Management of lung cancer

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Abstract

Lung cancer is a heterogeneous group of diseases at both the histopathological and molecular levels. Individual treatment plans should be based on the histological and molecular characteristics of the tumour as well as the stage of disease at diagnosis, performance status and co-morbidities. Surgery, chemotherapy including maintenance therapies, targeted therapies, radiotherapy and palliative care all have a role in the management of patients with lung cancer, depending on stage. Recent advances in non-small cell lung cancer (NSCLC) include the use of stereotactic radiotherapy for patients with medically inoperable stage 1 NSCLC, routine anaplastic lymphoma kinase testing and licensing for crizotinib and ceritinib, and licensing of nivolumab immunotherapy. There have been fewer advances in the management of small cell lung cancer but promising therapies are on the horizon. Management decisions should be made at multidisciplinary team meetings with core members including a respiratory physician, medical and clinical oncologists, a thoracic surgeon, a radiologist, a pathologist and a palliative care team member.

Keywords Chemotherapy; immunotherapy; non-small cell lung cancer; radiotherapy; small cell lung cancer; surgery; targeted therapies

Key points

- Optimum treatment of stage 4 non-small cell lung cancer (NSCLC) now depends on the tumour's molecular status
- Immunotherapy for stage 4 NSCLC (squamous carcinoma and adenocarcinoma) is superior to chemotherapy (docetaxel)
- Whole brain radiotherapy is suitable only for a selected group of patients
- Palliative thoracic radiotherapy can be used in selected patients with small cell lung cancer

Management of non-small cell lung cancer (NSCLC)

Early-stage disease (stage I–II)

Surgery: surgery is treatment of choice for patients with stage I–II NSCLC, offering the best chance of cure. Unfortunately, most patients present with inoperable disease, and major initiatives are underway to improve early diagnosis. Around 22% of patients in the UK undergo surgery, a figure that has markedly improved over 4 years. However, there is still a national variation in the UK (from 15% to 31%), probably based on access to thoracic surgical expertise and multidisciplinary team (MDT) functioning.

The standard surgical approach is anatomical lobectomy. Although pneumonectomy may be required for hilar and more proximal tumours, this is associated with poorer postoperative outcomes, including 30-day mortality (2.3% for lobectomy versus 5.8% for pneumonectomy), especially if postoperative radiotherapy is required. To increase the accuracy of pathological staging and optimize adjuvant therapy decisions, systematic nodal dissection or sampling should always be performed.

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Careful preoperative medical assessment is vital when assessing patients for surgery. This should include assessment of the risks of perioperative death and postoperative cardiac events, and assessment of postoperative lung function. Forced expiratory volumes in 1 second of more than 1 litre and more than 2.5 litres are usually required for lobectomy and pneumonectomy, respectively. However, lung volumes and gas transfer factor should also be assessed. Cardiopulmonary exercise testing and an assessment of postoperative lung function (perfusion scanning or quantitative computed tomography (CT)) are used in patients with abnormal respiratory function. If lobectomy is not possible because of co-morbidities or poor lung function, sublobar resections such as segmentectomy and wedge resections may be possible in patients with peripheral tumours.

Adjuvant therapy: the relapse rate after surgery is high; approximately 50% of patients subsequently develop metastases. Adjuvant (postoperative) chemotherapy may be indicated, depending on the stage of the resected tumour. This has been confirmed by several randomized Phase III trials and by meta-analyses of individual patient data. Cisplatin-based adjuvant chemotherapy (ideally cisplatin–vinorelbine) provides a significant survival advantage over no chemotherapy, with an absolute overall survival benefit of 11.6% at 5 years in patients with involved hilar nodes (N1), and 14.7% in patients with involved mediastinal (N2) nodes. For node-negative tumours, chemotherapy is considered on an individual patient basis (>4 cm). Postoperative radiotherapy is indicated after an incomplete resection (involved bronchovascular margins). Its role is otherwise controversial, some trials suggesting a role in completely resected tumours with involved N2 nodes.

Radical approaches in patients unfit for surgery: external beam radiotherapy given in a radical dose (e.g. 64 Gy) was traditionally indicated for patients with stage I–II NSCLC in whom surgery was inappropriate (e.g. co-morbidities). However, patients with poor lung function and co-morbidities medically unsuitable for surgery are now usually treated by stereotactic body radiotherapy (SBRT) or, if this is unavailable or not technically possible, radiofrequency ablation (RFA) for isolated lesions. To ensure an adequate treatment dose, conventional radical radiotherapy encompasses the tumour and a significant volume of normal tissue. SBRT is a technique that uses precise positioning and imaging to target the tumour, with little else treated, thereby reducing the volume of normal tissue exposed to radiation. SBRT is now standard in medically inoperable stage 1 NSCLC and an alternative to wedge resection, with less morbidity. RFA involves

placing an electrode into the tumour under image guidance. Radiofrequency waves are passed through the electrode, generating thermal energy that destroys the tumour. This technique is generally reserved for tumours unsuitable for SBRT.

Locally advanced disease – IIIA, IIIB

Patients with stage IIIA are a heterogeneous group ranging from those with no nodes (N0)/hilar nodes (N1), through those with microscopically involved mediastinal (N2) nodes incidentally discovered at surgery to those presenting with fixed bulky N2 nodes at many nodal stations. Patients with IIIA (N0–N1 disease) are candidates for surgery. These patients should be offered adjuvant chemotherapy after complete surgical resection. Postoperative radiotherapy is considered in selected patients with involved margins.

The role of surgery for patients with preoperatively proven mediastinal node involvement (N2) is controversial, and they should be managed by an MDT experienced in this. Patients with multi-station N2 are generally treated with chemo- and radiotherapy, either concurrently or sequentially. The concurrent approach is preferred as it is associated with optimal survival, although also with more local toxicity, and it is suitable only for patients with a good performance status (PS).

Pancoast tumours (superior sulcus tumours), although amenable to curative treatment, are difficult to treat because of their proximity to structures in the thoracic inlet, limiting radiotherapy dosage and surgical access. Although the standard treatment for these patients is chemoradiotherapy, some data suggest optimal outcomes with concurrent chemoradiotherapy followed by surgery.

Most patients with stage IIIB NSCLC are not candidates for radical therapy (radiation and/or surgery), and are best managed with palliative systemic therapy or palliative radiotherapy alone. Selected patients with disease that can be encompassed by radical radiotherapy and with a good PS may be candidates for chemoradiotherapy with curative intent.

Advanced disease – stage IV

This group constitutes the majority of patients with NSCLC. Patients with stage III disease unsuitable for radical radiotherapy or surgery are treated in a similar manner. Treatment is palliative in intent. It centres on systemic therapy and aims to improve symptoms and survival, recognizing that median survival with treatment is generally 9–12 months. Treatment pathways are summarized in Figure 1.

Adenocarcinoma of the lung

Adenocarcinoma with known driver mutations

***EGFR*-mutant NSCLC:** mutations in the *EGFR* tumour gene, first identified in 2004, characterize a biologically distinct subtype of NSCLC. Such mutations are almost exclusively observed in TTF1-positive adenocarcinomas. They are over-represented in women, never- or ex-light-smokers and East Asian patients, and occur in 5–10% of cases in Western Europe. *EGFR* genotyping at diagnosis of non-squamous NSCLC is now the normal standard of care.

Randomized Phase III trials[1] have consistently demonstrated that, in *EGFR*-mutant NSCLC, efficacy and quality-of-life outcomes are markedly superior with epidermal growth factor receptor (EGFR) inhibitors (gefitinib, erlotinib, afatinib) over platinum-doublet chemotherapy, with a median survival of around 2–3 years. These drugs are generally well tolerated, not myelosuppressive and typically cause acneiform rash, diarrhoea and/or paronychia.

Anaplastic lymphoma kinase (ALK)-translocated tumours: *ALK* translocation is observed in 4–7% of adenocarcinomas, rendering them profoundly sensitive to ALK kinase inhibition. Crizotinib therapy results in a marked tumour response, increased progression-free survival and improved quality of life over chemotherapy (both first and subsequent lines of therapy).[2] Ceritinib is a more potent ALK inhibitor with marked activity in patients relapsing on crizotinib (the current licensed indication), with a median survival of 4 years for the sequence of chemotherapy–crizotinib–ceritinib.

NSCLC with no identifiable driver mutations and NSCLC with driver mutations but no approved targeted agents

Chemotherapy is the first-line standard treatment in this group. The JMDB trial confirmed that cisplatin–pemetrexed is the platinum-doublet chemotherapy of choice for non-squamous NSCLC.[3] The addition of bevacizumab to chemotherapy for non-squamous tumours is also licensed.

Maintenance therapy

Chemotherapy is traditionally given 3-weekly and discontinued after four to six cycles, contingent on the CT response. Patients are then followed up, to consider second-line systemic therapy at relapse (median progression-free interval around 4–6 months). The concept of maintenance therapy involves giving second-line therapy to consolidate first-line therapy; it follows from observations that less than 30% of patients completing first-line therapy are well enough to receive second-line therapy on relapse. However, it means that patients continue hospital-based chemotherapy for most of their life.

Continuation maintenance pemetrexed monotherapy after four cycles of cisplatin–pemetrexed in non-progressors was licensed after demonstrating an overall-survival benefit over no maintenance. Although erlotinib is also licensed as maintenance therapy, this is limited to those patients with stable disease on chemotherapy.

Squamous cell lung cancer

Platinum chemotherapy doublets are standard first-line treatments. Pemetrexed is contraindicated in patients with squamous cell lung cancers.

Relapsed disease: patients with a good PS can be considered for second-line treatment and, on further progression, third-line treatment, with a survival benefit and improved quality of life over placebo. Licensed therapies include docetaxel (with nintedanib in adenocarcinomas) or pemetrexed, immunotherapy (see below) and erlotinib. Pemetrexed is superior to docetaxel for non-squamous tumours, but is rarely used second-line as it has usually already been used as first-line or maintenance treatment.

Immunotherapy

The PD-1 (PDCD1) receptor nivolumab has recently been licensed as second-line therapy for squamous subtype NSCLC, and is soon to be licensed in non-squamous NSCLC, having