Lung resection after pneumonectomy: is it worth the risk?

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Introduction

According to the National Cancer Database between 2004 and 2013, pneumonectomy for non-small cell lung cancer (NSCLC) (n=79,953 patients) accounted for 5 percent of all resections (1). After successful treatment however, patients remain at risk (1–5%) for developing malignant lesions (recurrence or second primary) in the contralateral lung (2,3). Although—for resectable lesions—cure could be attained by surgery, the previous contralateral lung resection is a relative (but no absolute) contra-indication for which the risk-benefit ratio of every case should be discussed multidisciplinary. Outcome after post-pneumonectomy lung resection has improved over the last years due to improvement in surveillance techniques [positron emission tomography-computed tomography (PET-CT)] resulting in early diagnosis, careful selection of surgical candidates, advances in anaesthesiology and increasing experience with minimal invasive surgical techniques.

In this paper we review these improvements and summarize the reported outcome of the largest reported single-center series.

Selection of surgical candidates

Successful long-term outcome of additional lung resection after pneumonectomy greatly depends on careful selection of patients which is based on both oncological as well as functional assessment (2,4). Oncological and functional criteria are summarized in *Tables 1,2*, respectively.

Oncological assessment

Extent of the lung tumor determines the long-term benefit of this high-risk surgery. Tumor size and location are evaluated with chest CT. For all patients, PET-CT is recommended and shows the likelihood of malignancy of the lung tumor, mediastinal lymphadenopathies, and distant metastases. Brain CT or magnetic resonance imaging (MRI) allows exclusion of intracranial metastases for lung cancer patients.

Mediastinal lymph nodes can be biopsied with endobronchial ultrasound (EBUS)-guided fine-needle aspiration (FNA). Cervical mediastinoscopy is more challenging due to the previous pneumonectomy with tracheal/mediastinal shift and radiation therapy. Previous N2 disease precludes surgery due to the anticipated inferior long-term outcome (5).

Tissue diagnosis of the tumor with transthoracic FNA, bronchoscopy guided biopsy or lavage is not mandatory for surgical resection but is useful to differentiate between a metastatic or metachronous tumor. A second primary tumor after pneumonectomy for non-small cell lung cancer (NSCLC) is more likely when the cell type of the lesions is different and the time interval between the lesions is more than 2 years (6). Surgical resection of a metastatic tumor is associated with inferior long-term outcome compared to a metachronous tumor (7-9).

Only patients with a small second primary stage Ia/Ib NSCLC or an isolated and small metastatic contralateral NSCLC tumor should be considered for limited resection.

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Table 1 Oncological work-up and criteria

Chest CT: evaluation of tumor size and location
Bronchoscopic or transthoracic tumor biopsy: tissue diagnosis
PET/CT: exclusion of mediastinal lymphadenopathies and distant metastases
Brain CT or MRI: exclusion of intracranial metastases
EBUS or cervical mediastinoscopy: assessment of mediastinal lymph nodes
Sublobar resection (or middle lobectomy) with 1-cm margins should be achievable
Second primary stage I NSCLC (ideal candidates)
Isolated metastatic contralateral NSCLC (inferior outcome)

Table 2 Functional tests and criteria

Spirometry: postoperative predicted FEV1 and DLCO ≥40%
Cycle ergometer test: peak oxygen consumption ≥10 mL/kg/min or ≥35% (borderline cases)
Cardiac ultrasound: exclusion of pulmonary hypertension or right heart failure
History of right pneumonectomy results in decreased functional capacity versus left pneumonectomy

Functional assessment

The cardiopulmonary reserve of post-pneumonectomy patients determines the risk for postoperative complications, mortality and quality of life. An acceptable surgical risk is indicated by a predicted postoperative FEV1 and DLCO higher than 40% of the predicted value, and for borderline cases a peak oxygen consumption higher than 10 mL/kg/min or 35% of the predicted value should be safeguarded.

Pneumonectomy strongly reduces the pulmonary vascular bed and predisposes for pulmonary hypertension and right heart failure. Preoperative cardiac ultrasound is mandatory to exclude pre-existing pulmonary hypertension or right heart failure which are contra-indications for additional lung resection. It is obvious that—based on an anatomic and physiologic difference in perfusion of 55% versus 45% for the right versus left lung—a previous right pneumonectomy entails a larger risk for functional impairment following additional post-pneumonectomy lung resections.

Anaesthesiologic technique

Anaesthesiologic management for additional lung resection after previous pneumonectomy includes the choice of a perioperative ventilation strategy, perioperative patient monitoring and postoperative care. During surgery, pulmonary gas exchange is monitored with pulse oximetry and capnography. An arterial line ensures hemodynamic monitoring and allows for serial blood gas analyses (2,4).

Since the patient only has one lung, the resection has to be performed while the lung is still ventilating. Finding the right balance between adequate surgical access and maintaining pulmonary gas exchange requires collaboration between the anesthesiologist and the surgeon. The choice of ventilation strategy depends on the surgical approach, location of the tumor, anatomy of the tracheobronchial tree and respiratory functional reserve capacity of the patient (10).

The use of the one-lung-protective ventilation principles cannot be underestimated. Limiting tidal volume to or less than 6 mL per ideal body weight with positive-end-expiratory pressure of at least 5 cmH_2O and intermittent lung recruitment reduces acute lung injury and improves outcome (2,7,11,12).

For open resections via thoracotomy or sternotomy, low tidal ventilation and short hyperventilation followed by intermittent apnea maintains the operative field (2). For video-assisted thoracic surgery (VATS) ventilation strategies are more challenging. However, allowing minimally invasive lung resection enables enhanced recovery of the patient. Strategies that were reported included high-frequency jet ventilation and selective lobar bronchial blockade. High-frequency jet ventilation is a continuous positive airway pressure applied to a bronchopulmonary segment during VATS (13,14). Selective lobar bronchial blockade is achieved with a bronchial blocker (15,16), or double-lumen tube (10,17). These strategies can also be used for open procedures that are technically challenging in order to reduce manipulation and injury to the lung tissue. For peripheral tumors intermittent apnea or standard ventilation with intrapleural CO2-insufflation can provide sufficient thoracoscopic access (2,16). Recently, also non-intubated (NI) VATS has been proposed to be a safe and feasible technique for thoracic surgery with the potential advantage of reducing postoperative complication rate, hospital stay, and chest pain (18). For these reasons, NIVATS could be considered in limited wedge resection post-pneumonectomy.

In cases where pulmonary gas exchange cannot be guaranteed with ventilation of the remaining lung, extracorporeal membrane oxygenation and cardiopulmonary bypass are available (2). These strategies are rarely necessary (5) and have only been discussed in a few cases (8,19,20). Advantages are creation of an optimal surgical field and the possibility of immediate postoperative extubation. Risks are vascular/cardiac injury due to cannulation, bleeding due to induced coagulopathy and thrombosis due to extracorporeal blood circulation.

Enhanced postoperative recovery is ensured by postoperative pain control, early ambulation, and chest physiotherapy. An epidural catheter can facilitate pain management and reduce the need for opioids. This strategy aims to improve bronchial clearance and ventilation and reduces the incidence of atelectasis or postoperative pneumonia (2,4).

Surgical technique

The approach and extent of additional lung resection are determined by the tumor location, depth and size. Sublobar resection is considered a safe and effective alternative for high-risk patients with a first primary stage I NSCLC (21). Similarly, a sublobar resection with a minimal margin of 1 cm has the best risk-benefit ratio after pneumonectomy. Single wedge resection of a peripheral lesion is associated with the best early and long-term outcome for a minimal risk. For more central lesions, segmentectomy and right middle lobectomy can be considered. For every lung resection an extended lymph node dissection should be performed if possible.

Historically, the open approach was routinely performed via median sternotomy (anteromedial tumor), lateral thoracotomy (central and posterior tumors) or muscle-sparing thoracotomy (peripheral tumors). Today VATS has become standard of care for oncologic resection of NSCLC. With modified ventilation strategies of these single-lung patients, single up to three-port VATS thoracoscopic additional lung resection is feasible and safe (13,15-17,22,23).

Recent techniques like pre-operative three-dimensional reconstruction and per-operative indocyanine-green injection might increase the accuracy of limited resections as required post-pneumonectomy (22,24).

Experience and outcome for lung resection after pneumonectomy for NSCLC

Experience and outcome for patients that underwent additional lung resection after pneumonectomy is limited. We retrieved ten retrospective cohort studies from the literature reporting on lung resection of metachronous or metastatic NSCLC in the residual lung accounting for a total of 166 patients. The reported population, intervention and outcomes of the papers are outlined in *Table 3*. The lung resections were performed between 1962 and 2012. All reported procedures were performed with an open approach (sternotomy/thoracotomy), however in the most recent series by Ayub *et al.* (63 patients) the type of approach was not mentioned (9). In the majority of cases, limited resections (wedge/segmentectomy) were performed and only 13 patients underwent lobectomy.

The earliest cohort studies—representing 47 patients—proved feasibility of lung resection for contralateral NSCLC after pneumonectomy. The authors reported an acceptable postoperative complication rate and an overall limited 30-day mortality of 8.5% (4/47) after wedge resection or segmentectomy for small lesions in carefully selected patients (25-29).

More recent cohort studies confirmed earlier findings with promising 1-month mortality and 5-year overall survival up to 44% (5,7,8). Patients undergoing a single wedge excision had less respiratory complications, lower 1-month mortality and improved 5-year survival (7). Patients that underwent surgery for metachronous disease had better 5-year survival over patients with resection for metastatic disease (7,8). Patients that underwent surgery less than 12 months after pneumonectomy had worse long-term survival compared to patients that underwent surgery after a longer interval (5). Patients that underwent surgery for N0-1 disease had better long-term survival than patients

Table 3 Single center case series of lung resection after pneumonectomy

Author	Year	Population		Intervention		Outcome						
		Patients No.	Post-pneumonectomy latency, mean (range)	Resection	Approach	Complications	30-day mortality	Median OS	3-year OS	5-year OS	Metast[h] 5-year OS	Metachron[j] 5-year OS
Kittle *et al.* (25)	1985	15[a]	57 M (4 to 192)	sW =3, mW =5, S =1, mS =4, S + mW =1, L =1	NA	NA	6.7%	NA	35%[g]	NA	NA	NA
Levasseur *et al.* (26)	1992	7	56 M (24 to 204)[b]	sW =5, mS =1, L =1	NA	NA	28.6%[g]	NA	NA	NA	NA	NA
Westermann *et al.* (27)	1993	8	45 M (14 to 135)	sW =2, S =5, L =1	Open =8	25%	12.5%	NA	63%[g]	NA	NA	NA
Massard *et al.* (28)	1995	4	36 M (12 to 71)	sW =1, S =1, L =2	Open =4	50%	0	NA	36%[g]	NA	NA	NA
Spaggiari *et al.* (29)	1996	13	39.3 M (9 to 90)	sW =7, mW =2, S =3, no resection =1	Open =13	31%	0	19 M	46%	NA	NA	NA
Donnington *et al.* (7)	2002	24	23 M[c] (2 to 213)	sW =14, mW =7, S =3, L =1[e]	Open =24	44%	8.3%	39 M	61%	40%	14%	50%
Terzi *et al.* (8)	2004	14	50 M (11 to 264)	sW =11, dW =2, S =2[f]	Open =14	21%	0	21 M	46%	30%	0%	37%
Grodzki *et al.* (5)	2008	18	24 M (4 to 106)	sW =18	Open =18	NA	0	NA	NA	44%	NA	NA
Ayub *et al.* (9)	2017	63	42 M[c] (40.8)[d]	SL =56, L =7	NA	NA	11.1%	39 M	52%	NA	50%[i]	53%[i]

[a], pneumonectomy not for lung cancer in two patients; [b], adapted from Asai *et al.* (2); [c], median; [d], standard deviation; [e], one patient underwent sW and mW; [f], one patient underwent two times sW; [g], adapted from Ayub *et al.* (9); [h], metastatic; only considering the cases with isolated metastasis of first contralateral NSCLC; [i], 3-year overall survival; [j], metachronous; only considering the cases with second primary contralateral NSCLC. OS, overall survival; NA, not available; sW, single wedge; mW, multiple wedge; S, segment; mS, multiple segments; SL, sublobar; L, lobar; M, months.

after surgery for N2 disease (5,30).

Most recently a large retrospective cohort study reported data on 170 patients with contralateral NSCLC after pneumonectomy, of which 63 underwent lung resection (9). Patients with shorter post-pneumonectomy latency, tumor size of 2 cm or smaller and earlier stage (I/II) were more likely to undergo lung resection. Improved 3-year survival was reported after sublobar resection (55%) compared to lobar resection (29%). Reported survival rates were higher for metachronous disease compared to metastatic disease. From a functional point of view, the patient should be informed that his/her performance status will further decrease after additional lung resection, as confirmed in a series of 18 patients by Grodzki *et al.* (5). Despite the high risk for development of pulmonary hypertension and right heart failure, these complications were not specifically reported after additional lung resection.

In most cases additional lung resection is not feasible due to limited pulmonary reserve, comorbidities, tumor-related and surgery-related difficulties. Stereotactic body radiation therapy (SBRT) is another treatment modality that can provide local control for NSCLC in the post-pneumonectomy patient (2,4,31,32). SBRT for medically inoperable patients with primary peripheral early stage NSCLC provides a 3-year local control rate higher than 90% and low radiation-associated toxicity (33). Despite earlier concerns, SBRT for primary central NSCLC tumors has also been proven safe (34,35).

Experience with SBRT for contralateral NSCLC after pneumonectomy is limited. A review of the series that reported data on SBRT after pneumonectomy reported a mean 1-year overall survival and 2-year local control rate of 80.6% and 89.4%, respectively. Significant pulmonary radiation toxicity was found in 13.2% of cases (31).

These favorable results support the choice for SBRT in patients suffering from contralateral NSCLC after pneumonectomy that are considered inoperable or refuse surgery. Head-to-head comparisons between additional lung resection and SBRT are not available. The question whether surgery is superior to radiotherapy for these high-risk patients remains unanswered. In clinical practice, the choice for local control with lung resection or SBRT should be evaluated by a multidisciplinary team of thoracic surgeons, radiation oncologists, radiologists and medical oncologists.

Conclusions

For selected patients with sufficient cardiorespiratory reserve capacity lung resection post-pneumonectomy is a safe and feasible treatment option. Adequate pre-operative surveillance imaging, improvement of lung protective anaesthetic management as well as less invasive and increased precision surgical techniques have led to improved outcome.

Based on the retrospectively collected data, limited sublobar lung resections provide the best risk-benefit ratio. Wedge resection of peripheral small sized (≤2 cm), N0-1 contralateral metachronous NSCLC after pneumonectomy appears to be associated with the best long-term outcome. Segmentectomy or right middle lobectomy can be considered for central NSCLC tumor lesions. In selected patients a 3-year survival rate of 50% can be attained for sublobar resection. Reported survival rates were higher for metachronous disease compared to metastatic disease. In case of inoperability, SBRT is an adequate alternative.

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