

# What is the role of surgery in potentially resectable N2 non-small cell lung cancer?

Matthew Evison,<sup>1</sup> Fiona McDonald,<sup>2</sup> Tim Batchelor<sup>3</sup>

<sup>1</sup>Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK

<sup>2</sup>Department of Clinical Oncology, The Royal Marsden Hospital NHS Foundation Trust, London, UK

<sup>3</sup>Department of Thoracic Surgery, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

## Correspondence to

Dr Matthew Evison, North West Lung Centre, University Hospital South Manchester, Manchester M23 0FN, UK; m.evison@nhs.net

Received 1 July 2018

Revised 17 September 2018

Accepted 17 September 2018

Published Online First

9 October 2018

## INTRODUCTION

Stage III/N2 non-small cell lung cancer (NSCLC) describes the metastatic spread of a primary tumour to the ipsilateral mediastinal lymph nodes. It is a heterogeneous disease stage ranging from unsuspected N2 disease only detected by intra-operative lymph node sampling during surgical resection of the primary tumour to conglomerate, bulky and invasive N2 disease that cannot be resected. For unresectable N2 NSCLC concurrent chemoradiotherapy is widely accepted as the standard of care in the context of appropriate physiological reserve.<sup>1–3</sup> Between these two ends of the spectrum sit those patients with discrete and potentially resectable N2 disease. The optimal treatment strategy in this patient group is keenly debated and a number of guidelines from the UK, Europe and America have made recommendations.<sup>1–3</sup> The aim of this article is to review these guidelines and provide an interpretation of their recommendations as a guide to clinicians involved in the care of patients with potentially resectable N2 NSCLC. A summary of the key randomised controlled trials (RCTs) in resectable N2 NSCLC that form the basis of these guideline recommendations is provided in [table 1](#).

## BRITISH THORACIC SOCIETY AND SOCIETY FOR CARDIOTHORACIC SURGERY IN GREAT BRITAIN AND IRELAND GUIDELINES ON THE RADICAL MANAGEMENT OF PATIENTS WITH LUNG CANCER (2010)

This guideline describes potentially resectable N2 NSCLC as non-fixed, non-bulky and single-zone N2 nodal disease where the primary tumour is likely to be completely excised with clear pathological margins.<sup>1</sup> In this setting, the guideline recommends that surgery is considered as part of multimodality therapy and this recommendation is graded as evidence level B (based on high-quality case-control and cohort studies with low risk of confounding or bias). In non-fixed, non-bulky, multi-zone N2 disease the guideline reports that no one management regime has been shown to be consistently superior to another and further RCTs are recommended.

This guideline, therefore, considers the distinction between single-zone and multizone N2 disease to be a critical factor in determining whether treatment with surgery is recommended. This recommendation was based on the large cohort of surgically resected lung cancers within the International Association for the Study of Lung Cancer (IASLC) staging databases.

## Key messages

- ▶ The optimum treatment for potentially resectable stage III N2 non-small cell lung cancer (NSCLC) is multimodality treatment targeting the prevention of distant disease with systemic therapy and achieving local control through surgery, radiotherapy or both.
- ▶ An approach of induction treatment followed by surgery and surgery followed by adjuvant treatment both appear justified, though there is evidence suggesting higher treatment completion rates with an induction approach.
- ▶ When definitive chemoradiotherapy is the preferred treatment option this should be delivered concurrently in the context of adequate physiological reserve.
- ▶ Single station versus multistation N2 disease should not be used as treatment defining factor.
- ▶ Complex multimodality treatments require experienced and high-volume multidisciplinary teams and centres to minimise the risks from treatment and maximise benefits. Consideration should be given to dedicated regional stage III NSCLC services.

Analysis of this database revealed that patients with single-station N2 disease have a similar 5-year survival to those with multistation N1 disease (approximately 35% 5-year survival) but a much better survival than those with multistation N2 disease (20% 5-year survival).<sup>4</sup> Given that N1 disease is considered a primarily surgically managed disease, these results have been interpreted by some to indicate that single-station or single-zone N2 disease should also be managed primarily by surgery. However, the authors of this article have some concerns about this interpretation. The IASLC database contains only surgical patients who have undergone extensive intra-operative lymph node sampling ensuring very accurate classification of nodal status. The N2 disease in this database is predominantly microscopic and occult N2 disease and represents a different population to those with clinically apparent N2 on preoperative CT and positron emission tomography (PET) imaging in whom the outcomes may be different. Furthermore, although those with multistation N2 had a worse 5-year survival than those with single-station N2 disease there is no comparator group within the single-station or multistation N2 patients to know if alternative treatments would have led to different outcomes.



© Author(s) (or their employer(s)) 2018. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Evison M, McDonald F, Batchelor T. *Thorax* 2018;**73**:1105–1109.

**Table 1** Summary of key randomised controlled trials comparing different treatment strategies in potentially resectable N2 NSCLC

Study	Notes	Study arms	Recruitment	Primary endpoint	Results
Induction chemotherapy followed by surgery versus induction chemotherapy followed by radiotherapy					
EORTC 08941 van Meerbeek <i>et al</i> <sup>5</sup>	<ul style="list-style-type: none"> <li>▶ Recruitment pre-PET and EBUS era.</li> <li>▶ High-volume mediastinal disease and considered unresectable at the outset.</li> <li>▶ Chemoradiotherapy given sequentially and not standard of concurrent.</li> </ul>	Three cycles of induction chemotherapy; if response, randomise: surgical resection versus 60–62.5 Gy in 30–32 fractions.	1994–2002 Target 358 patients 332 randomised	5-year OS	15.7% vs 14% HR 1.06 (0.84–1.35), p=0.596
Induction chemoradiotherapy followed by surgical resection versus definitive chemoradiotherapy					
Intergroup 0139 Albain <i>et al</i> <sup>6</sup>	<ul style="list-style-type: none"> <li>▶ Recruitment pre-PET and EBUS era.</li> <li>▶ Low-volume mediastinal disease, 74% single-station N2.</li> <li>▶ Statistically significant improvement in PFS (12.8 months vs 10.5 months, p=0.017) with surgical arm.</li> <li>▶ 26% mortality rate for pneumonectomy.</li> <li>▶ Post hoc analysis demonstrating improved survival in matched lobectomy group (33.6 months vs 21.7 months, p=0.002).</li> </ul>	Two cycles of induction chemotherapy. Induction radiotherapy 45 Gy. If stable disease, randomise: surgical resection versus complete radiotherapy to 61 Gy.	1994–2001 Target 612 patients 429 recruited	5-year OS	27% vs 20% HR 0.87 (0.7–1.1), p=0.24
ESPATUE Trial Eberhardt <i>et al</i> <sup>11</sup>	<ul style="list-style-type: none"> <li>▶ Highly heterogeneous study population.</li> <li>▶ 32% T4N1.</li> <li>▶ 37% IIIB based on T4N2 staging or N3 disease confined to the contralateral mediastinum.</li> </ul>	Three cycles of induction chemotherapy. Induction chemoradiotherapy (45 Gy+one cycle chemotherapy). If remains resectable, randomise: surgical resection versus chemoradiotherapy boost.	2004–2013 Target 300 patients 246 recruited 161 randomised following induction.	5-year OS	44% vs 40%, p=0.34 Overall survival at 5 years for all 246 recruited patients was 34.1%.
Induction chemoradiotherapy followed by surgery versus induction chemotherapy followed by surgery					
SAKK Trial Pless <i>et al</i> <sup>10</sup>	<ul style="list-style-type: none"> <li>▶ Low-volume N2 disease with less than 10% of patients having a total mediastinal bulk of disease &gt;5 cm.</li> </ul>	Three cycles of induction chemotherapy versus 3 cycles of induction chemotherapy plus 44 Gy radiotherapy. All patients for surgical resection after induction treatment.	2001–2012 Target 240 patients 232 recruited Stopped at third analysis.	EFS	11.6 vs 12.8 months HR 1.1 (0.8–1.4), p=0.67 No significant difference in OS.

EBUS, endobronchial ultrasound; EFS, event-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

While single-station N2 disease is a marker of better prognosis there is no evidence that it is a predictive factor that should influence treatment decisions. This is supported by the EORTC 08941 and Intergroup 0139 RCTs published prior to this guideline release.<sup>5,6</sup> The former showing no difference in overall survival between induction chemotherapy followed by radiotherapy versus induction chemotherapy followed by surgery in high-volume largely multistation N2 disease and the latter showing no difference in overall survival between induction chemoradiotherapy followed by surgery versus definitive chemoradiotherapy in low-volume N2 disease largely made

up of single-station N2 disease (76% of the study population, [table 1](#)). It is also important to address the confusion that may arise from the use of the terms ‘station’ and ‘zone’. The IASLC database uses individual lymph stations to describe the concept of ‘single’ or ‘multiple’ sites of nodal disease. There are several lymph node stations within each lymph node zone, for example, the subcarinal (station 7), paraoesophageal (station 8) and pulmonary ligament (station 9) lymph nodes are all located within the inferior mediastinum zone.<sup>7</sup> The British Thoracic Society (BTS) and Society for Cardiothoracic Surgery in Great Britain and Ireland (SCTS) guidelines have

opted to use the classification of zones whereas as much of the literature refers to lymph node stations. It would be possible to have multistation N2 disease based on individual stations but single-zone N2, for example, positive nodal metastases in stations 7 and 8.

The BTS and SCTS guideline also reviewed the evidence for giving induction chemotherapy before surgical resection versus adjuvant chemotherapy following surgical resection. It concluded that there were a relatively small number of studies on preoperative chemotherapy compared with the evidence base for postoperative chemotherapy with borderline significance of benefit in meta-analysis (HR 0.88, 95% CI 0.76 to 1.01,  $p=0.07$ ) for the preoperative approach. Therefore, adjuvant chemotherapy was recommended (stage IB >4 cm, II and III) whereas preoperative chemotherapy was not. The evidence reviewed included all radically treatable stages of NSCLC (stages I–IIIA) and was dominated by stage I NSCLC. The recommendation and the evidence it is based on does not, therefore, specifically consider this question in potentially resectable N2 NSCLC.

#### **NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE GUIDELINE: LUNG CANCER DIAGNOSIS AND MANAGEMENT (2011)**

The 2011 National Institute for Health and Care Excellence (NICE) guideline on the treatment of lung cancer stands alone as a guideline that does not recommend surgery as a treatment option in N2 NSCLC. The guideline group focuses the spotlight on the lack of consistent terminology and lack of clear definitions in potentially resectable N2 NSCLC (eg, bulky vs non-bulky lymph nodes). This inherent heterogeneity prevented meta-analysis of trial data at the time of the guideline development. Interpreting the evidence as imprecise, and in contrast to other guidelines, NICE does not recommend surgery in N2 disease but recommended further research in the field. However, the guideline group does make specific note of the EORTC 08941 and Intergroup 0139 trials as two RCTs that showed multimodality treatment including surgery was not significantly better or worse than multimodality treatment without surgery. Note is also made of a higher rate of grade 3–4 oesophagitis in the definitive chemoradiotherapy arm in comparison to the induction chemoradiotherapy followed by surgery arm in the Intergroup 0139 trial, with all other treatment-related toxicities being comparable between the two groups. The guideline acknowledges survival outcomes were acceptable with both strategies. It also acknowledges the importance of specialist multidisciplinary teams (MDT) and patient choice, recommending that if patients are being considered for multimodality treatment they should be referred to both a thoracic surgeon and a thoracic oncology team.<sup>8</sup> In contrast to the American guidelines described below, induction chemotherapy is not recommended outside of a clinical trial and adjuvant chemotherapy is supported following upfront surgical resection in stage III NSCLC. This was based on an extensive review of the evidence base for induction versus adjuvant chemotherapy which covers all stages of resectable NSCLC (I–IIIA) and does not focus solely on N2 NSCLC. The guideline group noted similar HRs favouring a survival advantage with both induction and adjuvant chemotherapy over surgery alone but were also clear about the limitations of their conclusions due to methodological weaknesses within trials and interstudy heterogeneity in meta-analyses. Overall, the evidence base in the adjuvant setting was felt to be marginally more robust than the induction setting. The NICE lung cancer guidelines are currently being updated with a planned publication in 2019.

#### **AMERICAN COLLEGE OF CHEST PHYSICIANS GUIDELINES: TREATMENT OF STAGE III NON-SMALL CELL LUNG CANCER (2013)**

This guideline defines potentially resectable N2 NSCLC as discrete, clinically evident N2 disease on preoperative imaging.<sup>2</sup> ‘Discrete’ N2 disease is described as easily measurable and defined lymph nodes free from major structures such as the great vessels and trachea. The authors highlight the significant heterogeneity even within the literature on resectable N2 subgroups due to differences in clinical staging, pathological nodal staging and thoroughness of pathological staging.

The guideline recommends that potentially resectable N2 NSCLC should be managed with either definitive chemoradiotherapy or induction therapy (chemotherapy or chemoradiotherapy) followed by surgery. The authors acknowledge that one multimodality treatment has not been shown to be superior to another and conclude ‘the benefits and harms are fairly closely matched. A treatment strategy with induction therapy and surgery is neither clearly better nor clearly worse than chemoradiotherapy.’ They also acknowledge that the Intergroup 0139 study did show a statistically significant improvement in progression-free survival (12.8 months vs 10.5 months,  $p=0.017$ ) with induction chemoradiotherapy followed by surgery over definitive chemoradiotherapy but that this did not translate into a survival advantage given it was offset by a high operative mortality in patients undergoing a pneumonectomy.<sup>6</sup> Many authors and guideline groups have expressed concern about the operative mortality in the pneumonectomy group in the Intergroup 0139 trial from several low-volume centres. Significantly better operative mortality is reported from high-volume expert centres and the importance of minimising risks through utilising such expert centres is highlighted within this guideline. In line with our concerns over the single-station versus multistation N2 distinction in the BTS and SCTS guidelines, the American College of Chest Physicians (ACCP) authors note that the evidence base ‘does not support the concept that surgery for stage III NSCLC can only be justified in patients with minimal burden of mediastinal disease.’

Primary surgery followed by adjuvant chemotherapy in resectable N2 NSCLC is not recommended in the ACCP guidelines, in stark contrast to the BTS/SCTS and NICE guidelines. The support of preoperative chemotherapy over adjuvant chemotherapy is based on the fact that the RCTs in resectable N2 used an induction treatment approach (rather than upfront surgery and adjuvant treatment) and a review of the evidence confirming that induction chemotherapy and surgery improves survival over surgery alone in stage I–IIIA NSCLC. This evidence consists of seven small trials from 1980 to 2011 including trials only published in abstract form and the use of chest radiograph staging. The concern is that this evidence is not comparing preoperative versus postoperative chemotherapy, but preoperative chemotherapy plus surgery versus surgery alone, and not specifically in patients with resectable N2 NSCLC. The fact that giving chemotherapy and surgery is better than surgery alone does not answer the question as to whether chemotherapy should be given before or after surgery.

#### **EUROPEAN SOCIETY OF MEDICAL ONCOLOGY: LOCALLY ADVANCED STAGE III NON-SMALL CELL LUNG CANCER GUIDELINES (2015 AND 2017)**

This guideline defines potentially resectable N2 NSCLC as minimal, non-bulky N2 disease and single-station N2 disease.<sup>3</sup> The authors raise concerns that the evidence base for resectable

N2 originates from an era prior to the widespread use of PET staging, widely available endoscopic nodal staging techniques and outdated surgical and radiotherapy practices. Therefore, the applicability of the results to modern-day practice is questionable.

The guideline recommends that potentially resectable N2 NSCLC can be managed with definitive chemoradiotherapy, induction chemotherapy followed by surgery, or induction chemoradiotherapy followed by surgery. Once again the lack of clear superiority of one treatment regime over another is acknowledged and the paramount importance of an experienced and high-volume MDT and treatment centres able to minimise risk and complications from multimodality treatment is highlighted.

In 2017 this guideline was updated with some notable additions.<sup>9</sup> The 2017 guideline recommends surgical-based multimodality treatment (surgery followed by adjuvant chemotherapy, induction chemotherapy followed by surgery, and induction chemoradiotherapy followed by surgery) in single-station N2 NSCLC. This recommendation however is classified as 'optional' due to insufficient evidence. Definitive chemoradiotherapy is 'preferred' in multistation but resectable N2 NSCLC. As previously stated within this article, we have concerns about the use of single versus multistation N2 as a determinant of whether surgery is indicated and we do not believe the evidence base reflects this. Once again, the 2017 guideline highlights the paramount importance of experienced and expert MDTs in defining and delivering multimodality treatment in N2 NSCLC that minimise risks and maximise outcomes.

#### NATIONAL COMPREHENSIVE CANCER NETWORK NON-SMALL CELL LUNG CANCER GUIDELINES (2018)

The most recent guideline from the National Comprehensive Cancer Network (NCCN) defines potentially resectable N2 NSCLC as low-volume, non-invasive and pathologically proven malignant lymph node disease, with malignant lymph nodes measuring <3 cm. Both this guideline and the 2017 European Society of Medical Oncology update had the opportunity to consider the results of the SAKK trial and ESPATUE trial both published in 2015.<sup>10 11</sup> The SAKK trial demonstrated no significant difference in progression-free survival or overall survival from induction chemoradiotherapy followed by surgery over induction chemotherapy followed by surgery. The ESPATUE trial enrolled a very heterogeneous group of stage III NSCLC including a third of patients with T4N1 disease and a third with stage IIIB NSCLC including N3 disease. The trial showed no difference in overall survival between induction chemoradiotherapy followed by surgery and definitive chemoradiotherapy (table 1). The NCCN guideline also notes the initial results of the PACIFIC trial published in 2017 reporting a statistically significant improvement in progression-free survival in patients given maintenance immunotherapy with durvalumab versus placebo following concurrent chemoradiotherapy in unresectable stage III NSCLC.<sup>12</sup>

The guideline recommends that potentially resectable N2 NSCLC can be managed with definitive chemoradiotherapy or induction chemotherapy followed by surgery or induction chemoradiotherapy followed by surgery. It also recommends that patients undergoing definitive chemoradiotherapy should proceed with maintenance durvalumab subsequently. The guideline is clear that patients with resectable N2 NSCLC should not be excluded from surgery as some will achieve a long-term survival. It is noted that among the NCCN member institutions performing induction treatment for resectable N2 NSCLC,

#### Box 1 Proposed definition of 'Potentially Resectable N2 NSCLC'

- ▶ Pathologically confirmed N2 lymph node disease as part of a thorough nodal staging procedure (surgical or endoscopic) with sampling of at least three lymph node stations.
- ▶ Thorough radiological staging including at least positron emission tomography (PET)-CT and MR brain with contrast.
- ▶ Primary tumour resectable with high probability of clear pathological margins and complete resection, preferably avoiding a pneumonectomy.
- ▶ Easily measurable and defined metastatic N2 lymph nodes free from major mediastinal structures including the great vessels and trachea with no individual lymph node measuring >3 cm.

NSCLC, non-small cell lung cancer.

approximately half are performing induction chemotherapy and half induction chemoradiotherapy.

The NCCN guideline reviews the evidence for chemotherapy given preoperatively versus postoperatively but once again this is a general surgical treatment review for all stages of resectable lung cancer not focused on N2 NSCLC. It concludes that the benefit from preoperative chemotherapy is similar to that of postoperative chemotherapy and either approach is justified. It does make note of evidence that more patients complete the full treatment regime when chemotherapy is given preoperatively compared with postoperatively; 90% vs 61% in an RCT of 624 patients.<sup>13</sup>

#### INTERPRETATION OF GUIDELINES

First, it is important to acknowledge the heterogeneity of N2 NSCLC and the challenges this inherently causes for the interpretation of the evidence base and the formation of consensus recommendations. Going forward, we believe the most useful solution would be an agreed definition of 'potentially resectable N2 NSCLC' that could be used for all further studies of this subgroup to allow a consistent and comparable population to be studied over time. We have proposed such a definition in box 1 by combining the opinions from within the guidelines discussed in this article.

There are some common agreements in this challenging subgroup of patients with potentially resectable N2 NSCLC. The majority of guidelines agree that multimodality treatment is the standard of care using chemotherapy for distant disease control and either surgery, radiotherapy or a combination of both for local control. When definitive chemoradiotherapy is the preferred treatment option this should be given concurrently. The evidence base confirms that no one treatment regime has been shown superior to another. Against some of the guideline recommendations, we believe there is no clear evidence to suggest that single-station or single-zone versus multistation or multizone nodal disease should be used to define different treatment strategies. Therefore, we would propose all forms of multimodality treatment with or without surgery can be considered for all levels of resectable N2 NSCLC.

It is very clear that multimodality treatment is complex and should be done in expert and high-volume centres with decision-making through an equally experienced MDT. In terms of the sequencing of treatment modalities, three of the five guidelines recommend using induction treatment prior to surgery

given this regime was followed within the RCTs from which the recommendations have been developed. The ACCP guidelines use studies of preoperative chemotherapy followed by surgery versus surgery alone as the reason for recommending preoperative treatment rather than in the adjuvant setting whereas the BTS and NICE guidelines suggest the evidence base is more robust in the postoperative setting. The NCCN guidelines sensibly suggest the benefits are relatively similar and either approach is justified. All these guidelines are based on studies looking at predominantly early stage disease which questions the applicability of recommendations specific to N2 NSCLC. We would agree with the NCCN authors that either approach is justified, however we make note of the finding that a significantly higher proportion of patients completed both components of treatment (surgery and chemotherapy) when an induction approach was used in comparison to an adjuvant approach in an RCT.<sup>14</sup> This warrants further investigation and clarification as the completion of both components of this multimodality treatment is critical to optimise outcomes. While the evidence base suggests a similar effect of benefit from chemotherapy in both induction and adjuvant settings, if more patients are able to complete both components of treatment in an induction setting this approach would lead to the best outcomes.

This discussion has all been predicated on the assumption of a patient's adequate physiological reserve to withstand the impact and potential toxicity of multimodality treatment. Robust physiological assessment aligned to that described in early stage lung cancer<sup>1 14</sup> surgery should also be applied in N2 NSCLC and strategies to optimise patients' physical status before, during and after multimodality treatment are considered best practice (smoking cessation, nutritional support, prehabilitation and rehabilitation). Fitness for treatment will be a critical factor in decision-making process and it is noted that patients over the age of 75 are under-represented in the evidence base, particularly, for example, in the adjuvant chemotherapy trials.

## CONCLUSIONS

Potentially resectable N2 NSCLC is a very challenging subgroup of NSCLC. The authors of this article suggest that the standard of care is multimodality treatment with chemotherapy for distant disease control and surgery, radiotherapy or a combination of both for local control. Joint decision-making with the patient is critical in defining the most appropriate regime. The sequence of treatments will be highly dependent on local services and expertise. Single-station or zone versus multistation or zone disease should not be a determining factor in treatment regimes.

Long-term survival in this group remains poor. In the UK only one in five patients are treated with multimodality treatment and only 1 in 100 with trimodality treatment. Further data are awaited from the PACIFIC trial on overall survival with adjuvant immunotherapy and additional studies of immunotherapy following surgical resection (eg, PEARLS Trial NCT02504372) are under way. These studies may improve patient outcomes,

further expand the treatment options and add to the challenge of management decisions in this important group of patients. Expert centres at a regional level that specialise in the management of multimodality and complex treatment regimens that monitor performance and outcomes robustly may be a potential solution to this and a way to maximise access to the most effective treatment in this subgroup of patients. This could also ensure access to emerging treatment strategies (eg, maintenance immunotherapy) and future clinical trials in a robust and systematic method allied to the same quality assurance processes.

**Contributors** ME, FM and TB all contributed to the concept, evidence review, content and editing of this manuscript. ME led the manuscript writing. ME, FM and TB are responsible for the overall content as guarantors.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

- Lim E, Baldwin D, Beckles M, *et al.* Guidelines on the radical management of patients with lung cancer. *Thorax* 2010;65:iii1–27.
- Ramnath N, Dilling TJ, Harris LJ, *et al.* Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e314S–40S.
- Eberhardt WE, De Ruyscher D, Weder W, *et al.* 2nd ESMO Consensus conference in lung cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol* 2015;26:1573–88.
- Rusch VW, Crowley J, Giroux DJ, *et al.* The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:603–12.
- van Meerbeeck JP, Kramer GW, Van Schil PE, *et al.* Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442–50.
- Albain KS, Swann RS, Rusch VW, *et al.* Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374:379–86.
- Rusch VW, Asamura H, Watanabe H, *et al.* The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568–77.
- Excellence NfHaC. Lung cancer: diagnosis and management. In: *NICE Clinical Guideline*, 2011:CG121.
- Postmus PE, Kerr KM, Oudkerk M, *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28:iv1–iv21.
- Pless M, Stupp R, Ris HB, *et al.* Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet* 2015;386:1049–56.
- Eberhardt WE, Pöttgen C, Gauler TC, *et al.* Phase III Study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and Selected iiib non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPAUE). *J Clin Oncol* 2015;33:4194–201.
- Antonia SJ, Villegas A, Daniel D, *et al.* Durvalumab after chemoradiotherapy in stage III Non-small-cell lung cancer. *N Engl J Med* 2017;377:1919–29.
- Felip E, Rosell R, Maestre JA, *et al.* Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010;28:3138–45.
- Brunelli A, Kim AW, Berger KI, *et al.* Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e166S–90.