cerebrovascular or cardiovascular diseases, pulmonary diseases, diabetes mellitus, and renal or liver diseases, is also essential for assessing patients' ability to tolerate surgery. Assessing the smoking history is important, as it correlates with various comorbidities. Furthermore, a current smoking history predisposes the patient to a high risk of developing postoperative complications (7). Medications currently being taken should be determined, and a perioperative plan concerning antiplatelets, anticoagulants, and immunosuppressants should be made. The recent administration of systemic treatment should also be precisely evaluated.

After cytotoxic chemotherapy, pulmonary resection should be planned following the recovery from a drop in the white blood cell count (generally about four weeks). In cases receiving bevacizumab, pulmonary resection should be planned at least six weeks after the last administration in order to reduce the risk of postoperative pulmonary fistula (8).

Although most candidates for PM do not present with any symptoms caused by pulmonary metastatic lesions, the presence of respiratory symptoms indicative of endobronchial involvement or centrally located bulky lesions should be investigated. Information on the activities of daily life should also be obtained from both the patient and the patients' family. If the patient is capable of only limited self-care or is confined to a bed or chair for more than 50% of waking hours (ECOG Performance Status 3), the patient is not indicated for surgery in general.

Physiological tests

Generally, the physiological indications can be determined in line with those for pulmonary resection of lung cancer (9,10). Objective and convenient assessments for cardiopulmonary function, such as the 6-minute walk test or stair-climbing test, are useful for determining the

physiological indications for pulmonary resection (11). A patient's ability to tolerate pulmonary resection is decided based on cardiovascular evaluation and spirometry, in order to measure the diffusing capacity of carbon monoxide (DLco) and the forced expiratory volume in 1 second (FEV1). Because candidates for PM often receive chemotherapy as treatment for the primary tumor, damage due to chemotherapy, such as cardiac toxicity from anthracycline, should be properly assessed. Smoking-related cancers, such as esophageal cancer and head and neck cancer, are associated with higher incidences of comorbidities such as hypertension and chronic obstructive pulmonary disease than non-smoking-related cancers, so the cardiopulmonary function should be carefully assessed in these patients (12-14).

The evaluation of pulmonary nodules in patients with a history of malignancy

Differential diagnoses are needed when pulmonary nodules are detected in patients with a history of malignancy. If there are multiple nodules, metastatic disease from the primary tumor is a possible diagnosis, but when there is only one, it becomes difficult to distinguish pulmonary metastases from primary lung cancer. Upon detection of a solitary pulmonary nodule (SPN), whether or not a further invasive examination procedure should be done must be based on the subsequent treatment strategy for the SPN. That treatment strategy is decided after considering various factors, such as the primary tumor type, type of resection (if pulmonary resection is applied), and the patients' general condition. In terms of the type of primary tumor, specifically when the primary tumor is breast cancer, a tissue diagnosis is recommended, since the first choice of treatment for metastatic breast cancer is systemic therapy (15). However, when the primary tumor is colorectal cancer (CRC), pulmonary resection can be the first choice, as PM is recommended for resectable distant metastases from CRC (16).

The combination of radiological findings, smoking history, and type of previous malignancy can reportedly improve the ability to predict primary lung cancer in the presence of a solitary pulmonary lesion that appears after treatment for a previous malignancy (17). The actual frequency of the diagnosis of SPN is also useful information. The reported frequencies of pulmonary metastases from a primary tumor and lung cancer in pulmonary nodule(s) with a history of malignancy are shown in *Table 1*. The ratio of pulmonary metastases among pulmonary nodules in patients with previous malignancies was observed to range from 16% to 62%. In cases of smoking-related cancers, such as

Table 1 Frequencies of pulmonary metastasis from primary tumor and lung cancer in pulmonary nodule(s) with a history of malignancy

Type of primary tumor	Total number of patients	Number of patients with solitary pulmonary nodule	Number of patients with primary lung cancer	Number of patients with pulmonary metastases
Colorectal cancer (18)	117	100 (85%)	44 (38%)	73 (62%)
Esophageal cancer (12)	28	27 (96%)	14 (50%)	10 (36%)
Head and neck squamous cell carcinoma (13)	39	32 (82%)	24 (62%)	15 (38%)
Breast cancer (19)	64	64 (100%)	37 (58%)	27 (42%)
Renal cell carcinoma (20)	41	19 (46%)	7 (17%)	24 (59%)
Urinary tract transitional cell carcinoma (14)	25	25 (100%)	19 (76%)	4 (16%)

esophageal cancer, head and neck cancer, and transitional cell carcinoma of the urinary tract, more than half of pulmonary nodules were primary lung cancer and were typically stage I. Based on these data, when a pulmonary nodule is detected in patients with a history of smoking-related cancer, surgery should be proactively indicated if the patient has a good general condition and can tolerate surgery. The differential diagnosis of SPN is often difficult in practical settings. In such situations, resection of SPN is considered beneficial (21).

Radiological examinations

The most important part of the preoperative evaluation for PM is the radiological examination. Its purposes include (I) the differential diagnosis of pulmonary nodules; (II) the evaluation of the precise number, location, and features of pulmonary nodules; and (III) the search for extrathoracic metastases. The standard modalities include thin-slice computed tomography (CT) and 18F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) (22).

Thin-slice CT is useful for the differential diagnosis and evaluation of the precise number and location of lesions as well as the prediction of their pathological aggressiveness. The differential diagnosis of pulmonary metastases from primary lung cancer is an important issue. In general, pulmonary metastases tend to present as well-defined solid and round nodules without ground-glass opacity (GGO). Differential diagnosis by preoperative CT is often challenging in patients with a history of breast cancer and biliary tract cancer (23,24). In CRC, whether or not nodules have a GGO component have been reported to be useful in making a differential diagnosis (18). In contrast, GGO is not a suitable criterion for discriminating

primary lung cancer from pulmonary metastases from breast cancer (25), pancreatic cancer (26), malignant melanoma (27), or transitional cell carcinoma of urinary tract (14). In cases with a small nodule (diameter <10 mm), discrimination of pulmonary metastases from a benign lesion are difficult. Previous studies have reported that in patients who underwent 2-mm slice thickness CT with a history of extrapulmonary malignancy, nodules smaller than 10 mm were more likely to be benign, whereas those greater than or equal to 10 mm were more likely to be malignant, while most nodules less than 10 mm from the pleura were benign (28). Thus, an evaluation by serial CT is important in patients with such nodules, and careful follow-up is needed (29).

Whether or not thoracic surgeons should palpate the lung during surgery remains controversial, as the sensitivity rate of high-resolution CT for detecting pulmonary metastases has been reported to be 75% (30). It is important to note that the ratio of small pulmonary metastases varies among tumor types. Pulmonary metastases from osteosarcoma tends to be small. Thus, the sensitivity of high-resolution CT for detecting pulmonary metastases is lower than that of other tumor types (31-33). Some authors recommend sufficient palpation during surgery in order to avoid missing small metastatic nodules in patients with pulmonary metastases from osteosarcoma, as preoperative CT may underestimate the number of metastatic lesions (32,34). However, the sensitivity of high-resolution CT for detecting pulmonary metastases in patients with non-osteosarcoma is sufficiently high (31), so the necessity of palpating the lung during surgery remains controversial (35,36). Because sufficient palpation of the lung via the video-assisted thoracoscopic surgery (VATS) approach is

often difficult, this issue is often replaced by a discussion of whether or not thoracic surgeons should perform thoracotomy at surgery. Although thoracotomy allows for the manual palpation of the ipsilateral hemithorax and, in some cases, may be superior to a VATS approach for radical resection, the impact of non-resected pulmonary metastases on patient survival has not been clearly evaluated (30). Recently, this issue was addressed in patients with CRC. Murakawa *et al.* (37) reported that thoracoscopic metastasectomy was associated with a better overall survival than an open approach in a cohort of 1,047 patients. They then concluded that, in terms of tumor identification and survival outcome, the thoracoscopic approach might be acceptable for resection of pulmonary metastases in the current era.

In addition to its utility for the differential diagnosis and evaluation of the number and location of pulmonary nodules, CT is also useful in predicting pathologic findings. The morphologic features of aerogenous spread of floating cancer (AFSC) cell clusters and vascular invasion at the pulmonary metastases in CRC have been reported as prognostic factors after PM (38,39). Welter *et al.* (40) reported that pulmonary metastases from CRC and other epithelial tumors were associated with a higher rate of having AFSC than melanoma, renal cell carcinoma (RCC), and sarcoma. Recently, Issa *et al.* (41) compared the radiomorphology and microscopic growth characteristics of 232 pulmonary metastases to evaluate the presence of aggressive patterns of local intrapulmonary dissemination. In this study, they drew the important conclusion that the radiomorphologic characteristics of lung metastases corresponded well with the microscopic appearance of the resected lesion. Thoracic surgeons should be aware of these radiomorphologic findings, as resection with a sufficient margin should be performed when treating tumors with microscopic aggressive patterns.

When PM is planned, the existence of extrathoracic metastases should be assessed in cooperation with the doctor who treated the primary tumor. Additionally, brain magnetic resonance imaging or CT should be performed in consideration of the possibility of brain metastases, depending on the primary tumor type. Although no data exists on the superiority of FDG-PET/CT to thin-slice CT in terms of sensitivity for detecting pulmonary metastases, FDG-PET/CT is useful and regarded as the standard examination for staging among various cancer types to search for extrathoracic metastases (22,42-44). In many tumor types, FDG-PET/CT showed a higher diagnostic

accuracy than PET or CT alone for detecting tumor recurrence. Thus, it is more appropriate to use for patient selection for PM than other conventional imaging modalities (45-47). Recently, it was reported that dual-time point FDG-PET/CT could be useful for distinguishing primary and metastatic lung adenocarcinoma in patients with SPN (48).

Thin-slice CT and FDG-PET/CT can also be used to evaluate mediastinal staging. However, information on the diagnostic ability of thin-slice CT or FDG-PET/CT for mediastinal lymph node (LN) metastases from pulmonary metastases remains limited. This is attributed to the following: if mediastinal LN metastases is strongly suggested by preoperative imaging examinations, surgery is often avoided, so the pathologic diagnosis of the mediastinal LN cannot be done. Winter *et al.* reported that preoperative CT had 84% sensitivity and 97% specificity for predicting LN metastases in pulmonary metastases from RCC (49). In contrast, the sensitivities of preoperative radiologic examinations for LN metastases were found to be relatively low in patients with metastatic CRC; the sensitivities of positive PET, a bulky LN on CT, and both were 35%, 25%, and 23%, respectively, and the specificities were 96%, 93%, and 97%, respectively (50). Additionally, the sensitivity of preoperative radiological examinations for LN metastases may differ among cancer types. Further data collection is needed concerning this issue. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has also been reported as an efficient modality for screening mediastinal LNs/masses for malignancy in patients with extrapulmonary malignancies (51). Based on the findings of thin-slice CT and FDG-PET/CT, EBUS-TBNA should be considered in each case.

Thus, Mediastinal LN dissection, or at least sampling during surgery, is recommended because many reports support the notion that mediastinal LN metastases are a significant negative prognostic factor for survival after PM (2,49,50,52,53).

Indications for PM

Eligibility criteria

The indication of PM is considered from both physiological and oncological points of view. The eligibility criteria of PM were first described by Thomford *et al.* in the 1960s (54), who reported that the indications for PM include control of the primary tumor, no other distant metastatic disease besides the lung, conditions that make surgery technically feasible, and sufficient cardiopulmonary function of the

Table 2 Criteria for pulmonary metastasectomy adapted from Kondo *et al.* (55)

Major criteria
The patient must exhibit a good risk profile for surgical intervention
The primary site is controlled
No other extrapulmonary metastasis, or if present, it can be controlled by surgery or another treatment modality
Pulmonary metastases are thought to be completely resectable
Additional indications
Existence of effective systemic chemotherapy as a combined modality
Difficulty of differential diagnosis from primary lung cancer
No other effective treatment, except for resection
Symptomatic pulmonary metastases, e.g., pneumothorax, hemoptysis

patient to tolerate surgery.

Since then, many advances in radiological assessments and surgical management approaches have been made, and the eligibility criteria for PM have been extensively modified. At present, the criteria summarized by Kondo *et al.* (55) are widely used (Table 2). One of the major criteria, “Pulmonary metastases are considered to be completely resectable,” is thought to be the most important, as it was observed that patients who undergo incomplete resection are associated with a poor outcome, regardless of the tumor type. The only case in which incomplete resection of pulmonary metastases is suitable is for the control of pneumothorax resulting from pulmonary metastases (56).

Thoracic surgeons should also pay close attention to whether the tumor is rapidly growing and/or spreading. A sufficient observation period is important when considering the indication for PM for patients with a high risk of recurrence, such as those with rapidly growing pulmonary metastases, multiple pulmonary metastases, a short disease interval, or a history of distant metastases other than in the lung. Observation for three months with or without chemotherapy after the first detection of pulmonary metastases is recommended in order to decide the indication of PM. A delayed operation seems justified if the indication for resection is questionable as no evidence has indicated that a longer interval between the detection of pulmonary metastases and PM worsens the outcomes of patients who undergo PM (57,58). Having an optimal observation period provides further information on the prognosis of the patient. Patients with pulmonary metastatic tumors that have a short doubling time have been reported to be associated with worse prognosis than those with a long

doubling time in various tumor types (59-63). Furthermore, patients with osteosarcoma who develop pulmonary metastases during chemotherapy have also shown worse survival rates than those who develop pulmonary metastases in the period without chemotherapy (64).

In addition to the criteria described above, it is also worth to consider whether patients have poor prognostic factors. There have been many reports on prognostic factors after PM in various tumor types (2). Having poor prognostic factors does not necessarily mean that the patient is not indicated for PM; however, in general, the indication should be carefully considered when patients have multiple poor prognostic factors, as these patients have a high probability of developing recurrence and would benefit more from systemic treatment than surgery.

Prognostic factors for each tumor type

CRC

CRC is the most common primary tumor in patients who undergo PM, followed by RCC, breast cancer, otorhinolaryngological cancer, and uterine malignancies (65). Numerous reports on the prognostic factors for PM for CRC are available (66-68). A general systemic review of PM for CRC has been discussed elsewhere (69). Noteworthy recent reports are therefore discussed in this section. In recent years, the survival prognosis after PM in patients with CRC has improved remarkably (70,71). Newer chemotherapy regimens may have played a positive impact on these patients (71). In this clinical context, the prognostic factors after PM in patients with CRC should be evaluated based on recent data.

The poor prognostic factors identified by a multivariate

analysis using a large cohort include the tumor number (72,73), tumor size (72), preoperative serum carcinoembryonic antigen (CEA) level (72,73), LN metastases (72), and completeness of resection (72). In addition, an age that is 70 years or older, a disease-free interval (DFI) of less than 2 years, and extrathoracic metastatic lesions treated curatively before PM resection have also reported as poor prognostic factors (73). Regarding patients with multiple metastases, Maniwa *et al.* (74), who analyzed 247 patients with multiple metastases, found that heterogeneity, defined as the difference between the maximum and minimum tumor diameter exceeding 5 mm, may be a prognostic indicator. In their report, heterogeneity, >five metastases, a high preoperative serum CEA level, and a DFI of <2 years were identified as prognostic factors among patients with multiple metastases. Whether or not a history of hepatic metastases is a prognostic factor remains controversial. A recent meta-analysis showed that a history of hepatic metastases worsens the prognosis. In contrast, in a report involving the largest cohort from Japan, a history of hepatic metastases were not a prognostic factor according to a multivariate analysis (72), and many reports from single institutions support this result (75-79). Currently, it is believed that PM remains a viable treatment option in patients with a history of hepatic metastases; however, stratification of patients who benefit from PM among these patients is necessary. Shimizu *et al.* (80) recently analyzed the outcomes of PM in patients with a history of liver metastases and showed that a high preoperative CEA level was an independent prognostic factor for the overall survival. Although there have been only a few reports on PM for patients with both pulmonary and hepatic metastases detected simultaneously with the primary tumor, PM for such patients was still shown to provide favorable long-term outcomes (81,82). However, a history of distant metastases other than to the liver is believed to be a poor prognostic factor (72,79). Thus, the indication of PM for such patients should be carefully considered.

RCC

RCC is the second-most common primary tumor in patients who undergo PM (65,83). Reports on PM for RCC published after 2001 are shown in *Table 3* (49,84-89,91-98). The factors associated with prognosis that suggested a poor overall survival that were shared among multiple reports included incomplete resection, a large number of metastases, a large size of metastases, and a short DFI. In the clinical guideline for RCC in Japan, PM is recommended in cases with a good performance status,

longer DFI, and good possibility of complete resection (99). Given marked advances in immunotherapy and molecular-targeted therapy in recent years (100,101), the further accumulation of data in the current era is needed.

Head and neck cancer

Squamous cell carcinoma is the most common histological type of head and neck cancer, and the utility of PM for these cancers has been reviewed elsewhere (102,103). Adenoid cystic carcinomas have been associated with a better prognosis than head and neck squamous cell carcinoma (104). Reports on PM for head and neck cancer published after 2001 are shown in *Table 4* (105-118). The factors associated with prognosis that suggested a poor overall survival and were shared among multiple reports included incomplete resection, a short DFI, an old age, oral cavity primary lesion, and recurrence before lung metastases.

Uterine malignancies

Uterine malignancies include uterine corpus cancer and uterine cervical cancer. In terms of the histologic type, these cancers can emerge as either carcinoma or sarcoma. Although they are considered independent entities, PM for uterine malignancies is often discussed together due to the limited number of such patients. Bilancia *et al.* recently published a comprehensive review of this issue (119). Reports on PM for head and neck cancer published after 2001 are shown in *Table 5* (120-126). The factors associated with prognosis that suggested a poor overall survival and were shared among multiple reports were a short DFI, cervix primary lesion, and a large number of metastases. However, a short DFI was only reported as a factor by three authors. Thus, careful consideration must be given for the indication of PM for patients with a short DFI.

Conclusions

The indication of PM should be considered from both physiological and oncological points of view. In addition to the general eligibility criteria of PM, prognostic factors of each tumor type should be considered when deciding the indication of PM. When patients have multiple poor prognostic factors and/or a short DFI, thoracic surgeons should not hesitate to observe the patient for a certain period before deciding on the indication of PM. In the current era, when treatment options besides PM, such as SBRT, immunotherapy, and molecular-targeted therapy are becoming increasingly accessible, a multidisciplinary discussion is needed in order to decide the indication of PM.

Table 3 Reports on pulmonary metastasectomy for renal cell carcinoma published after 2001

Author	Year	Number of patients	Overall survival (%)	Prognosis-associated factors suggesting a worse overall survival
Piltz (84)	2002	105	25	Incomplete resection, large number of metastases, large size of metastases
Pfannschmidt (85)	2002	191	37	Incomplete resection, short DFI, large number of metastases, LN metastases
Hofmann (86)	2005	64	33	Incomplete resection, short DFI, large number of metastases
Murthy (87)	2005	92	31	Incomplete resection, large size of metastases, LN metastases, decreased preoperative FEV1
Marulli (88)	2006	59	53	Old age
Assouad (89)	2007	65	34	Large size of metastases, LN metastases
Bandiera (90)	2009	65	46	Incomplete resection
Winter (49)	2010	110	54	LN metastases
Kanzaki (91)	2011	48	47	Incomplete resection, short DFI, large number of metastases
Kawashima (92)	2011	25	36	NA
Meimarakis (93)	2011	175	39	Incomplete resection, large size of metastases, positive nodal status of the primary tumor, synchronous metastases, pleural infiltration, LN metastases
Bolukbas (94)	2012	107	47	Nodal status, grade, stage group of the primary tumor
Kudelin (95)	2013	116	49	Old age, female gender, large number of metastases
Renaud (96)	2014	122	58	LN metastases
Ohtaki (97)	2017	84	60	Incomplete resection, large size of metastases, histologic type other than clear cell carcinoma
Meacci (98)	2017	27	75	Large size of metastases, short DFI

DFI, disease-free interval; FEV1, forced expiratory volume in 1 second; LN, lymph node; NA, not available.

Table 4 Reports on pulmonary metastasectomy for head and neck cancer published after 2001

Author	Year	Number of patients	Overall survival (%)	Prognosis-associated factors suggesting a worse overall survival
Chen (105)	2008	10	40	Short DFI, male gender
Winter (106)	2008	55	20	Incomplete resection, surgical complications
Geurts (107)	2009	8	25	NA
Shiono (108)	2009	114	26	Incomplete resection, short DFI, LN metastases, oral cavity primary
Mochizuki (109)	2010	23	4	Oral cavity primary
Haro (110)	2010	15	27	Old age
Daiko (111)	2010	27	22	Short DFI, oral cavity primary
Miyazaki (112)	2013	24	N.A.	Short DFI, recurrence before lung metastasis
Yamazaki (113)	2015	16	63	Incomplete resection, short DFI

Table 4 (continued)

Table 4 (continued)

Author	Year	Number of patients	Overall survival (%)	Prognosis-associated factors suggesting a worse overall survival
Yotsukura (114)	2015	34	58	Short DFI, old age, histologic type: squamous cell carcinoma
Hosokawa (115)	2016	21	67	Short DFI
Nakajima (116)	2017	58	36	Short DFI, oral cavity primary
Okada (117)	2018	26	58	Old age, high PD-L1 expression
Oki (118)	2019	77	54	Short DFI, histologic type: squamous cell carcinoma, large size of metastases, recurrence before lung metastasis

DFI, disease-free interval; LN, lymph node; NA, not available.

Table 5 Reports on pulmonary metastasectomy for uterine malignancies published after 2001

Author	Year	Number of patients	Overall survival (%)	Prognosis-associated factors suggesting a worse overall survival
Anderson (120)	2001	25	NA	NA
Anraku (121)	2004	133	55	Short DFI, large number of metastases, large size of metastases, cervix primary
Yamamoto (122)	2004	29	NA	Large number of metastases, histologic type: other than squamous cell carcinoma
Clavero* (123)	2006	70	47	Short DFI, cervix primary
Paramanathan (124)	2013	13	66	NA
Adachi* (125)	2015	23	82	Short DFI
Paik (126)	2015	29	48	Large number of metastases, symptomatic

*, includes gynecologic malignancies other than uterine malignancies. DFI, disease-free interval; NA, not available.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Khosro Hekmat) for the series “Pulmonary Metastases” published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: <http://dx.doi.org/10.21037/jtd-19-3791>). The series “Pulmonary Metastases” was commissioned by the editorial office without any funding or sponsorship. YS serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Sep 2019 to Aug 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: All authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

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Cite this article as: Kanzaki R, Fukui E, Kanou T, Ose N, Funaki S, Minami M, Shintani Y, Okumura M. Preoperative evaluation and indications for pulmonary metastasectomy. *J Thorac Dis* 2021;13(4):2590-2602. doi: 10.21037/jtd-19-3791