SURGERY FOR NON-SMALL CELL LUNG CANCER

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Abstract

Lung cancer remains the leading cause of cancer related deaths in Australia and worldwide. Despite recent advances in screening, diagnosis and treatment, long-term overall survival of lung cancer remains poor. Surgery, either alone or as part of a multimodality treatment regimen, plays an important role in the management of patients with non-small cell lung cancer. Complete surgical resection of early stage disease can be achieved by either lobectomy or pneumonectomy. Probably the greatest recent change in surgery for lung cancer is video assisted thoracic surgery. Controversy remains around the treatment of non-small cell lung cancer with mediastinal lymph node involvement (Stage IIIA – T1-3 N2). The potential role of surgery in the palliation of lung cancer patients is also addressed.

Lung cancer is the leading cause of cancer death in Australia[1] and worldwide.[2] The two main classes of lung cancer, with the classification based on biological behaviour, therapy and prognosis, are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is responsible for approximately 85% of all lung cancer cases.[3] Despite the recent advances in screening, diagnosis and treatment, the overall five year survival of lung cancer patients is 15.9%,[4] with late diagnosis being the major factor responsible for the poor overall prognosis.[5] Surgery, either alone or as part of a multimodality therapy, plays an important role in the treatment of lung cancer patients. The focus of this article is to review the current role of surgery in the management of NSCLC.

Pre-operative mediastinal staging

Accurate staging of lung cancer is essential for both prognostic and therapeutic reasons. When extra thoracic disease spread has been ruled out, mediastinal lymph node status must be assessed prior to intervention. Due to its high diagnostic accuracy, positron emission tomography, combined with computed tomography (PET-CT), has become the investigation of choice for staging NSCLC.[6] PET-positive mediastinal uptake should generally be confirmed by invasive means, thereby ensuring that patients are not denied a curative option in the setting of a falsely positive PET-CT scan.[7] This is of particular importance in large central tumours, where atelectasis distal to the mass can result in enlarged and reactive mediastinal nodes which may be positive on PET-CT. It should also be noted that negative PET-CTs do not exclude the presence of micro-metastatic disease and can also be particularly less helpful in tumours with low metabolic activity.[8,9]

Mediastinal lymph node status can be assessed by either mediastinoscopy or endobronchial ultrasound guided trans-bronchial needle aspiration (EBUS-TBNA). The choice of modality will often be dictated by local considerations in terms of available expertise and resources. Mediastinoscopy is the gold standard for evaluating mediastinal lymph nodes. It allows assessment of the following lymph node stations: high mediastinal station (station 1); right and left superior para-tracheal (station 2); right and left inferior para-tracheal (station 4); and subcarinal (station 7). The sensitivity of mediastinoscopy is reported between 72-89% (on average 81%), specificity is 100% and negative predictive value of 91%[10]. Recently, the use of video-mediastinoscopy has been introduced, improving visualisation of the surgical field and the accuracy of staging.[11,12]

In addition to those stations accessible by mediastinoscopy, EBUS-TBNA also allows sampling of hilar (station 10) and intrapulmonary nodes, with sensitivity of 88% and specificity of 100%.[13] As a result, it has greatly reduced the need for cervical mediastinoscopy. It is likely that mediastinoscopy will be increasingly used to confirm negative results of EBUS-TBNA, particularly when clinical/radiological suspicion persists, further increasing the sensitivity of this combined approach to 94%[14]. Similarly, the need for re-do mediastinoscopy after induction therapy can be avoided if pre-treatment assessment is carried out by EBUS-TBNA, thereby reserving mediastinoscopy for post-treatment restaging. Occasionally, endoscopic ultrasound fine needle aspiration may need to be used to assess stations 5, 7, 8 and 9, which are not accessible by the above two techniques.

Video assisted thoracic surgery (VATS) is used to definitively evaluate the hemithorax and mediastinum at the time of surgery. Ipsilateral pleural effusions (negative on cytology) should be proven to be reactive and pleural seeding excluded prior to embarking on definitive resection. In addition to lymph node stations 2, 4 and 7, VATS provides relatively easy access to lymph node stations 5, 6, 8 and 9, which are not readily accessible by the above discussed techniques.

Surgery for earlier stage lung cancer (stage I, II, IIIA – T3N0, 1, T4N0, 1)

The decision to perform surgery with curative intent is based on the stage of the disease, as defined by the 7th edition of tumour, node, and metastasis classification (TNM),[15] tumour resectability and the patient's operability/ fitness for surgery. The goal of surgery is complete resection of intra-thoracic disease. Currently, inoperable patients, surgery is the treatment of choice for patients with stage I, II and stage IIIA (T3N0, 1, T4 N0, 1) disease.

Complete surgical resection of early stage disease can be achieved by either lobectomy or pneumonectomy. Lobectomy is performed whenever technically possible in order to minimise perioperative morbidity and mortality (30 day mortality from the Society for Thoracic Surgeons for lobectomy is 2% v 5.6% for pneumonectomy).[16,17] Sleeve lobectomy with bronchoplastic techniques should be considered to decrease the requirement of pneumonectomy, if complete resections with clear margins can be obtained. T3-4 tumours (chest wall, pericardial, diaphragmatic and mediastinal invasion) require en block resection of invaded structures, with clear resection margins (R0) to ensure long term survival. Intra-operative mediastinal staging should be performed, but the extent of staging required remains controversial. Practice ranges from no formal assessment, to haphazard sampling, to systematic sampling, to nodal dissection. At a minimum, systematic lymph node sampling should be performed to accurately stage the disease.[18,19] Lymph node status is essential for predicting prognosis, as well as determining the need for adjuvant therapy. To date, a survival advantage of complete mediastinal lymph node dissection has been demonstrated by only one prospective randomised trial.[20]

In high risk surgical candidates, as judged by significant medical comorbidities or poor pre-existing lung function, sub-lobar resection with segmentectomy (preferred),[21,22] or wedge resection, can be performed. A segmentectomy is an anatomic resection similar to a lobectomy, with ligation of individual bronchovascular structures. This is in contradistinction to wedge resections, which involve transection of lung parenchyma only, generally with the use of staplers.

Sub-lobar resections have been associated with increased loco-regional disease recurrence rates and reduced long-term survival.[23, 24] There is growing evidence to support limited resections in some small tumours (<2 cm T1a),[21] i.e. adenocarcinoma in situ or minimally invasive adenocarcinomas,[25] or in elderly patients with small tumours.[26] Competing risks must be considered prior to embarking on surgical resection in this high risk subset.

Another offshoot of the use of CT based screening is the increased incidence of early small cancers. This trend began in Japan, where CT screening has been in place for decades. Intuitively, it seems that for small peripheral cancers, sublobar resections may be adequate, but to date lobectomy remains the standard of care. There are randomised control trials in progress comparing sublobar resections to lobectomy for small (<2cm) peripheral adenocarcinomas. The results are pending.

Another common scenario that presents itself with the increasing use of screening, as well as CT based surveillance of patients that have had previous resections, is that of patients presenting with second primary lung cancers years after an NSCLC resection. Often in these situations, a sublobar resection is performed for the compromised patient, who already has diminished pulmonary reserve. Similarly, it may be a valid choice in patients with other competing risks, for example, recently resected primaries from other sites (eg. head and neck).

Probably the greatest recent change in surgery for lung cancer is VATS. VATS lobectomies were first performed more than 20 years ago,[27] but are only now achieving more widespread acceptance and uptake. VATS lobectomy attempts to minimise the morbidity associated with a standard thoracotomy, a functionally debilitating incision. Two randomised trials performed in early stage non-small cell lung cancer patients have shown VATS lobectomy to be safer,[27] and have similar five year survival rates,[28] when compared with lobectomy performed through thoracotomy. Large case series have since been published, establishing VATS lobectomy as a safe procedure associated with low morbidity.[29-32]

Studies have also suggested that VATS lobectomy has been associated with reduced postoperative pain and earlier ambulation, as well as reduced pulmonary morbidity, making it possible to offer anatomical resection to the elderly, patients with poor lung function and with poor performance status.[33-36] Most importantly, VATS lobectomy has been shown to be oncologically sound, with no increase in loco-regional recurrence rate, as well as reduced systemic recurrence rate and improved five year survival rate when compared with open lobectomy.[37] Considering the available evidence (and the fact that large multicentre, randomised control trials are unlikely to ever be performed), VATS lobectomy should be considered as the procedure of choice for patients with early stage lung cancer.

Surgery for loco-regionally advanced lung cancer (stage IIIA – T1-3 N2)

Controversy remains around the treatment of NSCLC with mediastinal lymph node involvement (stage IIIA – T1-3 N2). Two large randomised control trials that compared surgery combined with neoadjuvant therapy and definitive chemo radiotherapy, did not demonstrate overall survival benefit with surgical resections.[38, 39] However, subgroup analysis has demonstrated better survival rates for patients who underwent lobectomy and patients down staged to N0, 1 disease following induction chemotherapy.[38,39] Outcomes in the pneumonectomy group were compromised by an extremely high operative mortality of 26%.[39] Large single institution case series have since shown that pneumonectomy can be performed safely after induction therapy.[40,41] Considering the above data, surgery can be considered as part of a multimodality treatment regimen for patients with N2 disease, particularly those who are judged completely resectable, have responded to/been down staged by induction therapy and have single station non bulky nodal disease.

Surgery for metastatic disease (stage IV)

The role of surgery for stage IV NSCLC is primarily focused on the improvement of patient quality of life. Malignant pleural effusions can be managed with VATS pleurodesis or, in cases where lung is trapped with cancerous peel and pleurodesis is unlikely to be successful, with a permanent subcutaneously tunnelled pleural drain insertion, which allows repeated fluid drainage. Similarly, airway intervention with laser, mechanical debridement and stenting play an important role in the management of malignant tracheo-bronchial stenosis and haemoptysis. In highly selected cases, where complete resection of intra thoracic and metastatic disease is possible, surgery can be considered in patients with solitary metastatic disease of the brain and adrenal glands, as part of a multimodality treatment regimen.[42, 43]

Overview

In addition to its role in diagnosis and staging, surgery remains at the forefront among therapeutic modalities in the treatment of NSCLC. Despite progress in non-invasive staging with PET-CT, histological sampling of mediastinal lymph nodes via EBUS or mediastinoscopy remains critically important in the assessment of many patients. The choice of which modality to use will often depend on the local availability of resources and expertise. Complete resection remains the best chance for cure for patients with disease not involving the mediastinum, i.e. stage I, II and non N2 IIIA (i.e. T3N0 or N1 and T4N0 or N1). The established benefits of adjuvant chemotherapy suggest that adequate intraoperative mediastinal lymph node staging is required. At a minimum, systematic sampling of lymph node stations should be performed. VATS lobectomy has emerged as an acceptable treatment for early stage lung cancer. Studies have shown decreased pain, faster return to function and decreased morbidity with at least equal oncological results. It is important that the same operation is performed on the inside (ie. lymph node dissection) as would have been performed via a thoracotomy. An area of increasing interest is that of sublobar resection (either segmentectomy or wedge) for very small peripheral adenocarcinomas. Studies are ongoing, but lobectomy remains the standard of care. In loco-regionally advanced disease, surgery can be used as part of a multi-disciplinary approach with good results. Patients who do best are those who have had their mediastinus pathologically downstaged, or sterilised by neoadjuvant therapies prior to resection. In advance disease, surgery can play an important role in the palliation of breathlessness resulting from either pleural effusions or airway compromise. As is often the case in lung cancer, patients tend to benefit most when a multi-disciplinary approach is used.

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