



# Surgery after pneumonectomy: it is all a matter of balance

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Pneumonectomy is a feasible and sometimes necessary therapeutic option in case of resectable central lung cancer (1); nevertheless, postoperative morbidity and mortality are higher compared with more limited lung resections. Consequently, pneumonectomy is often defined as “a disease itself” and a careful preoperative work-up providing good lung function and performance status is required (2). In case of a second metachronous cancer in the contralateral lung after pneumonectomy, the correct choice on the best therapeutic path to follow is not always easy to make and a multidisciplinary discussion is therefore mandatory. However, surgical option should not be a priori excluded, even though locally advanced cancer stages, lymph-node involvement after the first intervention as well as an impaired pulmonary function and cardiovascular performance status should be considered exclusion criteria for any additional lung resection.

Ayub and his colleagues (3) reported a retrospective analysis of the SEER database regarding surgical resection after a previous pneumonectomy. Among 459 patients who had a second lung cancer after pneumonectomy, 402 entered the inclusion criteria of the study; 232 were treated with non-surgical therapies, while 170 patients received a surgical resection (63 surgeries alone). Authors conclude that sublobar lung resection after pneumonectomy is feasible in highly selected patients with metachronous and small (<2 cm) non-small cell lung cancer (NSCLC), without evidence of loco regional spreading and with acceptable lung function. Moreover, additional surgery seemed to allow to these patients acceptable long-term outcomes

(median overall survival 39 months, while those treated with radiotherapy alone had a median overall survival of 20 months).

This issue was already been addressed in the past based on smaller and single institutional cohorts (4); more recently, Terzi (5), Donington (6), Grodzki (7) and Spaggiari (4) also reported their experiences with lung resection after pneumonectomy. All these authors agree that, although it might be feasible and worthwhile in terms of oncological long-term results, this procedure require a careful and attentive patients' selection.

After pneumonectomy, lung function is usually severely impaired and consequently functional reserve is decreased as well (8,9); as a result, a careful evaluation of lung and cardiac function is necessary in the work-up of this kind of patients (10). Forced Expiratory Volume in the first second (FEV1) and Carbon-monoxide Lung Diffusion Capacity (DLCO) are currently considered mandatory in all patients as they allow to assess the current respiratory function and predict the postoperative functional outcome. Further cardiac and pulmonary tests are suggested according to results of functional assessment, even if Brunelli and colleagues (9) suggest a routinary a cardio-pulmonary CPET before pneumonectomy. Concurrently, echocardiography has been advocated as necessary in the perioperative management of pneumonectomy to evaluate right ventricular function for the risk of developing or worsen pulmonary hypertension (11).

Bryant and colleagues (12) investigate 1-year post-surgical quality of life (QoL) in patients who undergo a

pneumonectomy, finding a significant reduction of physical QoL, with persistence of an acceptable mental QoL; a significant reduction in QoL after pneumonectomy was also found by Sartipy (13). Nevertheless, a direct relationship between pulmonary tests and performance status and QoL has been questioned (14). Based on these data, we can argue that a correct assessment of QoL should be mandatory in the evaluation of all patients who underwent a pneumonectomy and are candidate to additional surgical treatment.

Beside functional evaluation, a detailed staging is of paramount importance to better establish surgical indication. Endoscopic ultrasonography (namely EBUS and EUS) (15) and PET (16) were not always available in the past, leading to a higher rate of unexpected N2 disease; nowadays, these two techniques are widely spread and they might allow a more precise preoperative patients' work up and to contraindicate surgery for patients who had an otherwise unknown locally advanced disease. Furthermore, in case of a peripheral single nodule, a transthoracic biopsy should be considered to assess histopathology of the nodule; however, a careful evaluation of the risk/benefit balance considering possible complications, such as pneumothorax, should be carried out (17). Concurrently, in case of a new nodule it is always challenging to discern between a new primary lung cancer or a secondary malignancy from the previous disease; although Martini and Melamed (18) reported the well-known criteria that might help to differentiate primary and metastatic nodules based on histology type, localization, lymphatic invasion and time of appearance, there are still large areas of overlapping and establishing the correct origin of each tumor is not always immediate. However, the reported experiences (4-7) did not document a clear survival difference between metachronous tumor and metastasis, even though Grodzki (7) reported a significant better survival for those who had a more delayed appearance (more than 12 months from pneumonectomy) of the contralateral nodule.

Concerning the extent of resection on the remaining lung, lobectomy, segmentectomies or multiple wedge resection has been reported (4-6), but, based on functional and oncological outcomes, all authors suggest that a single sublobar, preferably non-anatomic, resection should be considered the "gold standard" approach in single-lung patients. Surprisingly, Ayub reported two cases of left lobectomy after right pneumonectomy which undoubtedly represent a very risky procedure and might result in a severe impairment of patients' pulmonary function and QoL. In

addition, Terzi and Spaggiari (4,5) suggested that the most extended anatomical lung resection that may be offered to a patient with a previous pneumonectomy is either middle lobectomy or lingulectomy. Conversely, Vaaler and his colleagues (19) reported three case of left pneumonectomy after a previous right upper lobectomy, with acceptable functional and QoL results; nevertheless, their oncological long term outcomes were not satisfactory in all cases.

Minimally invasive surgery is gaining a broad acceptance in the field of general thoracic surgery thanks to advances in technical equipment, reduced postoperative pain and hospitalization and similar oncological outcomes with open surgery (20). Concurrently, spontaneous breathing thoracic surgery procedures have been proposed with good results (21). In this perspective, the use of these ultimate techniques might enlarge the indications for selected patients with a previous pneumonectomy, avoiding thoracotomy pain and its possible mechanical impairment.

Beside surgery, other types of loco-regional treatments have been developed and they might be used as an alternative or following surgery. Stereotactic Ablative Radiotherapy (SABR) is an advanced technique of radiotherapy that allows to limiting the side effects of radiation to the surrounding tissues, allowing a lower incidence of toxicity, which might be vital for patients with only one lung. Giaj Levra and colleagues (22) reported a relatively small experience with the use of SABR, focusing on survival, toxicity and QoL; in this report, they found satisfactory survival outcomes and no high-grade toxicity. Similar outcomes were reported by Thompson *et al.* (23). Furthermore, Ambrogi (24) reported a case of radiofrequency ablation of a malignant nodule in the contralateral lung after a left pneumonectomy; oncological results appeared radical in the following 9 months, while pulmonary function test did not evidence any significant loss of performance.

In conclusion, the role of surgery in extraordinary cases, such as metachronous lung cancer after a previous pneumonectomy, should be taken into account as well as other therapeutic options. A patient-tailored decision should be based on several factors which account for patients' clinical condition status and willpower, features of the disease and institutional expertise. Clear guidelines or prospective randomized trials (25) are clearly difficult—if not even almost impossible—to conduct in these rare real-life scenarios; a multidisciplinary management of these complex patients it is therefore mandatory in order to design the best and most effective treatment, limiting

potential complications and focusing on long term oncological outcomes and patients' QoL.

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