Lung cancer: diagnosis and management (March 2019) (update)

Consultation on draft guideline - Stakeholder comments table
10/10/2018 – 7/11/2018

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Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Abbott Nutrition	Guideline	10	12	We are concerned that the dietitian is not mentioned as a part of the multi-disciplinary team, nor the speech and language therapist for assessment of dysphagia. Both therapies play a pivotal role in the nutritional management of patients, improving symptom control and quality of life and increasing the potential of reducing the risk of admissions and delayed treatments secondary to poor nutritional status[1].	Thank you for your comment. This area was out of scope for this update of the guideline.
Abbott Nutrition	Guideline	11	8	We are concerned that the 'Treatment' section does not include screening for malnutrition e.g. using the Malnutrition Universal Screening Tool (MUST), as per outlined for all inpatients and outpatients in NICE CG32[2]. Undernutrition and cachexia are common in cancer patients[3]. Evidence has indicated that around 40-60% of lung cancer patients experience unintentional weight loss[4,5] and that weight loss can have a negative impact on the effectiveness of treatments and overall prognosis of lung cancer patients [4,6]. Therefore, early identification of malnutrition is critical.	Thank you for your comment. This area was out of scope for this update of the guideline.
Abbott Nutrition	Guideline	11	8	We feel potential nutritional interventions should also be included in the 'Treatments' section. The NICE CG32[2] guideline states that healthcare professionals should consider using either 'oral, enteral or parenteral support, alone or in combination, for people who are either malnourished of at risk of malnutrition' (1.3.3). There is evidence to demonstrate that in cancer patients, if undernutrition already exists and normal food intake is insufficient, enteral nutrition should be started and that during radio- or radio-chemotherapy, intensive dietary	Thank you for your comment. This area was out of scope for this update of the guideline.

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				advice and oral nutritional supplements can help to increase dietary intake and prevent weight loss[3].	
Abbott Nutrition	Guideline	5	3	We feel a statement around ensuring the patient is aware of allied health care professionals e.g. the dietitian, speech and language therapist and/or referring to appropriate health care professionals is required.	Thank you for your comment. This area was out of scope for this update of the guideline.
Action on Smoking & Health	Guideline	11	8-19	ASH welcomes the continued inclusion of 'Stop smoking interventions and services' under NICE guidance on the treatment of lung cancer as well as the inclusion of reference to the recently updated NICE NG92 in place of reference to the now replaced NICE PH10 Smoking cessation services. It is important that smoking cessation and the treatment of tobacco dependency remain a fundamental and embedded component of the lung cancer treatment pathway. With regard to line 12, (recommendation 1.4.2) the importance of telling those diagnosed with lung cancer why it is important to stop smoking cannot be overstated. The risk is not only, as line 10 (recommendation 1.4.1) outlines, an increased risk of pulmonary complications after lung cancer surgery. Most importantly, those diagnosed with lung cancer who smoke should be informed that those who quit smoking after diagnosis of lung cancer live longer on average than those who continue to smoke, and should be offered support to quit. Recent research has shown those who stopped	Thank you very much for your comments. Thank you for your comment This specific advice with regards to stopping smoking was out of scope for this update of the guideline. We have however included a link to the NICE

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				smoking and survived their treatment lived 1.97 years on average compared to only 1.08 years for those who continue to smoke after diagnosis.[i] With nearly a third of lung cancer patients smoking at diagnosis, and estimates of between 13% to 60% of smokers with lung cancer continuing to smoke after diagnosis,[ii] it's essential that all smokers with lung cancer are given advice to quit and referral to specialist support. Such practice is in line with NICE NG92 and the recent Royal College of Physicians report, *Hiding in Plain Sight: Treating Tobacco Dependency in the NHS* (2018). The report examined NHS practices in addressing harms and costs arising from smoking among patients and argues for a comprehensive approach to treating their addiction: "*smoking cessation should be incorporated… as a systematic and opt-out component of all NHS services, and delivered in smoke-free settings. It is unethical to do otherwise*".[iii] Further, findings from an analysis of over 12,000 electronic patient records show that cancer patients receive less support from their GP to quit smoking, with just 24% being offered advice to quit, and only 13% being prescribed treatment.[iv] This is despite advice and treatment for smoking being capable of increasing a smoker's chances of quitting up to fourfold.[v] This is also despite treatment for smoking cessation costing between £300-£6,000 per QALY,[vi,vii] and thus proving to be highly cost-effective. Indeed, smoking cessation interventions compare favourably with new, high-cost drugs like pembrolizumab, which costs around £86,913	guideline on stop smoking interventions and services. This area was out of scope for this update of the guideline. We have however included a link to the NICE guideline on stop smoking interventions and services.

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				per QALY for an increased life expectancy of 1.32 years over chemotherapy according to recent research.[viii] Therefore, whilst the guidance as outlined under recommendation 1.4, lines 8-19 are positive in including smoking cessation as part of the treatment pathway, there is scope to improve the guidance by strengthening its messaging around the importance of smoking cessation, which, as poor performance of GP advice and treatment for smoking cessation in patients diagnosed with lung cancer demonstrates, is much needed.	
AstraZeneca UK	Guideline	General	General	The updated guidelines are difficult to navigate in a number of places and it is difficult to understand why certain recommendations have been presented in the order they have. For example: • on page 13, there is a single recommendation (1.4.19) in the section "Assessment before radiotherapy with curative intent" (line 5-8). Meanwhile, on page 14 under the section on "Radical radiotherapy for people not having surgery", recommendations 1.4.29, 1.4.30 and 1.4.31 all refer to what should happen to patients before they start radical radiotherapy. • Similarly, given that recommendations 1.4.40 - 2 on p15 refers to patients with "stage IIIA–N2 NSCLC who are well enough for multimodality therapy and	Thank you for your comment. The committee is in agreement. We have moved 1.4.29-31 to the beginning of this section.

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				can have surgery" (our emphasis), these recommendations ought to be placed with others referring to patients who are suitable for, and have given consent to, surgery (e.g. immediately before recommendation 1.4.26 which describes what to consider for eligible patients with stage IIIA NSCLC who cannot tolerate or decline chemoradiotherapy +/- surgery). We believe NICE could take this opportunity to rationalise the recommendations and present them in a much more logical way which is more aligned to clinical practice. In order to minimise the scope for confusion and uncertainty, NICE could consider including a diagram outlining the decisions and treatment options considered appropriate for patients with different diagnoses and staging (see Postmus 2017 for examples). Such diagrams of potential treatment options are commonly used by NICE themselves during Technology Appraisals and are extremely useful in understanding what treatment pathways are appropriate for different types of patients.	Thank you for your comments. NICE is mindful to make their guidelines user friendly. However this was a partial update of the guideline and it wasn't appropriate to significantly restructure the guideline as proposed.
AstraZeneca UK	Guideline	General	General	We note that the Committee are aware of the existence of relevant data from the PACIFIC study which was not included in the evidence base informing new recommendations due to the timing of the publication of this data and the availability of durvalumab to UK NHS patients. However, given the survival benefits demonstrated by this new treatment regimen (i.e. chemoradiotherapy followed by durvalumab for 12 months), an explicit reference should be	Thank you for your comment. This area was out of scope for this update of the guideline because of the reasons you have noted and because the review question only concerned patients with resectable disease. NICE technology appraisal guidance on durvalumab maintenance in unresectable disease is due to be published in May 2019.

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				made in the Guidelines to the rapidly changing evidence base in this area and emerging therapies.	
AstraZeneca UK	Evidence Review C	General	General	Recommendations 1.4.40 and 1.4.41 are not sufficiently supported by the evidence provided in Evidence Review C. The authors of the Evidence Review informing these recommendations explicitly note a number of issues in the evidence-base available as well as the outputs of the NMA and economic model produced, which do not appear to have been given an appropriate weighting by the committee. 1. The outcomes reported in the NMA were not directly reported in the underpinning trials (p9, line 32), which has the potential to introduce uncertainty and confusion in clinicians familiar with the original data when interpreting the outputs of the NMA. 2. The committee report that *"The available evidence showed that CRS are more effective than CR in people who are well enough for surgery."* (p12, line 16-17) but this statement ignores the observation in the same paragraph that: *"The key benefit associated with CRS is the longer PFS time. However, there are some uncertainties in the evidence:* • *It was not possible to tell whether CR or CS provide better survival outcomes* • *The evidence in favour of CRS involved indirect comparisons, and no head-to-head trials showed meaningful differences in outcomes for any of the interventions." (p12, lines 19-26)*	Thank you for your comment. Please see the thematic response on the management of resectable stage IIIA-N2 NSCLC at the end of this document for further information.

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				3. When interpreting the evidence the committee agreed that the outcome that matters most is mortality (p13, line 3), but acknowledge that none of the RCTs included in the NMAs found any difference in overall survival (p13, line 9-10). 4. It is unclear how the economic model produced from (primarily the outcomes of the NMA) could produce basecase ICERs of less than £20k/QALY for CRS vs CR, when CRS is acknowledged to be the most expensive option and is not associated with any survival benefit. 5. The committee noted that none of the trials included in the NMA and informing the economic model were conducted in a UK setting and many recruited patients before the widespread adoption of recent advances in surgical and radiotherapy techniques and newer targeted therapies and immunotherapies for advanced NSCLC (p14, lines 28-33). Taking all of the considerations above into account, we are concerned about how the committee decided that a 'consider' recommendation in favour of CRS was justified by the evidence available given the uncertainties described. We note that in the latest guidelines for early and locally advanced breast cancer (NG101), a table outlining the benefits and risks of radiotherapy- compared with no radiotherapy-containing regimens is provided (Table 5, recommendation 1.10.7, NG101). Given the uncertainties in the evidence described above, we strongly believe that clinicians would value a similarly clear presentation of the	

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				benefits and risks of the various multimodality treatment options under consideration for patients with defined characteristics.	
Barnsley Hospital NHS Foundation Trust	Quality Standard	11	6	I am concerned that the definition of a lung cancer nurse specialist specifies only 20 credits at 1st degree level in the specialised area. I feel that it should be a minimum of a 1st level degree	Thank you for your comment. NICE will be fully updating the quality standard for lung cancer (QS17) following publication of the updated guideline. We will consider your feedback accordingly. We expect to publish the updated quality standard in January 2020.
Barnsley Hospital NHS Foundation Trust	Guideline	16-18	General	The new algorithm for treating non-squamous NSCLC is excellent.	Thank you for your comment.
Barnsley Hospital NHS Foundation Trust	Guideline	18-19	General	The new algorithm for treating squamous NSCLC is excellent.	Thank you for your comment.
Barnsley Hospital NHS Foundation Trust	Guideline	21	5	Question: Has the age limit recommendation for people with small cell lung cancer receiving PCI been removed?	Thank you for your comment. There was no mention of patient age in PCI recommendations in the 2011 version of the guideline.
Barnsley Hospital NHS Foundation Trust	Guideline	4	7-9	We are concerned that the guideline for referral with suspected lung cancer doesn't specify that a person can be referred with a normal CXR and symptoms of concern but stated only symptoms of concern. Many people are being referred as suspected lung cancer with no imaging whatsoever which delays diagnosis and creates delays in OPA due to capacity and demand	Thank you for your comment. This area was out of scope for this update of the guideline. The recommendation was merely updated to refer to the guidance on Referral for Suspected Cancer, which had been published since the last time this guideline was updated.

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Belfast Health and Social Care Trust	Guideline	15/45	15-17	Guideline makes too strong a recommendation for pre-operative chemo radiotherapy for patients with operable IIIA-N2 NSCLC, and is not qualified enough The clinical trials evidence quoted to underpin this recommendation (over sequential chemotherapy and surgery, CS) does not seem to conclude that pre-op chemoradiation CRS should be considered as an improvement of pre-op chemotherapy The one randomised trial of definitive chemoradiation (CR) versus induction chemoradiation with surgery (CRS) shows improved progression free survival, but not overall survival and a higher rate of individuals dying without progression in the surgery group, in a very selected patient population IIIA-N2 disease is a very heterogeneous; the bulkiness of the mediastinal lymph nodes is often a criterion for trial entry (the bigger the bulk, the less likely to be effectively cleared with surgery). IIIA-N2 may notionally be subdivided into 1. IIIA-N2 low bulk (eg single station non- bulky / microscopic N2); Fit for surgery (may in fact be N2 only detected at surgery) 2. IIIA – N2 bulky 3. IIIA – N2 (between 1 nor 2) Prior to PACIFIC / Immunotherapy post CCRT) my thinking would have been ; Category one is the least frequent, but would seem notionally to be the best place for surgery. Requires fit	Thank you for your comments. Please see the thematic response to comments on the recommendations for management of resectable stage IIIA-N2 NSCLC at the end of this document.

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				patients who would also be able to have adjuvant chemotherapy. Category 3 is most frequent and would best be seen as place for definitive concurrent chemoradiation if fit… In practice many patients are not fit and in Uk receive radiotherapy alone (see Harden S WLCCC 2018 abstract – All stage III 13% radical surgery, 10% chemo and radiotherapy (6% sequential, 4% concurrent estimated), 6% radical radiotherapy alone, 71% palliative therapy only. Of those receiving surgery only approx. 50% receive chemotherapy (? due to fitness) The PACIFIC study using adjuvant immunotherapy post concurrent chemoradiation has now reported an improvement in overall survival. (Given that the current draft guideline is not likely to be updated for another two years it would seem prudent that the committee should review this PACIFIC trial evidence, given that it will have a major impact on the relative effectiveness of CR versus CRS). (perhaps the current standard of care has now shifted to Concurrent chemoradiation and immunotherapy) The clinical trials which are used in the analysis, to my mind conclude 1, Pre-op chemoradiation has by and large only been considered in clinical trials for fit PS0-1, non-elderly , operable patients 2. Clinical outcomes do not support CRS is better than CS	

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				3. Type of surgery is important; higher mortality with pneumonectomy 4. Some studies have used sequential chemotherapy followed by radiotherapy followed by surgery (best sequencing has not been defined- presumably requires further research.). 5. Only one RCT of CR vs CRS showing improvement in progression free survival for surgery arm but not overall survival (?? toxicity from surgery) ; 6.(adjuvant) Immunotherapy studies post definitive CCRT now do need to be taken into account by the committee; I would only advocate CRS if full dose definitive CR was given and surgical resection considered afterwards (without a pneumonectomy) in VERY fit patients The evidence quoted to underpin the recommendation for CRS (over sequential chemotherapy and surgery) does not seem to conclude that pre-op chemoradiation should be considered as an improvement of pre-op chemotherapy. Thomas M "Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III NSCLC" Lancet Oncol 2008 9 636-648 Phase III in operable IIIA-B PS0-1 (age < 70yr). Randomised preop EP followed by 45Gy/30 bd RTX with weekly carbo/vindensine then surgery versus preop EP then surgery with post op radiotherapy. 35% of patients required a pneumonectomy. There was no difference in progression free survival or overall survival. The mortality with	

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				pneumonectomy was high in the chemorad preop arm (14%). The trial concluded that whilst endpoints such as mediastinal downstaging might be improved "preoperative chemoradiation... does not improve overall survival" Pless M et al "Induction chemo radiation in stage IIIA/N2 NSCLC: a phase 3 randomised trial" Lancet 2015 386 1049-56. Randomised trial of sequential docetaxel cisplatin 3 cycles followed by 44Gy/22 fractions followed by surgery or doce cisplatin chemotherapy alone followed by surgery. Patients were pathologically proven N2 PS0-1, operable aged 18-75 years. There was no difference in overall survival or progression free survival. 25% of patients required a pneumonectomy. The trial concluded "Radiotherapy did not add any benefit to induction chemotherapy followed by surgery" A randomised study closed early due to slow accrual from WJ group. "A phase 3 study of induction treatment with concurrent chemo radiotherapy versus chemotherapy before surgery in patents with pathologically confirmed N2 stage IIIA NSCLC (WJTOG9903)" Katakami N Cancer 2012 118 6126-6135. Only 60 patients were randomised. Patients felt better suited for definitive concurrent chemoradiation were excluded. Patients had to be potentially operable. Patients were PS 0-1 and <= 70 years old. Patients were treated with either induction carboplatin and docetaxel for 2 cycles or carboplatin and docetaxel with 40Gy thoracic radiotherapy. The authors commented "overall survival also did not improve in the CRS arm versus the CR arm" and "Progression free survival did not improve".	

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				A hazard plot of NICE meta-analysis (appendix G page 88) shows confidence intervals cross 1. The randomised studies all concur that there is no benefit in the endpoints of progression free or overall survival. There may be some benefit in down staging of the mediastinum and an increase in treatment related toxicity, but these do not translate into hard endpoints of survival and progression-free survival. The trials include hyperselected patients (good performance status, fitness for surgery and age < 70 years). These results may not be applicable to the general stage III population in the UK. The committee's recommendation that chemoradiation should be considered seems at best too strong and at worst at odds with the available clinical evidence. In our centre's experience surgery is possible after concurrent chemoradiation but it is tough treatment and only feasible for the fit few. CRT vs C prior to surgery may benefit from larger clinical trials, although this seems unlikely given poor accrual in previous studies. We would agree with the authors from all the studies quoted; there is no evidence that the addition of radiation in the pre-operative setting improves survival. Advantage of CRS over CR; A meta-analysis of studies of CRT and CS found no overall survival or progression free survival difference, but noted an excess mortality rate ion first 6 months after surgery. Pottgen et al Oncotarget 2017 8(25) 41670-41678. 2 of the 6 studies included compared CRS vs CR.	

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				Only one clinical study hinging on the relative advantage of PFS over no advantage in Overall survival. This has two main concerns 1. Ability to reproducibly detect local progression over radiotherapy scarring 2. The higher number of non-cancer deaths in the surgical arm. Albain et al "Radiotherapy plus chemotherapy with or without surgical resection for stage III NSCLC: a phase III RCT" Lancet 2009 374 379-386. Randomised patients with pathologically proven N2 disease felt to be potentially resectable but in whom definitive concurrent chemoradiation was considered standard of care over surgical resection alone. Had to be PS 0-1. Median follow up was 23 months. The definition of local progression in the CR group was not defined in the paper. It can be very difficult to determine local radiation progression from radiation scarring even several years after radiotherapy. (our current algorithim requires PET/Ct and biopsy confirmation or enlarging mass). The only difference in relapse patterns was more local progression in the CR versus CRS arms. (progression free survival can be very difficult to interpret in radiation studies in which residual scarring is left ; obviously in the surgery arm this scarred lung would have been removed making it easier to define local progression). A better progression free survival was seen (+ 3 months progression free). 5yr PFS difference was noted (although median follow up was only 23m) 22% vs 11%. However more individuals died without	

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				progression in surgical arm 18% versus 10% (p=0.02) (? from complications/ physiological stress leading to mortality – heart/ lung). Pneumonectomy was found to have a high mortality in this study. The trial did allude to a survival improvement in the lobectomy group, but this is a post hoc analysis. It is however worthy of further study and may represent a patient population in whom to take this paradigm further forward in. The trial is unable to answer the question of whether induction chemotherapy would have been equivalent / better than induction chemoradiation. The trials conclusion that PFS is improved was not seen in the ESPATUTE study or EORTC 08941. Conclusions 1. It is likely that the SOC for stage III NSCLC will become CR and adjuvant I/O (PACIFIC study) and this should at least be considered in the modelling exercise to future proof the conclusions 2. There is no good evidence that CRS is better than CS in improving survival 3. The standard of care to date in this patient population has been definitive CR 4. It is possible for some patients that CRS may be a feasible option. But this is in a hyper-selected population (fitness for chemo, radiotherapy and surgery); good PS, few comorbidities, good respiratory and cardiac function, surgically operable (without pneumonectomy). This is a very limited	

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				patient population and this needs to be clearly stated in any recommendation 5. A recognition that stage III-N2 disease is a heterogeneous population and that subgroups may benefit from different treatment approaches would be welcomed.	
Boehringer Ingelheim Ltd	Systemic anti-cancer therapy management –non squamous visual summary	General	General	The recent phase 3 trial Keynote 189 results concluded that adding pembrolizumab to standard chemotherapy with pemetrexed and a platinum-based drug resulted in a risk of the two primary end points that was approximately 50% lower than the risks with standard chemotherapy alone in patients with untreated, metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations. TA [ID1173] is expected by December 2018 which is within time scope of final development and publication of this guideline. Based on these results, we propose the inclusion of Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer as first line option into "no gene mutation or fusion protein and PD-L1 <50% section" of visual summary above platinum doublet chemotherapy, Pemetrexed + Cisplatin and Pemetrexed and Carboplatin.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Boehringer Ingelheim Ltd	Guideline	7	23	The guidance on EGFR-TK mutation testing is referenced from "NICE diagnostics guidance on EGFR-TK mutation	Thank you for your comment. Although this recommendation was updated in

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				testing" dated 2013. Review of this guidance is stated to be every 3 years, and we note that this is overdue. Will consideration be given to updating this guidance? EGFR testing at primary diagnosis and at disease progression is an important aspect of management. The following has been incorporated recently into recent international guidelines. "Around 90% of the most common mutations comprise deletions in exon 19 and the L858R substitution mutation in exon 21. Any testing approach must cover these mutations [I, A]; however, complete coverage to include exons18–21 is recommended [III, B]. The T790M exon 20 substitution mutation is only rarely found in EGFR TKI-naive disease using standard techniques but is the most frequent cause of resistance to first- and second-generation EGFR TKIs (50%–60% of cases)" (Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up September 2018) It would be useful to see NICE guidance reflect the need for T790M testing on disease relapse to be carried out in each patient.	order to bring it into alignment with other NICE guidance, this area is out of scope for this update of the guideline and the committee were therefore unable to make any additional recommendations. As with all the biomarkers, gene rearrangements and fusion proteins that indicate certain systemic therapy options in that section of the guideline and treatment algorithms, the committee believe that the need for testing in appropriate patients is implicit.
Boston Scientific	Guideline	8-9	18-25 Line 1-11	We would kindly ask NICE to consider systematic prophylactic early screening of patients at risk for lung cancer through minimally invasive techniques. Early lung cancer detection and staging in this patient group improves clinical outcomes and increases survival benefit.	Thank you for your comments. Screening is beyond the remit of NICE. Endobronchial ultrasound miniforceps biopsy is out of scope for this update of the guideline.

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				We would suggest that NICE includes in this review 2 studies showing improved diagnostic yield of Endobronchial ultrasound miniforceps biopsy (EBUS-MFB) particularly when combined to EBUS-TBNA: • Ara Chrissian, David Misselhorn, and Alexander Chen. Endobronchial-Ultrasound Guided Miniforceps Biopsy of Mediastinal and Hilar Lesions. Ann Thorac Surg 2011;92:284 –9. • Felix J. F. Herth, Ross K. Morgan, Ralf Eberhardt, and Armin Ernst, MD, FCCP. Endobronchial Ultrasound-Guided Miniforceps Biopsy in the Biopsy of Subcarinal Masses in Patients with Low Likelihood of Non-Small Cell Lung Cancer. Ann Thorac Surg 2008;85:1874 –9.	
Bristol Myers Squibb Pharmaceutical Ltd	Guideline	16-19	General	In the systemic anti-cancer therapy for non-small cell lung cancer (NSCLC) space there are many HTA's undergoing review at this point in time which will impact the majority of the clinical landscape. So it may be worth delaying publication of the guidelines until the conclusion of these HTAs - to allow incorporation of the HTA recommendations.	Thank you for your comment. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Bristol Myers Squibb Pharmaceutical Ltd	Guideline	7	22	Our concern is that reference should be made to new biomarkers with an emerging evidence base in lung cancer, in addition to those that are fully established. We therefore feel that some guidance on these should be included. We recommend the following sentence be added: '*These*	Thank you for your comment. Although this recommendation was updated in order to bring it into alignment with other NICE guidance, this area is out of scope for this update of the guideline and the

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				include but are not exclusive to EGFR, ROS1, ALK, PD-L1 and tumour mutational burden (TMB)' Our rationale for suggesting that TMB be included stems from the recent publication of the new ESMO Guidelines for Lung Cancer which now advise that TMB status can be used to guide the use of immunotherapy in the first line setting.[1] Tissue availability for diagnostic testing is becoming increasingly important, particularly in the metastatic setting where samples are usually small and potentially inadequate for biomarker testing. We recommend a sentence be added to emphasise that clinicians pay close consideration to the testing and requisite tissue needs for each patient and that a repeat biopsy may be required to obtain more tissue for testing if clinically appropriate.	committee were therefore unable to make any additional recommendations.
British Dietetic Association	Guideline	11	21	This section should include a recommendation to nutritional screen these patients and refer those at risk or already malnourished to a dietitian for assessment and management	Thank you for your comment. This area was out of scope for this update of the guideline.
British Dietetic Association	Guideline	11	22	There is growing evidence of the importance and impact of prehabilitation prior to thoracic surgery which should encompass nutritional and exercise advice.	Thank you for your comment. This area was out of scope for this update of the guideline.
British Dietetic Association	Guideline	13	5	This section should include a recommendation to nutritional screen these patients and refer those at risk or already malnourished to a dietitian for assessment and management	Thank you for your comment. This area was out of scope for this update of the guideline.
British Dietetic Association	Guideline	14	17	This section should include a recommendation to nutritional screen these patients and refer those at risk or already malnourished to a dietitian for assessment and management	Thank you for your comment. This area was out of scope for this update of the guideline.

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British Dietetic Association	Guideline	15	19	This section should include a recommendation to nutritional screen these patients and refer those at risk or already malnourished to a dietitian for assessment and management	Thank you for your comment. This area was out of scope for this update of the guideline.
British Dietetic Association	Guideline	24	1	Before these symptoms can be managed they need to be detected and therefore some recommendations are required on the type of symptoms to assess for including weight loss, loss of appetite, difficulty swallowing, fatigue and depression using validated screening tools as appropriate or at least validated toxicity scores. Where there is evidence of weight loss and poor appetite a recommendation should be to consider referral to a registered dietitian.	Thank you for your comment. This area was out of scope for this update of the guideline.
British Dietetic Association	Guideline	General	General	There is inadequate consideration of the impact of poor nutritional status on the outcome to any treatment modalities when there is strong evidence that weight loss and muscle loss are independent predictors of outcomes in surgery, radiotherapy, and chemotherapy and TKI treatments.	Thank you for your comment. This area was out of scope for this update of the guideline.
British Dietetic Association	Guideline	General	General	In line with NICE guideline CG32 nutritional supports in adults all patients admitted or attending out-patient clinics should be nutritionally screened and this should be incorporated in this guideline.	Thank you for your comment. Screening is beyond the remit of NICE.
British Dietetic Association	Guideline	General	General	Given the high risk of malnutrition and cachexia in this population as well as the nutritional consequences of the different treatment modalities the importance of access to dietetic services should be included.	Thank you for your comment. This area was out of scope for this update of the guideline.
British HIV Association	Guideline	11	8	BHIVA suggests that, as part of statements about the treatment of lung cancer, the following is included: "Patients known to be HIV-positive with suspected lung cancer should be investigated and treated in the same way	Thank you for your comment. This area was out of scope for this update of the guideline.

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				as those in the general population. All HIV-positive patients with a lung cancer should be initiated on antiretroviral therapy and, if commencing anti-cancer therapy, particular attention to be paid to potential drug-drug interactions. Prophylaxis against opportunistic infections should be considered in all HIV positive patients undergoing systemic anticancer therapy for lung cancer."	
British Thoracic Oncology Group	Guideline	General	General	Systemic therapy: There are many recommendations for systemic therapies made in this draft document that are likely to be out of date by the time this draft guidance is finalized or shortly thereafter due to the large number of systemic therapy appraisals on-going at the moment eg first line osimertinib (ID 1302), consolidation durvalumab in stage 3 NSCLC (ID 1175), pembrolizumab in combination with platinum-pemetrexed chemotherapy (ID 1173). How do NICE plan to take account of rapidly changing systemic therapies in these guidelines and treatment algorithms? Mediastinal staging: A thorough work up for N2 disease pre-operatively is recommended as it would change the treatment paradigm from N0. We note that mediastinal staging recommendations refer to 'mediastinal nodes' throughout, thereby excluding hilar nodes (which could N1 or N3). Patients with enlarged N1 nodes & normal mediastinal nodes should undergo staging EBUS regardless of PET findings (false negative	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. Thank you for your comments. The committee is in agreement. Therefore, the word "mediastinal" has been changed to "intrathoracic" for recommendations 1.3.16 and 1.3.20. All references to neck ultrasound has also been removed in the recommendations. Furthermore, for recommendation 1.3.20, the committee have added:

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				rate for N2-3 of 25% - see 2013 ACCP guidelines and meta-analysis data). The current draft guidelines encourages a lack of nodal staging in cN1 disease because the mediastinal nodes seem normal on CT and this lack of pathological staging may lead to missed N2/3 disease.	"using a systematic approach". In order to clarify this, there is now a footnote describing the systematic approach. This systematic approach is consistent with the methodology used in the ASTER and BOOST trials. The algorithm of intrathoracic staging has also been revised accordingly.
				Role of SABR: SABR treatment for early lung cancer is only offered by around 50% of UK radiotherapy centres (unpublished data - UK SABR Consortium survey 2018) these recommendations therefore need to trigger a significant change in practice in the remaining centres and thinking within NHS England to facilitate that change. SABR fractionation schedules are not specifically mentioned in these guidelines. It is assumed that the SABR consortium schedules of 54Gy/3#, 55Gy/5#, or 60Gy/8# would be reasonable.	Thank you for your comment. The committee were in agreement. Therefore, for recommendations mentioning SABR, we have added the following footnote: "For SABR fractionation schedules, use the SABR Consortium's SABR Guidelines".
				1.3.20 We suggest Neck USS and biopsy should be performed in any patient with enlarged or FDG avid nodes in the neck regardless of mediastinal node size. In the context of normal neck nodes on CT then routine neck USS will add delay to the diagnostic pathway and is based on single centre retrospective data and does not reflect national or	Thank you for your comments. The committee is in agreement. Therefore, the word "mediastinal" has been changed to "intrathoracic" for recommendations 1.3.16 and 1.3.20. All references to neck ultrasound has also been removed in the recommendations.

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				international practice. In the algorithm of mediastinal staging, neck USS and biopsy is recommended only when neck nodes are abnormal / pathological on CT and this is agreed with, although there is no obvious reason to restrict it to only those with mediastinal nodes >20mm, but to be the case for all patients. We recommend removing the statement about doing neck USS in all patients with mediastinal nodes >20mm (it could be an option based on local services but straight to PET and sonographic staging of the mediastinum also entirely appropriate and likely most efficient).	Furthermore, for recommendation 1.3.20, the committee have added: "using a systematic approach". In order to clarify this, there is now a footnote describing the systematic approach. This systematic approach is consistent with the methodology used in the ASTER and BOOST trials. The algorithm of intrathoracic staging has also been revised accordingly.
				1.3.24-1.3.26: The draft guidelines propose withholding brain imaging to patients with stage 1 NSCLC, staged contrast enhanced CT and the MRI in stage 2 NSCLC if initial CT suspicious and MRI in stage 3 NSCLC. However, when faced with a patient undergoing staging, the histology of the lesions are unknown and brain imaging is routinely ordered alongside a PET so as not to delay patient staging. To wait for histology and PET results to then go back to the patient having completed staging (perhaps with a neck ultrasound also) for stage-specific CNS imaging is not a good use of resources and will inevitably result in delay to treatment. It is also incompatible with the NOLCP. Moreover, those patients with a normal CT are conversely those most likely no need an MRI to exclude occult metastatic	The review, analyses and economic model conducted for this area of the guideline were confined to patients who had already been deemed candidates for radical treatment. This decision was based on NICE's surveillance review and scoping workshop with stakeholders showing the availability of evidence in this population as well as discussions with the committee. The economic model concluded that offering brain imaging in stage II and III would be cost-effective (see Evidence Review B for a full discussion). Indeed, any increase in brain imaging in stage IIIA disease leads to net cost-savings through reduction in

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				disease. Therefore, it makes more sense for all patients potentially likely to be radically treated to undergo dedicated contrast enhanced brain MRI staging. If stage 1 NSCLC is known and staging completed *a priori* then not imaging the brain is reasonable.	the use of expensive radical treatments. The committee were mindful of the potential delay to treatment for some patients associated with the new recommendations and the potential cost-effectiveness of adding CT brain to initial chest CT and made recommendation for research in this area. The committee were also aware that there are pressures on imaging services, particularly MRI scanners and that some patients prefer not to receive MRI scans but agreed that these considerations should not affect the recommendations. It should be borne in mind that the cost-effectiveness considerations are quite different at initial staging as many patients would not have gone on to have radical treatment regardless of the brain imaging result.
				1.4.24-25 Contraindications for SABR do exist and should be highlighted: e.g. central / ultra-central NSCLC would need to be highlighted contra-indication to SABR. This section on role of radiotherapy does not mention stage IIB, in particular T1a-cN1M0 and the subsequent sections moves to stage 3 NSCLC.	Thank you for your comment. Unfortunately, there is a paucity of evidence on this specific aspect. For example, almost all of the studies are retrospective. As a result, they do not have details of how participants were selected on the basis of suspicious node location.

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				1.4.26-28 At least 10 centres still routinely use CHART across the UK. Randomised phase III trial evidence that CHART is superior to conventional XRT (60/30#) so this should not be recommended as an equivalent alternative. There is very limited evidence for 66Gy / 33# being superior and conversely, there is good evidence in the concurrent chemoradiotherapy setting that conventional dose-escalated schedules give worse outcomes (RTOG 0617).	Thank you for your comment. There is one RCT on CHART: Saunders 1999. This is not sufficient evidence to replace conventional radiotherapy with CHART. In addition, since 1999 the technology for both CHART and conventional radiotherapy has no doubt improved. Without a more up-to-date study, it is difficult to speculate what difference there is between them, if any. Furthermore, the committee agreed that there is very little difference between CHART and CHARTWEL. The one RCT that has CHARTWEL showed very similar results to conventional fractionation. RTOG 0617 is Bradley 2015. This RCT compares conventional radiotherapy doses of 60 Gy to 74 Gy. This study was included in our evidence review. Mortality (all-cause hazard ratio) favoured the CF 60 Gy group compared to the CF 74 Gy group. This finding supports the current wording of the updated recommendations. In addition, CHART is a seldom used (NCLA Annual Report 2017) intervention that is far

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					more costly than conventionally fractionated radiotherapy. A number of different fractionation schedules were included in the review but without a bespoke economic evaluation in the UK context it was difficult to tell which would be the most cost-effective. The committee also noted that patient choice was important and therefore decided to word the recommendations to recommend either conventional or hyperfractionated forms of radical radiotherapy. Thank you for your comment. This area was out of scope for this update of the guideline.
				1.4.34: This seems to recommend postoperative chemotherapy to T1a-4 N1-2 M0 NSCLC. There is no trial evidence to support giving postoperative chemotherapy to patients with N0 disease where the primary tumour is less than 40mm. This is supported by current ESMO, ASCO, and NCCN guidelines. This recommendation should therefore be modified accordingly.	Thank you for your comment. This area was out of scope for this update of the guideline.

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				1.4.36: The only trial that has demonstrated a survival benefit in patients with N0 tumours 4cm in size or more used a carboplatin-based chemotherapy regime (CALGB 9633 trial, Strauss et al. J Clin Oncol 2008). Therefore carboplatin-based regimes should be allowed (not just cisplatin-based regimes), especially in the case of baseline hearing deficit or renal co-morbidities where cisplatin use would be clinically inappropriate. 1.4.40: The draft guidelines now recommend stage IIIA NSCLC patients to undergo chemoradiotherapy and surgery trimodality therapy. This role of surgery for stage IIIA NSCLC is extremely controversial and is hotly debated between experts. The Network meta-analysis performed by NICE takes considerable weight from unplanned subset analyses from key trials supporting a benefit from the additional of surgery to chemoradiotherapy. Moreover, supporting evidence provided from the Network meta-analysis cites (p12 bullet points commencing on line 22 and 24 that "it was not possible to tell whether chemoradiotherapy alone or chemotherapy and surgery provide better survival outcomes" and "the evidence in favour of chemoradiotherapy and surgery involved indirect comparisons, and no head-to-head trials showed meaningful differences in outcomes for any of the interventions," reflecting that the 2 major trials for the additional of surgery to radical chemoradiotherapy have been unable to	Thank you for your comments. Please see the thematic response on the management of resectable stage IIIA-N2 NSCLC for further information.

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				demonstrate a survival benefit for surgery (Eberhardt J Clin Oncol 2015; Albain Lancet 2009) in intention-to-treat populations. The meta-analysis recognizes these uncertainties and states (p12 line 9) "The key benefit associated with chemoradiotherapy and surgery is the longer progression free survival time. However, there are some uncertainties in the evidence." These data are therefore over-interpreted without enough emphasis on the lack of survival benefit to make such a strong statement to recommend surgery after chemoradiotherapy to all operable stage 3A NSCLC in face of markedly uncertain evidence. Currently, less than 2% of patients with N2 involved NSCLC currently receive trimodality treatment in the UK not due to barriers in commissioning but due to expert review of current trial data. Current trial data has failed to identify patients likely to benefit from trimodality therapy *a priori*. Moreover, stage 3A NSCLC represents a markedly heterogenous group of patients ranging from those with single station pathologically proven mediastinal lymph node involvement (for whom trimodality therapy may be appropriate) to multi-station involved nodes for who the benefit from the addition of surgery is far from evident given the clinical trial data and findings from the current Network Meta-analysis.	

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				Additionally, the Network Meta-analysis has not been able to adequately take account of the significant morbidity (and additional mortality) associated with the addition of surgery when considering this for all patients particularly when an overall survival benefit is not evident. Finally the meta-analysis did not take account of the most impactful randomized phase 3 trial performed in stage III NSCLC to date, the PACIFIC trial (Antonia NEJM 2017; Antonia NEJM 2018). This trial which included 53% of patients with stage 3A NSCLC demonstrated that for stage III NSCLC chemoradiotherapy alone followed by consolidation durvalumab not only markedly increased progression-free survival (HR=0.52, p<0.001), but also overall survival (HR=0.68, p=0.0025) with an unprecedented landmark 2-year survival rate of 66% for patients receiving durvalumab. For stage 3A NSCLC, the progression-free survival HR=0.53, (0.40-0.71) and the overall survival HR=0.63 (0.46-0.85). Durvalumab is currently being evaluated for cost effectiveness by NICE (ID 1175). Thus, the standard of care for stage III NSLCC should remain chemoradiotherapy due to the lack of proven survival benefit identified from surgery and the increased morbidity from surgery, as the NICE meta-analysis itself has identified, and if deemed cost effective from appraisal ID 1175, chemoradiotherapy with durvalumab consolidation	

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				should be the favoured, evidence-based treatment. Surgery should not currently be routinely recommended for all stage 3 NSCLC, but remain a research objective awaiting a trial showing a survival benefit before being routinely recommended. However, surgery after chemoradiotherapy could be considered for selected cases only (eg single station N2 involvement). In centres considering such trimodilty cases, performance monitoring and quality control needs are great and the committee is urged to recommend publication of outcomes, treatment related mortality & treatment completion rates for centres noting the difficulty in successfully completing trimodality treatment without complication in trials patients, let alone routine care patients. A national registry for this challenging treatment regime should be the ambition and regional stage III trimodality MDTs and services could be advocated. 1.4.43 Osimertinib is being considered for cost effectiveness (ID 1302) for first line EGFR mutant NSCLC and therefore should be considered alongside approved afatinib, erlotinib and gefitinib if proven cost effective. Subsequent treatments on relapse will likely be combination atezolzimab in combination with chemotherapy and bevacizumab (ID 1210) and this should be stated.	We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.

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				1.4.44 Brigatinib is currently under review for ALK+ patients progressing on crizotinib and will likely be the preferred treatment over Ceritinib if found cost effective (ID 1328). The draft document recommends Alectinib on progression after first-line crizotinib. Whilst this is most welcome, I wanted to check this is not an error as the corresponding technology appraisal (TA438) was terminated and the cost effectiveness of alectinib post crizotinib has never been evaluated by NICE. Similarly to EGFR mutant NSCLC, after progression on ALK inhibitors, the favoured chemotherapy regime will be combination atezolizumab in combination with chemotherapy and bevacizumab (ID 1210) if found cost effective. P17 line 12: instead of "PDL1≥50%" this should state "PDL1≥50%, EGFR wild type, ALK negative, ROS1 negative" as the PDL1 status of the tumour cannot be interpreted in isolation of the genomic status of the tumour, since the pembrolizumab indication is for EGFR and ALK wild type tumours and ROS1+ tumours are preferentially treated by crizotinib. For some of these patients, instead of pembrolizumab monotherapy, combination with platinum-pemetrexed-pembrolizumab may be favoured (eg in never smokers where the combination has a lower primary progression rate). This combination is	Neither the draft guideline nor the algorithm recommend alectinib after first line crizotinib. Alectinib is recommended for first-line treatment for ALK positive patients only (TA536). We have updated the indications for pembrolizumab to reflect the wording in the TA but are unable to say anything about ROS-1 status in this population.

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				currently being reviewed in (ID 1173) and may represent a treatment option if found cost effective. Another option may be atezolizumab in combination with chemotherapy and bevacizumab (ID 1210) if found cost effective 1.4.47: For these patients the favoured regime is combination platinum-pemetrexed-pembrolizumab (ID 1173) if found cost effective. 1.4.48: For some of these patients, instead of pembrolizumab monotherapy, combination with platinum-paclitaxel-pembrolizumab may be favoured (eg in never smokers where the combination has a lower primary progression rate). This combination is currently being reviewed in (ID 1306) and may represent a treatment option if found cost effective. 1.4.49: For these patients the favoured regime is combination with platinum-paclitaxel-pembrolizumab (ID 1306) if found cost effective. 1.4.52: The guidelines have omitted the preferred and recommendation regime of twice daily hyper-fractionated radiotherapy for SCLC, which has been proven in randomized trials to offer the best outcome with no major increase in oesophageal toxicity (CONVERT trial).	Thank you for your comment. The committee have re-considered the evidence and have now included an offer of twice-daily radiotherapy. They have added a recommendation that says that if a patient declines or is unable to have twice-daily radiotherapy, then offer once-daily radiotherapy. They have also added another recommendation that advises healthcare professionals to discuss with patients whether once or

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					twice a day radiotherapy would be best for them.
				1.4.55: the preferred first line systemic treatment for patients with extensive stage SCLC is carboplatin-etoposide-atezolizumab (ID 1504) if found cost effective.	
				1.4.59-60: PCI is recommended for both limited-stage and extensive-stage SCLC on the basis of randomized phase 3 trials and the recommendations should reflect this, alongside any contraindications eg neurological comorbidities.	PCI for limited stage SCLC was out of scope for this update of the guideline. The recommendations for patients with extensive stage SCLC were amended to a 'consider', which implicitly takes into account the fitness of the patient. To quote the 'Benefits and harms' section of the evidence review: "The committee agreed that "consider" is the appropriate strength for the recommendation on PCI. This is because there is a mix of evidence in the two main trials. In addition, in the clinical experience of the committee, PCI is beneficial in a small and selected subgroup of people. The committee pointed out that both Slotman 2007 and Takahashi 2017 had exclusion criteria. These exclusion criteria included low performance status, life expectancy

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					less than 3 months, age over 75 years, mental disorders, not being able to give informed consent and not being able to comply with the protocol and follow-up schedule. While not explicitly listed in the recommendation, these exclusion criteria reflect current UK practice when considering PCI. They felt that clinicians would be able to select which people were likely to benefit from PCI on a case-by-case basis."
British Thoracic Society	Guideline	10	7	Recommendation 1.3.30 is rather vague – what is meant by "without undue delay"? Would be more helpful to set a time limit.	Thank you for your comment. This recommendation was updated to remove reference to outdated policies but making more specific recommendations was outside the scope of this update.
British Thoracic Society	Guideline	14-15		N2 NSCLC The committee's analysis of this highly debated area is welcomed and appears thorough and considered. All relevant evidence has been included with appropriate consideration to limitations. The recommendation of induction chemoradiotherapy followed by surgery based in network meta-analysis demonstrating improved progression free survival and a strong suggestion of improved survival appears robust. The committee rightly acknowledge this significant change to practice this entails. It is worth noting that in the Intergroup 0139 study concerns were raised about the mortality rate from pneumonectomy and largely due to centres performing small numbers of this surgical procedure.	Thank you for your comments. Please see the thematic response on management of IIIA-N2 disease at the end of this document for further information.

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				Given only 1.6% of patients with N2 NSCLC received trimodality treatment in 2015 in the UK then a sudden increase in this unfamiliar practice could result in harms without performance monitoring and quality control. We urge the committee to recommend publication of outcomes, treatment related mortality & treatment completion rates for centres performing induction chemoradiotherapy and surgery. A national registry for this challenging treatment regime should be the ambition. Regional stage III trimodality MDTs and services could be advocated.	
British Thoracic Society	Guideline	15	15	Recommendation 1.4.40 – It is disappointing that the option of offering patients with stage IIIA N2 NSCLC chemotherapy and surgery, as opposed to chemotherapy and radiotherapy, is excluded on the grounds of cost. There are patients who prefer to undergo surgery as opposed to a course of radiotherapy.	Thank you for your comment. The NMAs and associated health economic model developed for this guideline suggest that chemotherapy and surgery is not cost-effective compared to chemoradiotherapy alone because it is unlikely to be more effective and is substantially more costly. In addition, tri-modality therapy is cost-effective compared to chemotherapy and surgery. Nevertheless, due to the acknowledged uncertainties in the underlying evidence base and heterogeneity in the patient population, the committee chose not to explicitly exclude chemotherapy and surgery via a "do not offer" recommendation or an "offer" recommendation for tri-modality therapy.

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					Please see the thematic response to comments on the recommendations for management of resectable stage IIIA-N2 NSCLC at the end of this document for further information.
British Thoracic Society	Guideline	8-9		Mediastinal staging It is very important to note that the mediastinal staging recommendations refer to 'mediastinal nodes' throughout, thereby excluding hilar nodes (which could N1 or N3). Patients with enlarged N1 nodes & normal mediastinal nodes should undergo staging EBUS regardless of PET findings (false negative rate for N2-3 of 25% - see 2013 ACCP guidelines and meta-analysis data). The way the NICE guidelines are written encourages a lack of nodal staging in cN1 disease because the mediastinal nodes are normal. We believe this is wrong and lead to missed N2/3 disease. This is now particularly important as the guidelines recommend induction chemoradiotherapy then surgery for resectable N2 disease so there should a thorough work up for N2 disease pre-operatively as it would change the treatment regime. We support the rest of the recommendations in mediastinal staging with the exception of one: the statement that neck USS should be performed in patients with mediastinal nodes >20mm. (1.3.20)	Thank you for your comments. The committee is in agreement with you. Therefore, the word "mediastinal" has been changed to "intrathoracic" for recommendations 1.3.16 and 1.3.20. All references to neck ultrasound have also been removed. Furthermore, for recommendation 1.3.20, the committee have added: "using a systematic approach". In order to clarify this, there is now a footnote describing the systematic approach. This systematic approach is consistent with the methodology used in the ASTER and BOOST trials. The algorithm of intrathoracic staging has also been revised accordingly.

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				Neck USS and biopsy should be performed in any patient with enlarged or FDG avid nodes in the neck regardless of mediastinal node size. In the context of normal neck nodes on CT then routine neck USS will add delay to the pathway and is based on single centre retrospective data and does not reflect national practice. The algorithm of mediastinal staging does not mention doing neck USS and biopsy only when neck nodes abnormal / pathological on CT. While this is appropriate it should not be restricted to only those with mediastinal nodes >20mm, this is true for all patients. We would support removing the statement about doing neck USS in all patients with mediastinal nodes >20mm (it could be an option based on local services but straight to PET and sonographic staging of the mediastinum also entirely appropriate).	
British Thoracic Society	Guideline	General		Thank you for the opportunity to comment on this updated guideline.	Thank you for your comment.
Eli Lilly & Company Ltd	Algorithm and guideline	General		The technology appraisal for Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173] is likely to publish guidance in the near future. Any recommendations should be recognised in the Systemic anti-cancer therapy recommendations algorithm (non-squamous visual summary) and short guideline (and any other relevant guideline documents) to ensure the new guideline documents are up to date upon publication.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that

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					published between consultation and publication of this guideline update. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Illumina Cambridge	Systemic anti-cancer therapy management - non-squamous visual summary	1	General	Suggestion: Include some information on TMB to anticipate for upcoming immunotherapy approvals.	Thank you for highlighting this. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.

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Illumina Cambridge	Guideline	16	General	Rationale for this comment: ESMO guidelines state TMB was evaluated in patient tissue as well as blood samples in different trials, with preliminary data showing TMB is associated with improved clinical benefit in patients with NSCLC. 1 Other preliminary data has shown encouraging results for TMB as a predictive biomarker in retrospective studies in NSCLC and SCLC. 2,3	Thank you for highlighting this. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Illumina Cambridge	Guideline	7	20-22	Suggestion: further define commonly used biomarkers and include Tumour Mutational Burden (TMB) Suggested wording: When taking samples, ensure they are adequate (without unacceptable risk to the person) to permit pathological diagnosis, including tumour subtyping and assessment of predictive markers (e.g. EGFR-TK mutation testing, ALK gene rearrangement, PDL1, ROS1 and tumour mutational burden).	Thank you for your comment. Although this recommendation was updated in order to bring it into alignment with current practice, this area is out of scope for this update of the guideline and the committee were therefore unable to make any additional recommendations. We are unable to pre-empt the recommendations arising from NICE

[1] Gandara DR, Paul SM, Kowanetz M et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med 2018; 24: 1441–1448.
[2] Velcheti V, Kim ES, Mekhail T et al. Prospective clinical evaluation of blood-based tumor mutational burden (bTMB) as a predictive biomarker for atezolizumab (atezo) in 1L non-small cell lung cancer (NSCLC): interim B-F1RST results. J Clin Oncol 2018; 36: 12001–12001.
[3] D. Planchard, S. Popat, K. Kerr, S. Novello, E. F. Smit, C. Faivre-Finn, T. S. Mok, M. Reck, P. E. Van Schil, M. D. Hellmann & S. Peters, on behalf of the ESMO Guidelines Committee. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2018 – Ann Oncol (2018) 29 (suppl 4): iv192–iv237. Available at: https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer (Accessed 1 November 2018)

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				Rationale for this comment: Recent advancements in Non-Small Cell Lung Cancer (NSCLC) therapies and patient management have led to the use of TMB measurement at the onset of NSCLC diagnosis. Recently published guidelines in the United States by the National Comprehensive Cancer Network (NCCN) 4 and in Europe by the European Society for Medical Oncology (ESMO) 5 mention TMB as one of the emerging biomarkers that may be helpful in selecting patients for immunotherapy. Adding some wording around TMB would also to align with recommendations from other guidelines around the world like ESMO and NCCN.	Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Medtronic UK	Guideline	43	Table section 1.3.15	Consider inclusion of ENB on treatment plan for this high risk cohort with performance status profile including FEV 1 score of < 40% prediction, TLCO score < 40% prediction, Lung function (resistance-based cardiopulmonary), thoracoscore with a lesion location of peripheral/middle third of lung with a lesion size < 40 mm (mean +/- SD 23 +/- 14.4)	Thank you for your comment. This area was out of scope for this update of the guideline.

[4] National Comprehensive Cancer Network. NCCN Guidelines Version 1.2019. Non-Small Cell Lung Cancer. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed 1 November 2018)
[5] D. Planchard, S. Popat, K. Kerr, S. Novello, E. F. Smit, C. Faivre-Finn, T. S. Mok, M. Reck, P. E. Van Schil, M. D. Hellmann & S. Peters, on behalf of the ESMO Guidelines Committee. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. October 2018 – Ann Oncol (2018) 29 (suppl 4): iv192–iv237. Available at: https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer (Accessed 1 November 2018)

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Medtronic UK	Guideline	43	Table section 1.3.15	A decision analytic model was developed to evaluate the cost-effectiveness and cost consequences of ENB using superDimension™ navigation system in the NHS setting. Overview of the model: – To allow the user to assess the cost effectiveness of multiple comparators such as TTNA, REBUS, and surveillance – To demonstrate health and cost outcomes over time using suitable charts – To undertake deterministic sensitivity analysis for a range of scenarios using tornado diagrams and threshold analysis	Thank you for your comment. This area was out of scope for this update of the guideline.
Medtronic UK	Guideline	8	10	If PET-CT scans are positive in peripheral lesions but not in lymph nodes, patients are referred to a CT-guided biopsy (TTNA), radial endobronchial ultrasound (REBUS), needle aspiration biopsy. These tests are recommended when SPNs are located peripherally and the nodules may be beyond the reach of conventional bronchoscopies. However, these methods of sampling can result in increased risks to the patients such as a pneumothorax requiring a drainage tube and may not be suitable for patients who have underlying comorbidities With respect to offering an alternative solution for an imaged-guided biopsy, ENB aims to provide a medium in which to gain a biopsy of lesion within the middle and out third of the lung anatomy where other methods have failed or those patients who are deemed too high a risk for percutaneous or surgical approaches.	Thank you for your comment. Although this recommendation was updated in order to bring it into alignment with other NICE guidance, this area is out of scope for this update of the guideline and the committee were therefore unable to make any additional recommendations.

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Medtronic UK	Guideline	8	9	Peripheral primary tumours _ recently published evidence (pdf attached) supports consideration for the role of Electromagnetic Navigational Bronchoscopy (ENB) as a viable diagnostic & staging modality for patients who are deemed clinically unfit to undergo transthoracic needle aspiration (TTNA) or wedge thoracotomy. Recent evidence reported a 12 month diagnostic yield of 73% (N=1053) c/o study NAVIGATE (Folch EE et al, ATS 2018).	Thank you for your comment. Although this recommendation was updated in order to bring it into alignment with other NICE guidance, this area is out of scope for this update of the guideline and the committee were therefore unable to make any additional recommendations.
Medtronic UK	Guideline	General		Having reviewed the pathway guidelines for the biopsy of peripheral lesions with low probability of mediastinal malignancy, it would appear that the existing recommendation of radial EBUS is becoming outdated based on data available since 2010 (https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/diagnosis-and-staging-of-lung-cancer.xml&content=view-node%3Anodes-peripheral-lesion-with-low-probability-of-mediastinal-malignancy-nodes-10-mm	Thank you for your comment. There will be no mention of radial EBUS in the updated guidelines. This update included EBUS-TBNA.
Merck Sharp & Dohme UK Ltd	SACT management – non-squamous visual summary	General	General	The outcome of NICE single technology appraisal ID1173 (Pembrolizumab in combination with chemotherapy for untreated non-squamous non-small cell lung cancer) is expected to be published by 20 December 2018 and should, we suggest, be considered once published and then reflected in the algorithm.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. We are unable to pre-empt the recommendations arising from NICE

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					Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Merck Sharp & Dohme UK Ltd	Guideline	17 18	13-26 14-26	The outcome of NICE STA ID1173 (Pembrolizumab in combination with chemotherapy for untreated non-squamous non-small cell lung cancer) is expected to be published by 20 December 2018 and should, we suggest, be considered once published and then reflected in the content of these sections of the guidelines relating to systemic anti-cancer treatment.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated

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					periodically to reflect new technology appraisals.
Merck Sharp & Dohme UK Ltd	Evidence Review E	7 9 10 10	- 37-41 1-5 18-29	The outcome of NICE STA ID1173 (Pembrolizumab in combination with chemotherapy for untreated non-squamous non-small cell lung cancer) is expected to be published by 20 December 2018 and should, we suggest, be considered once published and then reflected in the algorithm and the relevant sections of Evidence Review E.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
National Cancer Research Institute / Royal College of Physicians /	Guideline	15	15-17	The new recommendation is for neoadjuvant chemoradiation followed by surgery, based on a single trial from 2009 (Albain et al), is flawed and totally contrary to current practice and review of the wider literature for this area including meta-analyses. In particular there was no difference in the primary endpoint of overall survival	Thank you for your comments. Please see the thematic response to comments on the recommendations for management of resectable stage IIIA-N2 NSCLC at the end of this document.

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Royal College of Radiologists / Association of Child Psychotherapists				between the two arms within the trial and clearly chemoRT is more cost effective than the addition of a third surgical treatment. Additional exploratory analysis and secondary endpoints (PFS) from a trial which is over 10 years old should not be used as the basis for limiting curative intent treatment options for this patient group. The current draft appears to dismiss the option of surgery with adjuvant (or neoadjuvant chemotherapy) based on meta-analyses showing similar outcomes as for chemo-radiation and dismissing it on cost grounds. In fact stage IIIA(N2) patients able to undergo surgery are often a very different sub-group and certainly, based on national 'real world' NLCA outcomes reported at WCLC 2018, overall survival is better for those stage III patients undergoing surgery with chemotherapy. As a country that generally UNDERTREATS lung cancer (compared to the rest of Europe) we should not block access to a similarly effective bimodality treatment - both bimodality options (chemoRT and surgery with chemotherapy) should be considered on an individual basis through MDT discussion and joint clinic consultations. There is a very balanced BTS review of this literature by Evison et al (Thorax 2017) which concludes this. Furthermore, based on the 'real world' NLCA data presented at WCLC 2018, only 0.7% of stage III lung cancer patients diagnosed in England during 2016 received any version of 'triple' modality treatment at all (including radiotherapy delivered in the adjuvant setting), so this new	

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				recommendation for neoadjuvant chemoRT then surgery is totally unrealistic and unrepresentative. The draft is also flawed for stage III treatment recommendations because it does not take into account or discuss the newly published randomised trial of adjuvant durvalumab (Antonia NEJM) after chemoradiation for stage III patients.	
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child Psychotherapists	Guideline	19	25-29	There is very strong evidence from the UK CONVERT trial that twice daily RT should be viewed as the gold standard treatment with 66/33 once daily also being acceptable. The trial data shows no difference in oesophagitis between these two arms. It is therefore wrong of the NICE committee, in their rationale, to use personal fears to dilute their recommendation. In my experience from treating patients within that trial and subsequently, twice daily RT is well tolerated as does not limit delivery of PCI any more than once daily RT.	Thank you for your comment. The committee have re-considered the evidence and have now included an offer of twice-daily radiotherapy. They have added a recommendation that says that if a patient declines or is unable to have twice-daily radiotherapy, then offer once-daily radiotherapy. They have also added another recommendation that advises healthcare professionals to discuss with patients whether once or twice a day radiotherapy would be best for them.
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists	Guideline	30	4-10	It is not routine to go straight to brain MRI in patients with known cancers suspected of cerebral metastases, so we're not sure about going straight to MRI in stage IIIA. It'll be small numbers, but we're not sure how interpretable the MRI would be if the CT would have been negative.	Thank you for your comment. The 2011 guideline includes strong 'offer' recommendations for MRI in people with metastases that are suspected either following imaging (rec 1.3.23) or via suggestive clinical features (rec 1.3.27) and the committee confirmed that this is routine. MRI is not recommended

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/ Association of Child Psychotherapists					following negative CT brain in any of the sub-populations examined in this guideline update (people with stage I, II or III NSCLC being considered for radical treatment in whom brain imaging is not otherwise indicated). The health economic model conducted for this review question found that MRI brain in stage III patients being considered for radical treatment was a 'dominant' strategy (more clinically effective [patients received more appropriate treatment] and cost-saving [less use of expensive radical treatment]). The full write up is contained in the appendices of Evidence Review B.
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child Psychotherapists	Guideline	4	10-15	Reporting radiographers report chest X-rays, including those for suspected lung cancer. Evidence suggests that reporting radiographers are accurate at chest X-ray reporting [1,2] and that it is feasible for radiographers to provide immediate reports for patients' referred from primary care and to communicate reports directly to patients at the time of the chest X-ray [3] 1 - Woznitza et al *Acad Radiol* https://www.academicradiology.org/article/S1076-6332(18)30177-6/fulltext	Thank you for your comment. This area was out of scope for this update of the guideline.

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				2 - Woznitza et al *Radiography* https://www.radiographyonline.com/article/S1078-8174(18)30013-0/abstract 3 - Woznitza et al *Clin Radiol* https://www.clinicalradiologyonline.net/article/S0009-9260(17)30536-6/fulltext	
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child Psychotherapists	Guideline	6	24-26	Ultrasound is rarely helpful here; we would suggest replacing 'Ultrasound' with 'MRI'.	Thank you for your comment. This particular area was out of scope for this update of the guideline.
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child	Guideline	7	8-9	The statement 'Do not routinely use MRI to assess the stage of the primary tumour 8 (T-stage) in non-small-cell lung cancer (NSCLC). [2005]' may not be necessary as it is doubtful that any centre is doing this.	Thank you for your comment. This area was out of scope for this update of the guideline

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Psychotherapists					
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child Psychotherapists	Guideline	9	3-6	We are unsure whether there's any benefit of suggesting an ultrasound of the neck if there are no nodes identified on the CT. The way it is written is for an US to be performed based upon the mediastinal nodes being > 20mm.	Thank you for your comment. The committee agrees that the yield is low. Therefore all references to neck ultrasound in the recommendations has been removed.
National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child Psychotherapists	Guideline	General	General	The new guideline looks fairly sensible to me and should not significantly impact on workload.	Thank you for your comment.
National Cancer Research	General	General	General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the responses submitted by the British Thoracic	Thank you for your comment.

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Institute / Royal College of Physicians / Royal College of Radiologists / Association of Child Psychotherapists				Society (BTS) and British Thoracic Oncology Group (BTOG) respectively. We have also liaised with our experts and would like to make the following comments.	
NHS England – Clinic Expert Group for Lung Cancer	SACT algorithms	General	General	It is noted that the SACT algorithms are now satisfactory but that these will likely be out of date very quickly; we ask how they will be updated.	Thank you for your comment. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	10	14	We note that you are not accepting comments about guidance you have not updated but some members have noted that recommendation 1.3.32 may now be worthy of update to reflect the perceived over-use of MDTs and the lack of full work-up of patients before they are discussed. This is something that is addressed in the NOLCP and the MDT streamlining project, where agree national standards of care should be used prior to MDT discussion. Some qualification about what are appropriate investigations that define "suspected lung cancer" are required and an acknowledgement that work-up should normally be done before the MDT discussion.	Thank you for your comment. The committee agreed to revert this recommendation to the original 2005 wording because they feel it is clearer. The recommendation now refers to people with a 'working diagnosis of lung cancer'.
NHS England – Clinic Expert	Guideline	10	45	1.3.34 Suggest that this reads " ...should have at least one trained lung cancer nurse specialist available at all times to:"	Thank you for your comment. This area was out of scope for this update of the guideline.

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Group for Lung Cancer				First bullet point: could read "Support people...." rather than "See people..."	
NHS England – Clinic Expert Group for Lung Cancer	Guideline	10	7	1.3.30 "Without undue delay" is too subjective. As this is a guideline document a time frame should be specified in line with current national guidance (the NOLCP)	Thank you for your comment. This recommendation was updated to remove reference to outdated policies but making more specific recommendations was outside the scope of this update.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	13	26	The guideline suggests that all patients should be offered radical radiotherapy regardless of underlying lung pathology and performance status. The guideline should be amended to reflect these issues and altered to consider	Thank you for your comment. The committee assumes that clinicians will not offer treatments that are contraindicated The committee reviewed the evidence on radical radiotherapy and concluded that it is an effective and cost-effective treatment in this population. They therefore agreed that this recommendation merits an 'offer'.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	13-14	22-7	1.4.24-1.4.28 NOTE: Definitions amongst clinical oncologists can vary regarding eligibility for radical RT and for Chemo-RT. Thresholds for treatment should be included in NICE Guidance (or reference standard given) for respiratory reserve, anatomical location etc to ensure uniformity in decision making across MDTs.	Thank you for your comment. Specific thresholds for treatment eligibility were out of scope for this update of the guideline. The committee therefore saw no evidence on these and are unable to make recommendations.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	15	1 and 6	1.4.34 This recommends postoperative chemotherapy to T1a-4 N1-2 M0 NSCLC. There is no trial evidence to support giving postoperative chemotherapy to patients with N0 disease where the primary tumour is less than 40mm. This is supported by current ESMO, ASCO, and NCCN	Thank you for your comments. This particular area was out of scope for this update of the guideline. Therefore the committee were unable to make specific

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				guidelines. This recommendation should therefore be modified accordingly 1.4.36 The only trial that has demonstrated a survival benefit in patients with N0 tumours 4cm in size or more used a carboplatin-based chemotherapy regime (CALGB 9633 trial, Strauss et al. J Clin Oncol 2008). Therefore carboplatin-based regimes should be allowed (not just cisplatin-based regimes). 1.4.37 Would this be better phrased as "Neoadjuvant chemotherapy should not be offered to people with stage I-II NSCLC suitable for surgery outside of a clinical trial."	recommendations about post-operative chemotherapy Thank you for your comments. This particular area was also out of scope for this update of the guideline. Therefore the committee were unable to make specific recommendations about adjuvant chemotherapy regimens. Thank you for your comment. The committee decided to retain the wording of this recommendation as it is in line with NICE's editorial preferences whereby the action to be taken is placed at the start of the recommendation.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	15	15-22	Stage IIIA N2 NSCLC – There was considerable concern about the recommendations 1.4.40 and 1.4.41 The issue is that this is a well discussed area of research and the evidence for the additional benefit of adding surgery in this group of patients with an overall poor prognosis remains limited. This role of surgery for stage IIIA NSCLC is extremely controversial and is hotly debated between experts. The Network meta-analysis performed by NICE takes too much weight from unplanned subset analyses from key trials supporting a benefit from the additional of surgery to	Thank you for your comments. Please see the thematic response to comments on the recommendations for management of resectable stage IIIA-N2 NSCLC at the end of this document.

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				chemoradiotherapy. Moreover, supporting evidence provided form the Network meta-analysis cites (p12 bullet points commencing on line 22 and 24 that "it was not possible to tell whether chemoradiotherapy alone or chemotherapy and surgery provide better survival outcomes" and "the evidence in favour of chemoradiotherapy and surgery involved indirect comparisons, and no head-to-head trials showed meaningful differences in outcomes for any of the interventions," reflecting that the 2 major trials for the additional of surgery to radical chemoradiotherapy have been unable to demonstrate a survival benefit for surgery (Eberhardt J Clin Oncol 2015; Albain Lancet 2009). The meta-analysis recognizes these uncertainties and states (p12 line 9) "The key benefit associated with chemoradiotherapy and surgery is the longer progression free survival time. However, there are some uncertainties in the evidence" I feel that the committee has unduly placed too much weight on the putative progression-free benefit and no enough on the lack of survival benefit to make such strong statement to recommend surgery after chemoradiotherapy in face of uncertain evidence and clinical judgement. Moreover, surgery for stage IIIa NSCLC is not favoured by the vast majority of experts in the UK and practiced at a tiny minority of centres, usually due to vociferous surgical presence. Additionally, the Network Meta-analysis has not been able to adequately take account of the significant morbidity associated with the addition of surgery. Finally the meta-analysis did not take account of the most impactful	

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				randomized phase 3 trial performed in stage III NSCLC to date, the PACIFIC trial (Antonia NEJM 2017; Antonia NEJM 2018). This trial demonstrated that for stage III NSCLC chemoradiotherapy alone followed by consolidation durvalumab not only markedly increased progression-free survival (HR=0.52, p<0.001), but also overall survival (HR=0.68, p=0.0025) with an unprecedented landmark 2-year survival rate of 66% for patients receiving durvalumab. Durvalumab is currently being evaluated for cost effectiveness by NICE (ID 1175). Thus, the standard of care for stage III NSLCC should remain chemoradiotherapy due to the lack of proven survival benefit identified from surgery and the increased morbidity from surgery, as the NICE meta-analysis itself has identified, and if deemed cost effective from appraisal ID 1175, chemoradiotherapy with durvalumab consolidation should be the favoured, evidence-based treatment. Surgery should remain a research objective awaiting a trial showing a survival benefit (perhaps after chemoradiotherapy + durvalumab) before being routinely recommended. The recommendation implies that CRS is preferred to CR and is based on very limited evidence for an improvement in PFS, a measure less appropriate to potentially curative and markedly invasive treatment. In addition the concern is that this recommendation will discourage badly needed research and may be irrelevant once we enter an era of adjuvant immunotherapy.	

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				There was general agreement that the group of Stage IIIA N2 needs to be better defined and the place of surgery clarified by better clinical trials, which themselves may need to incorporate newer systemic treatments. 1The results of the PACIFIC trial are likely to result in practice changing effects globally. Consideration should be given to the inclusion in the Guideline of the use of maintenance Durvalumab after chemoradiotherapy for Stage III NSCLC. The emerging OS benefit (in a clear sub group) would inform this standard of care. NICE, we assume, will review the evidence soon. The CEG do not support recommendation 1.4.40 and believe that at most the recommend should be worded so as to "consider offering patient the choice"… of either approach but probably should be worded to indicated that CR is the standard and consider offering surgery in addition.	
NHS England – Clinic Expert Group for Lung Cancer	Guideline	16	4-27	This will be out of date very soon given the evidence for Osimertinib, Brigatenib and loralatanib. 1.4.43 (5th Bullet Point), 1.4.44 (5th Bullet Point) and 1.4.45 (4th Bullet Point) In these, the option to use docetaxel is given first with the newer (and more efficacious) options given later as alternatives, even though they are approved by NICE. I suggest reversing the order of option i.e. giving the option of docetaxel after the more commonly used and effective options.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. Your suggested amendment re: docetaxel has also been made.

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					We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	17	12	Instead of "PDL1≥50%" this should state "PDL1≥50%, EGFR wild type, ALK negative, ROS1 negative" as the PDL1 status of the tumour cannot be interpreted in isolation of the genomic status of the tumour, since the pembrolizumab indication is for EGFR and ALK wild type tumours and ROS1+ tumours are preferentially treated by crizotinib. For some of these patients, instead of pembrolizumab monotherapy, combination with platinum-pemetrexed-pembrolizumab may be favoured (eg in never smokers where the combination has a lower primary progression rate). This combination is currently being reviewed in (ID 1173) and may represent a treatment option if found cost effective. Another option may be atezolizumab in combination with chemotherapy and bevacizumab (ID 1210) if found cost effective	Thank you for your comment. We have amended this to be compatible with the TA on first line pembrolizumab, specifying that patients should be PDL1=>50% and have no gene rearrangement or fusion protein. The committee were unable to say anything about ROS-1 status in this group. We have added the TA on pembrolizumab combination therapy to the algorithm but are unable to pre-empt the results of TAs that will publish after this guideline update.

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NHS England – Clinic Expert Group for Lung Cancer	Guideline	18	29	1.4.48 For some of these patients, instead of pembrolizumab monotherapy, combination with platinum-paclitaxol-pembrolizumab may be favoured (eg in never smokers where the combination has a lower primary progression rate). This combination is currently being reviewed in (ID 1306) and may represent a treatment option if found cost effective.	Thank you for your comment. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	19	8	1.4.49 For these patients the favoured regime is combination with platinum-paclitaxol-pembrolizumab (ID 1306) if found cost effective.	Thank you for your comment. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
NHS England – Clinic Expert	Guideline	21	2 and 5	1.4.59 and 60 It would give more clarity to use the term "PS 0-2".	Thank you for your comment. The committee were in agreement. This

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Group for Lung Cancer				The CEG is not sure why one recommendation is offer and the other consider when both have a randomised phase III trial evidence base.	change to the recommendations has been made.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	22	23	1.5.8 IPC not mentioned ?should be offer talc pleurodiesis or IPC, or least mention IPC as an option in palliative section somewhere Guideline should reflect use of indwelling catheters e.g. pleurx	Thank you for your comment. This subject is out of scope for this update of the guideline. The committee reverted to the wording of the original 2005 recommendation – 'Patients who benefit symptomatically from aspiration or drainage of fluid should be offered talc pleurodesis for longer-term benefit'. The committee are aware that this subject may require updating. Therefore, we will pass your comment to the NICE surveillance team, which monitors guidelines to ensure that they are up to date, for consideration when future updates of the guideline are planned.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	31	1	The evidence base for this statement is not strong. The lack of successful randomised trials is a problem, the meta-analysis actually hints at better outcomes for SABR. The level II/III evidence also paints a mixed picture, not all studies show surgery giving the best outcomes. The statement at least needs more qualification about fitness for lobectomy - those that are high risk surgical candidates may be better served by SABR and this is in line with current practice. The new recommendations on SABR are a change from the 2011 guideline and improve choice for people with NSCLC.	Thank you for your comment. The committee noted the lack of good quality randomised evidence supporting this statement but took into account the matched observational evidence, which favoured surgery, when forming recommendations. They were unable to provide further evidence-based guidance on the circumstances under which SABR or lobectomy is the best treatment choice because of the lack of good

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				However, practice has also changed since 2011, and SABR is now widely used, so implementing the recommendations may not involve a significant change in practice. The remaining changes to the recommendations reflect current practice.	quality studies investigating prognostic factors. The study that suggests that SABR is better than lobectomy is Chang 2015. As discussed in 'The quality of evidence' section of the evidence review and in the evidence table, this RCT has a high risk of bias due to the limited information on the inclusion criteria. If a patient were a high-risk surgical candidate, this could be a contraindication for surgery and SABR may be a good alternative. In order to provide some guidance as to what constitutes a high-risk surgical candidate we would need good quality prospective studies. Unfortunately, much of the evidence is retrospective in nature and therefore the inclusion and exclusion criteria for surgery are not provided. In order to provide good detailed guidance on what constitutes high risk for surgery, a study should be done that specifically looks at this. It would need to have a great many participants to reflect the multitude of reasons as to why a person might be a better candidate for SABR compared to surgery. In the absence of such evidence, no recommendations

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					were able to be made in this update of the guideline.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	32	16-21	This section appears to contradict recommendation 1.4.40 on grounds of cost effectiveness	Thank you for your comment. It is not clear to us where this section contradicts recommendation 1.4.40.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	33	19	Typo Chemotherapy should read radiotherapy but see comment 33 below	Thank you for your comment. These sections have now been revised.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	8	6 -24	1.3.14 Consider changing to "...contrast enhanced CT..." 1.3.21 PET positive: is this defined?	Thank you for your comment. The committee agrees with you. Therefore, this change has been made to recommendation 1.3.14. Thank you for your comment regarding 1.3.21. The relevant studies did not specify what was PET positive. Therefore, it is not possible to provide further guidance regarding this.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	9	13-24	The draft guidelines propose withholding brain imaging to patients with stage 1 NSCLC, staged contrast enhanced CT and the MRI in stage 2 NSCLC if initial CT suspicious and MRI in stage 3 NSCLC. However, when faced with a patient undergoing staging, the histology of the lesions are unknown and brain imaging is routinely ordered alongside a PET so as not to delay patient staging. To wait for histology and PET results to then go back to the patient having completed staging (perhaps with a neck ultrasound also) for stage-specific CNS imaging is not a good use of resources	Thank you for your comment. The review, analyses and economic model conducted for this area of the guideline were confined to patients who had already been deemed candidates for radical treatment. This decision was based on NICE's surveillance review and scoping workshop with stakeholders showing the availability of evidence in this population as well as discussions

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				and will inevitably result in delay to treatment. It is also incompatible with the NOLCP. It would make more sense for all patients potentially likely to be radically treated to undergo dedicated contrast enhanced brain MRI.	with the committee. The economic model concluded that offering brain imaging in stage II and IIIA would be cost-effective (see Evidence Review B for a full discussion). Indeed, any increase in brain imaging in stage IIIA disease leads to net cost-savings through reduction in the use of expensive radical treatments. The committee were mindful of the potential delay to treatment for some patients associated with the new recommendations and the potential cost-effectiveness of adding CT brain to initial chest CT and made recommendation for research in this area. It should be born in mind that the cost-effectiveness considerations are quite different at initial staging as many patients would not have gone on to have radical treatment regardless of the brain imaging result.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	9	3	This recommendation is rather limited. Neck USS and biopsy should be performed in ANY patient with enlarged or FDG avid nodes in the neck regardless of mediastinal node size. In the context of normal neck nodes on CT then routine neck USS will add delay to the pathway and is based on single centre retrospective data and does not reflect national practice or the findings on CT that includes the neck. In the	Thank you for your comments. The committee is in agreement with you. Therefore, the word "mediastinal" has been changed to "intrathoracic" for recommendations 1.3.16 and 1.3.20. All references to neck ultrasound has also been removed. Furthermore, for

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				algorithm of mediastinal staging it does mention doing neck USS and biopsy only when neck nodes abnormal / pathological on CT; this should not be restricted to nodes >20mm. Identification of potentially involved supraclavicular nodes may be of value if this changes the clinical paradigm, (IE significantly alters the radical radiation field to not make radical radiotherapy possible) in which case neck ultrasound would be valid, but this can be identified on review of the patient PET scan where neck staging can be performed in suspiciously involved cases. In most cases, concerning nodes on PET will be encompassed in the radical radiation field regardless of the staging result, if possible.	recommendation 1.3.21, the committee have added: "using a systematic approach". In order to clarify this, there is now a footnote describing the systematic approach. This systematic approach is consistent with the methodology used in the ASTER and BOOST trials. The algorithm for intrathoracic staging has also been revised accordingly. Thank you for your comment. The committee did not review any evidence which would enable them to change this.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	General		Most members of the committee have raised concern about the draft new guidance. There is a real risk that, as it stands, some of the new recommendations will not be adopted by some leading MDTs leading to an exacerbation of the currently unacceptable variation in practice. The sections often have statements that begin 'the committee felt.....' The concern the CEG has is the level of clinical expertise on the group and the fact that whole subspecialties were represented by only one individual. Furthermore we are aware that some of the members are relatively inexperienced in lung cancer and some have views that do not represent the majority within their specialty. You are aware of our previous comments on the chemotherapy algorithm where some relatively basic mistakes were seen and corrected after our advice.	Thank you for your comments. Committee recruitment is achieved through open competition and are appointed for their quality of experience and expertise. We are grateful to the committee for their enthusiasm, hard work and expertise and are confident of their ability to make recommendations. In addition, we are grateful for the input of the NHS England Clinic Expert Group for Lung Cancer for their input on the systemic anti-cancer therapy algorithms during development.

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				It is therefore imperative that NICE take these comments seriously and make modifications, especially where the evidence is weak. There are many MDTs in the country that have very expert clinicians who will know the evidence well and make strong arguments against some of the recommendations as detailed below.	
NHS England – Clinic Expert Group for Lung Cancer	Guideline	General	General	For a document that is titled "diagnosis and management", there is no mention at all of what is required from pathologists, or what other specialties should expect from pathology. We appreciate the NICE review process may not have identified this for an area worthy of comment but nevertheless this is a key area that is important to flag to pathologists. We recommend that that there is a statement in the summary recommendations that conveys this message: In relation to pathological diagnosis of lung cancer, health care professionals should follow the Royal College of Pathologist guidelines within the *Dataset for histopathological reporting of lung cancer* which can be accessed from the website: https://www.rcpath.org (Data for UK pathologists are updated regularly within the RCPath dataset).	Thank you for your comment. This area was out of scope for this update of the guideline.
NHS England – Clinic Expert Group for Lung Cancer	Guideline	General	General	In general, there are many recommendations for systemic therapies made in this draft document that are likely to be out of date by the time this draft guidance is finalized or shortly thereafter. This is due to the large number of systemic therapy appraisals ongoing at the moment eg first line osimertinib (ID 1302), consolidation durvalumab in stage 3 NSCLC (ID 1175), pembrolizumab in combination with	Thank you for your comment. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated

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				platinum-pemetrexed chemotherapy (ID 1173). How do NICE plan to take account of rapidly changing systemic therapies in these guidelines?	periodically to reflect new technology appraisals.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review F	20	1	1.4.53 although the recommendation is for concomitant chemoRT in the adjacent text (line 23 onwards) a case is made against twice daily RT! This does not seem to support a rigorous examination of the evidence or appropriate interpretation and is thought by some experienced members of the CEG to reflect the inexperience of the GL group members. That the committee takes a view and suggest that patients would not be able to tolerate twice daily RT is simply a bias of individuals. The CONVERT study clearly demonstrated there was no increase in oesophagitis in the twice daily group.	Thank you for your comment. The committee have re-considered the evidence and have now included an offer of twice-daily radiotherapy. They have added a recommendation that says that if a patient declines or is unable to have twice-daily radiotherapy, then offer once-daily radiotherapy. They have also added another recommendation that advises healthcare professionals to discuss with patients whether once or twice a day radiotherapy would be best for them.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review D	13	14-26	Radical RT for NSCLC – They do not recommend any SABR fractionation regimes – I presume the SABR consortium schedules of 54Gy/3# 55Gy/5# or 60Gy/8# would be reasonable. Both 1.4.24 & 1.4.25, they are effectively saying the same thing except that in 1.4.24 only SABR is mentioned which might not be possible if the small tumour is centrally located i.e. in the 'no fly zone'.	Thank you for your comment. The committee were in agreement. Therefore, for recommendations mentioning SABR, we have added the following footnote: "For SABR fractionation schedules, use the SABR Consortium's SABR Guidelines." With regards to your comment about 1.4.24, we would like to clarify the difference between the recommendations in that lobectomy is preferred to sublobar resection (if

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				There is no mention of stage IIB disease, a small group, but nonetheless it seems tardy to miss and skip from IIA to IIIA. In particular T1a-c N1 M0.	lobectomy is an option). Unfortunately, we cannot specify when SABR should or should not be used with regards to the anatomical location of lesions because there was no evidence on this in the review. The committee trusts that practitioners will only offer SABR where clinically indicated. We do not mention stage IIB because there is insufficient evidence to provide specific guidance.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review D	28	General	There is no mention of how this applies to stage IIB	Thank you for your comment. We do not mention stage IIB because there is insufficient evidence to provide specific guidance.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review C	General	General	Stage IIIA N2 NSCLC – There was considerable concern about the recommendation 1.4.26 the recommendation of CRS over CR is surprising given the lack of evidence. Their recommendation seems to be solely based on PFS with, as they mention, with many uncertainties. In addition as we are likely to enter an era of adjuvant immunotherapy [they can't be blamed for not including this given the recent PACIFIC data!] so as we have mentioned to them previously there needs to be a	Thank you for your comment. Please see the thematic response on the management of resectable stage IIIA-N2 NSCLC at the end of this document for further information.

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				mechanism for updating guidance more quickly than their current processes.	
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review B	General	General	The major concern that the CEG had about this section is the strength of the evidence that was used to base the calculations of cost effectiveness. The decision to use a test with lower sensitivity in earlier stage disease and a higher sensitivity test for later stage disease is based on too few patients to reliably assess the true difference in the positive predictive value of the respective tests. Instead the committee should consider the potential impact on the whole population. In surgically resected patients, the majority of the incidental isolated brain metastases in the post PET-CT era are found in the early stage disease patients, purely because there are many more early stage disease patients operated upon. Thus, as a whole a test with a better sensitivity will detect more metastases overall than a less sensitive test and provide an updated prognosis in more patients and the opportunity for treatment of oligometastatic disease in more patients. The prognosis from stage IIIa is also poor in relation to stage II so the value of detecting brain metastases in early stage disease is greater, again both in relation to the difference in prognosis and the potential for treatment. We understand that there will be many more negative MR scans if this is also applied to the earlier stage group but think the committee should either recommend CE-CT for both groups or CE MR for both, rather than make a distinction based on very weak clinical data applied to a sophisticated cost effectiveness model.	Thank you for your comment. The recommendations were based on the findings from the economic model. The committee acknowledged the low quality of the evidence informing the precise values for sensitivity and specificity that were used in the model but wide ranges of plausible values for these were tested and did not alter the model's conclusions. This is largely because detecting positive patients does not generate many QALYs for the net cost involved (put another way, the downstream care pathway is very expensive compared to its effectiveness so the value of imaging a largely negative cohort is finely balanced). The base case ICER for MRI vs CT-MRI was >£45,000/QALY gained. This is partly because an influential parameter in the model was the proportion of positive patients that were expected to have 4+ brain metastases. The sensitivity of both contrast enhanced imaging modalities in detecting this sub-population was assumed to be 100% (although in fact the sensitivity of CT in this subgroup

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				CE-CT currently fits more easily into the rapid diagnostic approach and the overall number of patients missed is not known with confidence. Pathway delays are important, as is stated elsewhere in the guideline and may offset any small benefit from MR. Moving towards MR for all (assuming CT technology does not improve further) is desirable. A pragmatic approach is needed with an option for CE-CT or MR in both stage groups	could be lowered to 60% without MRI becoming the most cost-effective strategy). This sub-population are an important driver of cost-effectiveness in the stage I and II economic models because there is a greater reduction in costly radical treatment than for patients with 1-3 brain metastases (in whom the sensitivity of CT was modelled at ~74% and MRI at ~94%, the values drawn from the meta-analysis of included studies). The expected prevalence of brain metastases was taken from O'Dowd 2014 as the best source of evidence in patients post PET-CT/staging who were being considered for radical treatment. The prevalence values were ~4.6% in stage I, ~9.5% in stage II and ~9.3% in stage III (the equivalent values among the last two subgroups may be the result of brain metastases having been detected on PET-CT in more stage III patients). While we acknowledge the stepped recommendations for stage II disease could lead to a delay in treatment for some patients, the results of the economic model show that the confirmatory MRI scan would only be

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					needed in between 4% to 6.5% of stage II patients being considered for radical treatment. As you have highlighted, access to CT is often more readily available and therefore these recommendations probably result in more timely imaging for the stage II cohort overall than recommendation MRI in all patients. Because the detection of brain metastases results in much greater reductions in radical treatment in the stage IIIA subgroup, the test with the highest sensitivity, MRI, was the most cost-effective.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review A	19	23-31	This statement feeds the notion of simply going for the most obvious target depending upon the imaging rather than fully staging the mediastinum. This is not in keeping with the approach to accurately staging the mediastinum where this impacts treatment choice	Thank you for your comments. The paragraph that you are referring to in the guideline has been removed. The committee resolved your comment by including the phrase: "using a systematic approach" in recommendation 1.3.20. This systematic approach is consistent with the methodology used in the ASTER and BOOST trials. The algorithm of intrathoracic staging has also been revised accordingly.
NHS England – Clinic Expert	Evidence Review A	19	32	The committee state that 'the availability of PET-CT is more limited than EBUS-TBNA and EUS-FNA, so specifying that PET-CT is done first may cause delays. As a result the	Thank you for your comments. The committee agreed that PET-CT prior to EBUS-TBNA is what should happen but

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Group for Lung Cancer				committee did not recommend a specific order for investigations. This is counter-intuitive and not in-line with current recommendations because having all imaging up front prior to any biopsy (particularly for staging procedures) has previously been deemed essential. Furthermore the statement does not fit with the flow chart on page 8 or recommendations 1.3.19, 1.3.20 and 1.3.21. Did the committee have any evidence for this statement and was there any attempt to factor in the expansion in the availability of PET-CT? NICE guidance would normally not recommend suboptimal practice because of a poorly evidence based perceived lack of available equipment.	it does not happen on every occasion. Therefore, the committee agreed to re-phrase this recommendation to: 1.3.19 Offer PET-CT (if not already done), followed by one or both of EBUS-TBNA and EUS-FNA, as the initial investigations for people with lung cancer who have an intermediate probability of mediastinal malignancy (lymph nodes between 10 and 20 mm maximum short axis on CT) and who could potentially have treatment with curative intent. [2019]
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review A	20	17	EUS-FNA is NOT widely used as stated here. There are only a few centres that use EUS currently in the lung cancer staging setting.	Thank you for your comment. The committee decided to delete the comment about EUS-FNA and EBUS-TBNA being widely used. However, the recommendations will reinforce best practice and result in a more streamlined diagnostic service with more timely diagnosis. The evidence for EUS-FNA is strong. For example, the ASTER trial.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review A	21	7	There is no mention anywhere in this section about the difference between full EUS and EUS(B) – using the EBUS scope in the oesophagus. Kang et al deployed EUS(B) and NOT full EUS. This subtle but important point (which may affect results and implementation) seems to have bypassed the committee.	Thank you for your comment. The committee agreed to acknowledge that Kang 2014 used EUS(B). However, this does not change any of the recommendations because this study had been relatively unimportant in the

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					committee's consideration of the evidence.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review A	General Page 18	General	Concern expressed about the evidence used and the interpretation thereof being less rigorous than for the 2011 guideline: E.g. Two papers Tournoy 2008 and Larsen 2005 that were available in 2011 were not selected at that time but appear in the 2019 update.	Thank you for your comments. Tournoy 2008 and Larsen 2005 met the inclusion criteria for this evidence review. Larsen 2005 was included in the 2011 guideline: It was included within the review, Detterbeck 2007. Larsen 2005 and Annema 2010 show that EBUS-TBNA and/or EUS-FNA as a first invasive test for people with a probability of having mediastinal malignancy, reduces the number of avoidable thoracic surgeries compared to people who go straight to surgical staging. Therefore, the findings in Larsen 2005 were not reviewed in isolation. With regards to Tournoy 2008, there is no documentation in the 2011 guideline to explain why it was not included. We assume the paper met the inclusion criteria in the review protocol. However, concerning this update, the committee felt that studies other than Tournoy 2008 were more helpful with regards to making recommendations.
				Mediastinal staging recommendations refer to 'mediastinal nodes' throughout, thereby excluding hilar nodes (which	Thank you for your comments. The committee was in agreement. Therefore,

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				could N1 or N3). Patients with enlarged N1 nodes & normal mediastinal nodes should undergo staging EBUS regardless of PET findings (false negative rate for N2-3 of 25% - see 2013 ACCP guidelines and meta-analysis data). The guidelines seem to encourage a lack of nodal staging in cN1 disease because the mediastinal nodes are normal. This may lead to missed N2/3 disease. This is now particularly important as these guidelines are recommending induction chemoradiotherapy then surgery for resectable N2 disease so there should a thorough work up for N2 disease pre-operatively as it would change the treatment regime. Members felt that on reading the entire section there is no clear recommendation whether to recommend EBUS-TBNA or EUS-FNA or both procedures. In different places the emphasis is subtly different. As a result this section is a bit confusing and could do with tightening up. e.g. Recommendation 1.3.19 Offer PET-CT and one or both of EBUS-TBNA and EUS-FNA as initial investigation….This wording implies that you could do EUS-FNA as the first test if you have access to EUS only for instance. This would clearly be the wrong test for the majority of people.	the word "mediastinal" has been changed to "intrathoracic" for recommendations 1.3.16 and 1.3.21. Furthermore, for recommendation 1.3.21, the committee have added: "using a systematic approach". In order to clarify this, there is now a footnote describing the systematic approach. This systematic approach is consistent with the methodology used in the ASTER and BOOST trials. The algorithm of intrathoracic staging has also been revised accordingly. Much consideration was given to this. Unfortunately, there is insufficient evidence to be specific about when EBUS-TBNA and/or EUS-FNA should be used. The updated recommendations assume that clinicians have access to both EBUS-TBNA and EUS-FNA (the decision should not be dependent on availability of procedure). To quote 'The quality of the evidence section": The committee agreed that the quality of evidence for using EBUS-TBNA as a first invasive test was good particularly with regard to the study by Navani et al. (2015). The committee also confirmed

					that the evidence for when EUS-FNA should be used as a first invasive test or as a second invasive test following EBUS-TBNA was of a lower quality: The methods section of Navani 2015 says the following: "If a target node was inaccessible with EBUS-TBNA then EUS-FNA as an alternative procedure was allowed." The word "inaccessible" is an inexact term. For example, this term does not specify which lung stations are inaccessible by EBUS-TBNA. In Navani 2015, EUS-FNA was conducted for 2 people who met the inclusion criteria out of 66 (the others had EBUS-TBNA because they had suspicious lesions in lung stations accessible by EBUS-TBNA). To specify a more exact treatment protocol that includes EUS-FNA, there is an issue of collecting enough data. Therefore, the committee agreed that it might never be possible to have a study that specifies the exact usage of EUS-FNA. This is because the outcomes depend on too many variables such as the study population. In addition, Kang 2014 had vague inclusion criteria, non-significant results and had indirect evidence because the in the UK clinicians aim to give patients fewer than 3 endoscopic interventions. The

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					committee also noted that EUS-FNA is particularly good at reaching lung stations 8, 9 and 4L.
NHS England – Clinic Expert Group for Lung Cancer	Evidence Review A	various	various	Navani et al 2015 For clarity, it should be stated that as EBUS was used rather than EBUS and EUS in all but 2 patients the related recommendations are stringer for EBUS than for EUS. It should also clarify that findings described from the post hoc analysis should be interpreted with caution.	Thank you for your comments. These points have already been discussed in 'The quality of the evidence' section. We agree that these specific outcomes (duration of survival) should be downgraded. However, even with this downgrade incorporated, the evidence statement is not affected – the outcomes are still high to moderate quality evidence with the following explanation: The survival data was post-hoc analysis and we used the survival hazard ratio for our evidence statement. Originally, we rated this outcome as being high quality evidence. With the downgrade, it becomes moderate quality evidence. Nevertheless, the following outcomes remain high quality evidence and are statistically significant favouring EBUS-TBNA and/or EUS-FNA: time to treatment decision, number of people who had diagnosis and staging completed by 14 days, number of investigations per person, and number of

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					people diagnosed and staged with one investigation. The committee did interpret the mortality data with caution. However, the combination of mortality data, avoidable thoracotomies and time to treatment decision was important in the committee's considerations.
Northern Ireland Cancer Network	Guideline	15/45	15-17	Guideline makes too strong a recommendation for pre-operative chemo radiotherapy for patients with operable IIIA-N2 NSCLC, and is not qualified enough The clinical trials evidence quoted to underpin this recommendation (over sequential chemotherapy and surgery, CS) does not seem to conclude that pre-op chemoradiation CRS should be considered as an improvement of pre-op chemotherapy The one randomised trial of definitive chemoradiation (CR) versus induction chemoradiation with surgery (CRS) shows improved progression free survival, but not overall survival and a higher rate of individuals dying without progression in the surgery group, in a very selected patient population IIIA-N2 disease is a very heterogeneous; the bulkiness of the mediastinal lymph nodes is often a criteria for trial entry (the bigger the bulk, the less likely to be effectively cleared with surgery). IIIA-N2 may notionally be subdivided into	Thank you for your comments. Please see the thematic response to comments on the recommendations for management of resectable stage IIIA-N2 NSCLC at the end of this document.

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				4. IIIA-N2 low bulk (eg single station non- bulky / microscopic N2); Fit for surgery (may in fact be N2 only detected at surgery) 5. IIIA – N2 bulky 6. IIIA – N2 (between 1 nor 2) Prior to PACIFIC / Immunotherapy post CCRT) my thinking would have been ; Category one is the least frequent but would seem notionally to be the best place for surgery. Requires fit patients who would also be able to have adjuvant chemotherapy. Category 3 is most frequent and would best be seen as place for definitive concurrent chemoradiation if fit… In practice many patients are not fit and in UK receive radiotherapy alone (see Harden S WLCCC 2018 abstract – All stage III 13% radical surgery, 10% chemo and radiotherapy (6% sequential, 4% concurrent estimated), 6% radical radiotherapy alone, 71% palliative therapy only. Of those receiving surgery only approx. 50% receive chemotherapy (? due to fitness) The PACIFIC study using adjuvant immunotherapy post concurrent chemoradiation has now reported an improvement in overall survival. (Given that the current draft guideline is not likely to be updated for another two years it would seem prudent that the committee should review this PACIFIC trial evidence, given that it will have a major impact on the relative effectiveness of CR versus CRS). (perhaps the current standard of care has now shifted to Concurrent chemoradiation and immunotherapy)	

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				The clinical trials which are used in the analysis, to my mind conclude 1, Pre-op chemoradiation has by and large only been considered in clinical trials for fit PS0-1, non-elderly , operable patients 2. Clinical outcomes do not support CRS is better than CS 3. Type of surgery is important; higher mortality with pneumonectomy 4. Some studies have used sequential chemotherapy followed by radiotherapy followed by surgery (best sequencing has not been defined- presumably requires further research.). 5. Only one RCT of CR vs CRS showing improvement in progression free survival for surgery arm but not overall survival (?? toxicity from surgery) ; 6.(adjuvant) Immunotherapy studies post definitive CCRT now do need to be taken into account by the committee; I would only advocate CRS if full dose definitive CR was given and surgical resection considered afterwards (without a pneumonectomy) in VERY fit patients The evidence quoted to underpin the recommendation for CRS (over sequential chemotherapy and surgery) does not seem to conclude that pre-op chemoradiation should be considered as an improvement of pre-op chemotherapy.	

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				Thomas M "Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III NSCLC" Lancet Oncol 2008 9 636-648 Phase III in operable IIIA-B PS0-1 (age < 70yr). Randomised pre-op EP followed by 45Gy/30 bd RTX with weekly carbo/vindensine then surgery versus preop EP then surgery with post op radiotherapy. 35% of patients required a pneumonectomy. There was no difference in progression free survival or overall survival. The mortality with pneumonectomy was high in the chemorad pre-op arm (14%). The trial concluded that whilst endpoints such as mediastinal down staging might be improved "preoperative chemoradiation... does not improve overall survival" *Pless M et al "Induction chemo radiation in stage IIIA/N2 NSCLC: a phase 3 randomised trial" Lancet 2015 386 1049-56.* Randomised trial of sequential docetaxel cisplatin 3 cycles followed by 44Gy/22 fractions followed by surgery or doce cisplatin chemotherapy alone followed by surgery. Patients were pathologically proven N2 PS0-1, operable aged 18-75 years. There was no difference in overall survival or progression free survival. 25% of patients required a pneumonectomy. The trial concluded "Radiotherapy did not add any benefit to induction chemotherapy followed by surgery" A randomised study closed early due to slow accrual from WJ group. "*A phase 3 study of induction treatment with concurrent chemo radiotherapy versus chemotherapy before surgery in patents with pathologically confirmed N2 stage IIIA NSCLC (WJTOG9903)" Katakami N Cancer 2012 118*	

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				6126-6135. Only 60 patients were randomised. Patients felt better suited for definitive concurrent chemoradiation were excluded. Patients had to be potentially operable. Patients were PS 0-1 and <= 70 years old. Patients were treated with either induction carboplatin and docetaxel for 2 cycles or carboplatin and docetaxel with 40Gy thoracic radiotherapy. The authors commented "overall survival also did not improve in the CRS arm versus the CR arm" and "Progression free survival did not improve". A hazard plot of NICE meta-analysis (appendix G page 88) shows confidence intervals cross 1. The randomised studies all concur that there is no benefit in the endpoints of progression free or overall survival. There may be some benefit in down staging of the mediastinum and an increase in treatment related toxicity, but these do not translate into hard endpoints of survival and progression-free survival. The trials include hyperselected patients (ood performance status, fitness for surgery and age < 70 years). These results may not be applicable to the general stage III population in the UK. The committee's recommendation that chemoradiation should be considered seems at best too strong and at worst at odds with the available clinical evidence. In our centre's experience surgery is possible after concurrent chemoradiation but it is tough treatment and only feasible for the fit few. CRT vs C prior to surgery may benefit from larger clinical trials, although this seems unlikely given poor accrual in previous studies. We would agree with the authors from all	

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				the studies quoted; there is no evidence that the addition of radiation in the pre-operative setting improves survival. Advantage of CRS over CR; Only one clinical study hinging on the relative advantage of PFS over no advantage in Overall survival. This has two main concerns 3. Ability to reproducibly detect local progression over radiotherapy scarring 4. The higher number of non-cancer deaths in the surgical arm. *Albain et al "Radiotherapy plus chemotherapy with or without surgical resection for stage III NSCLC: a phase III RCT" Lancet 2009 374 379-386*. Randomised patients with pathologically proven N2 disease felt to be potentially resectable but in whom definitive concurrent chemo-radiation was considered standard of care over surgical resection alone. Had to be PS 0-1. Median follow up was 23 months. The definition of local progression in the CR group was not defined in the paper. It can be very difficult to determine local radiation progression from radiation scarring even several years after radiotherapy. (our current algorithm requires PET/Ct and biopsy confirmation or enlarging mass). The only difference in relapse patterns was more local progression in the CR versus CRS arms. (Progression free survival can be very difficult to interpret in radiation studies in which residual scarring is left; obviously in the surgery arm this scarred lung would have been removed making it easier to define local progression). A better progression free	

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				survival was seen (+ 3 months progression free). 5yr PFS difference was noted (although median follow up was only 23m) 22% vs 11%. However more individuals died without progression in surgical arm 18% versus 10% (p=0.02) (? from complications/ physiological stress leading to mortality – heart/ lung). Pneumonectomy was found to have a high mortality in this study. The trial did allude to a survival improvement in the lobectomy group, but this is a post hoc analysis. It is however worthy of further study and may represent a patient population in whom to take this paradigm further forward in. The trial is unable to answer the question of whether induction chemotherapy would have been equivalent / better than induction chemoradiation.	
Nutricia Advanced Medical Nutrition	Guideline	6	General	Inclusion of the steps of the management pathway of the Lung Cancer Pathway http://lungcancernutrition.com/A%20Practical%20Guide%20to%20Lung%20Cancer%20Nutritional%20Care.pdf	Thank you for your comment. This area was out of scope for this update of the guideline.
Nutricia Advanced Medical Nutrition	Guideline	General	General	Inclusion of 'MUST' screening on first contact and re-screening as the patient moves through care settings	Thank you for your comment. The MUST screening tool is recommended in the NICE Nutrition support for adults guideline CG32.
Nutricia Advanced Medical Nutrition	Guideline	General	General	Should cross reference to CG32 for the nutritional management of patients with lung cancer.	Thank you for your comment. This area was out of scope for this update of the guideline
Pfizer	Systemic anti-cancer therapy manageme	General	General	This figure appears verbatim from the evidence review E, page 7 figure summarising the recommendations on management options for people with non-squamous and non-small cell carcinoma from the NICE guideline on lung	Thank you for your comment. Please see the response to the comment you reference.

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	nt (non-squamous visual summary)			cancer. We therefore express the same comment as in comment number 3 above.	
Pfizer	Guideline	16	28-30	The wording of this sentence appears to imply that both crizotinib and ceritinib are equally adequate second-line treatment options for patients who have progressive disease following first-line crizotinib, ceritinib or alectinib. In fact, ceritinib is available as a second-line treatment only after progressive disease on crizotinib whilst crizotinib has a broader indication for use in progressive disease following previous (systemic) treatment in ALK positive NSCLC. It is worth noting however, that the recommendation for crizotinib (NICE TA 422) was made during an era when the first-line therapy was chemotherapy as there were no other ALK inhibitors in the market at that time. In the contemporary era of newer generation ALK Tyrosine Kinase Inhibitors (TKIs) however, the clinical effectiveness of crizotonib as a second line following ALK TKIs such as alectinib or ceritinib is unknown. The latest ESMO guidelines on metastatic NSCLC states that 'any patient with NSCLC harbouring an ALK fusion should receive crizotinib as next-line therapy if not received previously' (Planchard *et al*., 2018). In other words, these are patients who have been treated with first-line chemotherapy rather than crizotinib. The ESMO guidelines further clarifies that ALK re-arranged patients progressing on crizotinib should be treated with next-generation ALK TKIs such as ceritinib as second-line (Planchard *et al*., 2018).	Thank you for your comment. We have now amended the ALK section so that the only second-line ALK TKI is ceritinib if people have had crizotinib. In the updated recommendations the committee chose not to include TA guidance on crizotinib as a 2nd line treatment as they believed that the evidence only relates to people who are ALK positive but have been treated with chemotherapy first line, a population that no longer exists as ALK testing is routine and crizotinib, ceritinib and alectinib are all 1st line options.

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				Additionally, the NICE technology appraisal documents on alectinib (TA536) and ceritinib (TA500) use as first-line both states that there are currently no further ALK TKIs that are recommended for use as a second-line in patients who progress on these medications. Thus, we would recommend that this section is expanded to make it clearer to the readers that although ceritinib is a recognised second-line treatment for patients who have progressive disease on crizotinib (when given first-line), there are currently no other ALK inhibitors in the market that can be routinely used in patients who progress on the newer generation ALK inhibitors when used as a first-line treatment (alectinib or ceritinib).	
Pfizer	Evidence review E	7	General	In this figure summarising the recommendations on management options for people with non-squamous and non-small cell carcinoma from the NICE guideline on lung cancer, we would like to comment on the section regarding ALK positive patients. Here, crizotinib, alectinib and ceritinib are shown as options for the first-line treatment of patients with ALK positive NSCLC. Crizotinib however, is also shown as a second-line treatment option for patients who progress on first-line alectinib or ceritinib in this algorithm. Although we recognise that crizotinib has a broad indication for use in patients with progressive disease following previous (systemic) treatment in ALK positive NSCLC, this	Thank you for your comment. We have now amended the ALK section so that the only second-line ALK TKI is ceritinib if people have had crizotinib. In the updated recommendations the committee chose not to include TA guidance on crizotinib as a 2nd line treatment as they believed that the evidence only relates to people who are ALK positive but have been treated with chemotherapy first line, a population that no longer exists as ALK testing is routine

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				recommendation was made during an era when chemotherapy was the only first-line treatment modality for patients with ALK positive NSCLC. Thus, the clinical effectiveness of crizotinib as a second line following newer generation ALK TKIs (such as alectinib or ceritinib) is currently unknown. The latest ESMO guidelines on metastatic NSCLC states that 'any patient with NSCLC harbouring an ALK fusion should receive crizotinib as next-line therapy if not received previously' (Planchard *et al*., 2018). In other words, these are patients who have been treated with first-line chemotherapy rather than crizotinib. The ESMO guidelines further clarifies that ALK re-arranged patients progressing on crizotinib should be treated with next-generation ALK TKIs such as ceritinib as second-line (Planchard *et al*., 2018). Additionally, the NICE technology appraisal documents on alectinib (TA536) and ceritinib (TA500) use as first-line both states that there are currently no further ALK TKIs that are recommended for use as a second-line in patients who progress on these medications. Thus, we recommend that the reference of crizotinib as a second-line option following the use of alectinib or ceritinib first-line is removed from this diagram. When crizotinib is used as first-line agent however, ceritinib is the only current NICE approved agent that can be used in this second-line setting, which we feel is accurately represented in this figure.	and crizotinib, ceritinib and alectinib are all 1st line options.
Pfizer	Evidence review E	9	25-26	This sentence appears verbatim in the final draft document as described above (guideline, pg 16, lines 28-29). We	Thank you for your comment. This has been addressed as noted above.

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				therefore express the same comment as in comment number 1 above.	
Roche Diagnostics Limited	Guideline	7	20 - 22	We believe that clinicians are most likely to consult this short document and are therefore concerned that the recommendations around diagnosis using predictive markers are not clear enough to support them. We would therefore suggest including a recommendation on the companion diagnostic tests that are required to prescribe the systemic anti-cancer therapies listed in the management section e.g ALK or ROS-1 for Crizotinib, ALK for Ceritinib, PD-L1 for Pembrolizumab etc. Please see the summary of product characteristics for Criztonib, Ceritinib and Pembrolizumab which provide information on which tests have to be conducted prior to their prescription. 1. EMC. Summary of product characteristics. Xalkori 200mg hard capsule. Available at https://www.medicines.org.uk/emc/product/2857/smpc. Last accessed 5/11/18. 2. EMC. Summary of product characteristics. Zykadia 150mg hard capsules. Available at https://www.medicines.org.uk/emc/product/7109. Last accessed 5/11/18. EMC. Summary of product characteristics. Keytruda 50 mg powder for concentrate for solution for infusion. Available at https://www.medicines.org.uk/emc/product/6947.	Thank you for your comment. Although this recommendation was updated in order to bring it into alignment with other NICE guidance, this area is out of scope for this update of the guideline and the committee were therefore unable to make any additional recommendations.
Roche Diagnostics Limited	Guideline	7	23 - 25	We believe that clinicians are most likely to consult this short document and are therefore concerned that the recommendations around EGFR-TK mutation testing are not	Thank you for your comment. Although this recommendation was updated in order to bring it into alignment with other

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				clear enough to support them. Although a link to DG9 has been provided, we would suggest that details of EGFR-TK testing are included alongside the link to aid clinicians with their decision making.	NICE guidance, this area is out of scope for this update of the guideline and the committee were therefore unable to make any additional recommendations. The approach we have taken throughout this document when referring to other NICE products is that of simple cross-referral so as not to compromise the readability of the guideline.
Royal College of General Practitioners	scope	General	General	Include prevention re smoking cessation services	Thank you for your comment. Stop smoking services were out of scope for this update of the guideline. The guideline does have a section on "Stop smoking interventions and services". Within this section there is a link at 1.4.3 that links to the separate "Stop smoking interventions and services" guideline, which includes smoking cessation services.
Royal College of General Practitioners	scope	General	General	Earlier diagnosis, look at evidence re case finding/ screening in high risk populations e.g. smokers ex-smokers c long pack year history	Thank you for your comment. Screening is beyond the remit of NICE.
Royal College of General Practitioners	General	General	General	Public health messages in alerting the public with regard to their symptoms need to be balanced and evidence based	Thank you for your comment. This area was out of scope for this update of the guideline.
Royal College of General Practitioners	General	General	General	Patient support and advocacy during diagnosis and treatment remains of paramount importance.	Thank you for your comment. This area was out of scope for this update of the guideline.

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Royal College of Nursing	Quality standard 4	11	6	We are concerned that the definition of the programme of study for a lung cancer nurse specialist specifies only 20 credits at 1st degree level in the specialised area. We believe this should be a module at Master level as per *Career and education framework for cancer nursing - Guidance for pre-registration nursing students, support workers in health and social care, and registered nurses providing general or specialist cancer care* (Page 15) https://www.rcn.org.uk/professional-development/publications/pub-005718	Thank you for your comment. NICE will be fully updating the quality standard for lung cancer (QS17) following publication of the updated guideline. We will consider your feedback accordingly. We expect to publish the updated quality standard in January 2020.
Royal College of Nursing	Guideline	16 - 18	General	The new algorithm for treating non-squamous NSCLC is excellent	Thank you for your comment.
Royal College of Nursing	Guideline	18 - 19	General	The new algorithm for treating squamous NSCLC is excellent.	Thank you for your comment.
Royal College of Nursing	Guideline	21	5	Question: Has the age limit recommendation for people with small cell lung cancer receiving prophylactic cranial irradiation (PCI) been removed?	Thank you for your comment. There was no mention of patient age in PCI recommendations in the 2011 version of the guideline.
Royal College of Nursing	Guideline	4	7 - 9	We are concerned that the guideline for referral with suspected lung cancer does not specify that a person can be referred with a normal chest X-ray and symptoms of concern but stated only symptoms of concern. Many people are being referred as suspected lung cancer with no imaging whatsoever which delays diagnosis and creates delays in OPA due to capacity and demand.	Thank you for your comment. This area was out of scope for this update of the guideline. The recommendation was merely updated to refer to the guidance on Referral for Suspected Cancer, which had been published since the last time this guideline was updated.
Royal College of Nursing	General	General	General	The Royal College of Nursing (RCN) welcomes proposals to update the NICE Lung Cancer: diagnosis and management guideline.	Thank you for your comment.

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				The RCN invited members who care for people with lung cancer to review the draft document on its behalf. The comments below reflect the views of our reviewers.	
Royal College of Pathologists	General	General	General	For a document that is titled "diagnosis and management", there is no mention at all of what is required from pathologists, or what other specialties should expect from pathology. I realise that there may be a limitation on how long the document should be, so if there cannot be a section on pathologic diagnosis (and all the data for UK pathologists are updated regularly within the RCPath dataset), please can there be a statement in the summary recommendations that "In relation to pathological diagnosis of lung cancer, health care professionals should follow the Royal College of Pathologist guidelines within the Dataset for histopathological reporting of lung cancer which can be accessed from the website https://www.rcpath.org	Thank you for your comment. This area was out of scope for this update of the guideline.
Royal Devon & Exeter NHS Foundation Trust	Guideline	10	1	I am concerned that guideline does not recognised the role of CT which is often preferable to patients and gives additional information re the overall status of disease.	Thank you for your comment. This area was out of scope for this update of the guideline.
Royal Devon & Exeter NHS	Guideline	10	14	The comment that all patients with suspected lung cancer should be discussed at MDT is outdated. These patients	Thank you for your comment. The committee agreed to revert this

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Foundation Trust				should be appropriately investigated according to agreed pathways e.g. nodule follow up. Only patients with a clinical or pathological diagnosis of malignancy need to be registered and formally discussed.	recommendation to the original 2005 wording because they feel it is clearer. The recommendation now refers to people with a 'working diagnosis of lung cancer'.
Royal Devon & Exeter NHS Foundation Trust	Guideline	13	26	I am concerned that the guideline suggest that all patients should be offered radical radiotherapy regardless of underlying lung pathology and performance status. The guideline should be amended to reflect these issues and altered to consider	Thank you for your comment. The committee assumes that clinicians will not offer treatments that are contraindicated The committee reviewed the evidence on radical radiotherapy and concluded that it is an effective and cost-effective treatment in this population. They therefore agreed that this recommendation merits an 'offer'.
Royal Devon & Exeter NHS Foundation Trust	Guideline	14	12	The wording of this is very vague and does not reflect the complexity of decision making. The guideline could consider using predicted risk of complication rather than size.	Thank you for your comment. The committee have decided to delete this recommendation because it has been superseded by other recommendations included in this update.
Royal Devon & Exeter NHS Foundation Trust	Guideline	15	12	The wording suggests that patients should be treated with Cisplatin and Vinorelbine- Routine clinical practice and the evidence base suggests that Platinum and Etoposide would be the standard of care	Thank you for your comment. This area was out of scope for this update of the guideline.
Royal Devon & Exeter NHS Foundation Trust	Guideline	15	15	This guidance concerns me greatly. The evidence does not strongly support the use of surgery in stage 3 disease. Great caution should be used for pts with > 1 nodal station involvement and surgeons need to be committed to	Thank you for your comment. Please see the thematic response to comments on the recommendations for

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				operating in a timely manner otherwise the radiotherapy will have been compromised.	management of resectable stage IIIA-N2 NSCLC at the end of this document for further information.
Royal Devon & Exeter NHS Foundation Trust	Guideline	16	4-27	This will be out of date very soon given the evidence for Osimertinib, Brigatenib and loralatanib.	Thank you for your comment. The guideline and algorithms have been updated to reflect positive technology appraisal guidance on first line pembrolizumab combination therapy and on brigatinib after crizotinib that published between consultation and publication of this guideline update. We are unable to pre-empt the recommendations arising from NICE Technology Appraisals that will publish after this update of the guideline. We recognise that this is an area where Technology Appraisals are frequently conducted and that there are several in development at this time. The accompanying pathway for the guideline will be reviewed and updated periodically to reflect new technology appraisals.
Royal Devon & Exeter NHS Foundation Trust	Guideline	18	28	Guideline needs to reflect flexibility to offer chemotherapy first for patients who are deteriorating rapidly. Also the evidence for combination therapies in the first line setting for both NSCLC and SCLC means with EAMS this will soon be out of date.	Thank you for your comment. The committee drew on published NICE guidance to make recommendations and construct algorithms to reflect what they believe is best practice in most

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					situations. These recommendations are not intended to be a substitute for clinical judgement or to cover every scenario that might be seen in clinical practice. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.
Royal Devon & Exeter NHS Foundation Trust	Guideline	19	20	There is very little evidence to suggest that 6 cycles of chemotherapy is preferable to 4. 4 should be the standard of care Also consider enabling single agent for very poor PS pts who are not fit for doublet.	Thank you for your comment. This area was out of scope for this update of the guideline.
Royal Devon & Exeter NHS Foundation Trust	Guideline	20	16	The guidance should include guidance for pts treated with primary surgery too	Thank you for your comment. These areas were considered as part of this guideline update. Please see sections "Maintenance treatment for small-cell lung cancer", "Prophylactic cranial irradiation in small-cell lung cancer" and "Second-line treatment for small-cell

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					lung cancer that has relapsed after first-line treatment".
Royal Devon & Exeter NHS Foundation Trust	Guideline	20	6	The early stage data from the Convert Study suggests excellent outcomes- Unless surgeons are able to operate within the one week window that oncologists do- pt may come to harm. Room to formally evaluate against Chemo-RT in trial	Thank you for your comment. The comparison of surgery and RT in this patient population was out of scope for this update of the guideline.
Royal Devon & Exeter NHS Foundation Trust	Guideline	21	1	Guideline should reflect the evidence is in younger patients and should not suggest it is appropriate for all patients	Thank you for your comment. Prophylactic cranial irradiation for patients with limited-stage SCLC is out of scope for this update of the guideline. The recommendations for patients with extensive stage SCLC were amended to a 'consider', which implicitly takes into account the fitness of the patient.
Royal Devon & Exeter NHS Foundation Trust	Guideline	21	15	Hard to justify 6 cycles	Thank you for your comment. This area was out of scope for this update of the guideline.
Royal Devon & Exeter NHS Foundation Trust	Guideline	22	23	Guideline should reflect use of indwelling catheters e.g. pleurex	Thank you for your comment. This subject is out of scope for this update of the guideline. The committee reverted to the wording of the original 2005 recommendation – 'Patients who benefit symptomatically from aspiration or drainage of fluid should be offered talc pleurodesis for longer-term benefit'. The committee are aware that this subject may require updating. Therefore, we will

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					pass your comment to the NICE surveillance team, which monitors guidelines to ensure that they are up to date, for consideration when future updates of the guideline are planned.
Royal Devon & Exeter NHS Foundation Trust	Guideline	24	7	The advice of routine follow up in out of kilter with the living and beyond agenda. There is little to be gained in bringing patients unfit for further systemic therapy to clinic. With the inclusion of ESC in commissioning specification and availability of acute oncology- this guidance is outdated	Thank you for your comment. This area was out of scope for this update of the guideline.
Society & College of Radiographers	Guideline	4	10-15	1.1.3 When a chest X-ray has been requested in primary or secondary care and is incidentally suggestive of lung cancer, send a copy of the report to a designated member of the lung cancer multidisciplinary team (usually the chest physician). The multidisciplinary team should have a mechanism in place to follow up these reports, to enable the person's GP to prepare a management plan. [2005] The Society and College of Radiographers feels that clarity is required in this statement as reporting radiographers can also report chest X-rays, including those for suspected lung cancer. Evidence suggests that reporting radiographers are accurate at chest X-ray reporting [1-4] and that it is feasible for radiographers to provide immediate reports for patients' referred from primary care and to communicate reports directly to patients at the time of the chest X-ray [5]	Thank you for your comment. This area was out of scope for this update of the guideline.

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				1 - Woznitza et al Acad Radiol https://www.academicradiology.org/article/S1076-6332(18)30177-6/fulltext 2 - Woznitza et al Radiography https://www.radiographyonline.com/article/S1078-8174(18)30013-0/abstract 3 - Piper et al Radiography https://www.radiographyonline.com/article/S1078-8174(14)00004-2/abstract 4 - Woznitza et al Radiography https://www.radiographyonline.com/article/S1078-8174(14)00016-9/abstract 5 - Woznitza et al Clin Radiol https://www.clinicalradiologyonline.net/article/S0009-9260(17)30536-6/fulltext	
Society for Cardiothoracic Surgery in GB & Ireland	Guideline	13	11	(and with ref to p13 line 22) We welcome the recognition that there is still uncertainty re relative benefit of VATS and open lobectomy (and lobectomy vs sublobar resections and SABR) and that surgical approach should be based on patient fitness, wishes and technical aspects of treatment.	Thank you very much for your comment.
Society for Cardiothoracic Surgery in GB & Ireland	Guideline	15	15	The management of N2 disease remains controversial but to have more specific guidance regarding the benefits of chemo-RT and surgery vs upfront surgery or induction chemotherapy then surgery is very helpful.	Thank you for your comment.
Society for Cardiothoracic	Guideline	6	21	And also with ref to p9 line 19. The early development of brain relapse following radical treatment is devastating but	Thank you for your comment. The review, analyses and economic model

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Surgery in GB & Ireland				the routine brain imaging of all patients with stage II or greater disease at presentation having radical treatment will have a huge imaging resource implication. It will potentially also further delay the lung cancer pathway which is already one of the most complex and challenging and will require 3 separate imaging episodes (initial CT CAP+ neck + PET–CT and now brain CT) within the 62 days not including any imaging required for diagnosis. Including brain imaging in initial CT in good performance status patients might offset this.	conducted for this area of the guideline were confined to patients who had already been deemed candidates for radical treatment. This decision was based on NICE's surveillance review and scoping workshop with stakeholders showing the availability of evidence in this population as well as discussions with the committee. The economic model concluded that offering brain imaging in stage II and III would be cost-effective (see Evidence Review B for a full discussion). The NICE Resource Impact Assessment Team conducted an analysis seeking to determine the overall budget impact associated with each brain imaging recommendation and have concluded that this wasn't significant. Indeed, any increase in brain imaging in stage IIIA disease is likely to lead to net cost-savings through reduction in the use of expensive radical treatments. The committee were mindful of the potential delay to treatment for some patients associated with the new recommendations and the potential cost-effectiveness of adding brain CT to initial chest CT and made a recommendation for research in this area. The committee

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					were also aware that there are pressures on imaging services, particularly MRI scanners and that some patients prefer not to receive MRI scans but agreed that these considerations should not affect the recommendations. It should be borne in mind that the cost-effectiveness considerations are quite different at initial staging as many patients would not have gone on to have radical treatment regardless of the brain imaging result.
Society for Cardiothoracic Surgery in GB & Ireland	Guideline	8	23	(and with ref to p9 line 9) We approve the recognition that EBUS / EUS is first line intervention for staging mediastinum and only minority of patients should require surgical mediastinoscopy	Thank you for your comment.
Society for Cardiothoracic Surgery in GB & Ireland	Guideline	General		There is increasing evidence regarding the benefits of closer radiological surveillance after radical treatment. There is also lack of clarity regarding responsibility for lung cancer follow-up in previous guidance. There appears to be little guidance as to how and by whom long-term follow-up should be provided by, what imaging is recommended and estimation of resource implications.	Thank you for your comment. This area was out of scope for this update of the guideline.
Wirral University Teaching Hospital NHS Foundation Trust	Guideline	7	6	There should be a specified time from PET request to formal report of maximum 7 days (this is a crucial test which commonly guides invasive investigations).	Thank you for your comment. Specifying time limits for tests was out of scope for this update of the guideline. The committee saw no evidence review and were therefore unable to make specific recommendations. Recommendation

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					1.3.5 was updated to reflect newer terminology but no evidence was reviewed.

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Thematic Response to stakeholder comments on the management of resectable stage IIIA-N2 NSCLC

Thank you for your comments on the management of resectable stage IIIA-N2 NSCLC, which the committee considered at the post-consultation committee meeting. A number of points have been raised by consultees which are addressed in the composite response below.

The population to whom these recommendations apply are people with operable stage IIIA-N2 NSCLC who can have surgery and are well enough for multimodality therapy. The committee have restructured the recommendations to make this clearer.

The PACIFIC trial included only people with unresectable stage III N2/N3 disease and would therefore not have met the inclusion criteria for this review. The new guideline recommendation in favour of CRS only applies to patients in whom surgery is being considered. The committee were aware of the promising results of the PACIFIC trial, however, and made a research recommendation seeking to clarify the role of immunotherapy following surgery in patients with stage IIIA-N2 NSCLC. NICE Technology Appraisal ID1175 on the use of durvalumab maintenance in unresectable disease is due to publish in May 2019. We are aware of other studies that have synthesised trial data in resectable stage IIIA-N2 NSCLC in meta-analysis (Pottgen et al 2017 e.g.) and not found statistically significant results. These analyses are confined to conventional pairwise meta-analysis of hazard ratios and dichotomous outcomes, however. It is not surprising that our results differ because firstly, they did not include the same trials (i.e. pooling interventions that were not of interest [see para below] or including studies that would not have met our protocol [e.g. conference abstracts]), secondly, we drew a distinction between CS and CRS as separate interventions rather than pooling them and thirdly, because the proportional hazards assumption does not hold for the vast majority of the OS and PFS Kaplan-meier data in the included trials and hazard ratios may therefore have been inappropriate to pool. It is quite common for survival curves to exhibit non-proportional hazards properties in trials of surgical vs non-surgical treatment because one might reasonably expect mortality to be initially higher and subsequently lower in the surgical arms. It was for this reason that, in consultation with NICE's technical support unit (a group of medical statisticians based at the University of Bristol), it was felt more appropriate to pool data using the area-under-the-curve method rather than hazard ratios.

The analysis of progression-free survival was planned in all of the trials included in the network meta-analysis (NMA). Indeed, the trial protocol for the INT0139 RCT (Albain et al 2009), which found a statistically significant difference in progression-free survival between the CRS and CR arms, specifies PFS along with OS as a joint primary outcome. We note that the direction of effect data for PFS in the NMA are broadly consistent (Albain 2009, Eberhardt 2015, Pless 2015 and Katakami 2012 all have PFS estimates where the direction of effect favours CRS over the comparator and PFS data in van Meerbeeck 2007 were very similar between CR and CS). The NMAs and economic model did not only consider a subset of the available trials in that they included the only trials in the systematic review that examined pairwise comparisons of the three interventions of interest for this review question; CR, CS and CRS. The review question and associated analysis concerned only those patients who might be considered eligible for any of these three interventions. Thus, pairwise comparisons of radiotherapy alone (Stephens 2005 and Shepherd 1998) were not included in the NMA and neither were pairwise comparisons of different regimens of tri-modality treatment (Thomas 2008). The very low quality data on 75 patients from Johnstone 2002 was excluded from the NMA because it did not provide OS and PFS Kaplan-Meier data. We

do not expect this exclusion to affect the results as point estimates of OS and PFS from this trial are similar between the CR and CS arms, which is a finding that is not inconsistent with the results of the NMAs. The committee were shown the descriptive statistics of the patient populations included in the various RCTs and concluded that they were similar enough to one another to be combined in NMA and were similar enough to patients seen in UK clinical practice to be relevant for decision making.

We are aware that PFS is a less reliable outcome than OS but the committee did not think that radiotherapy scarring would lead to systematic over diagnosis of disease progression in the non-surgical arms of the RCTs and thereby overestimation of the PFS benefit associated with surgery. Indeed, they noted that it is possible that subtle changes in disease status are missed in patients undergoing CR because of radiotherapy scarring. They therefore felt that if bias towards incorrect recording of progression exists, it could work in either direction.

The committee recognised that patients with stage IIIA-N2 disease represent a heterogeneous group and that interventions should be offered accordingly, which was one of the reasons for only opting for a weaker 'consider' recommendation in favour of CRS in patients being considered for surgery (a group who are likely to represent the fitter patients among the IIIA-N2 cohort). It is important to emphasise that the evidence base for this question only relates to patients who were considered by the triallists to be candidates for surgical intervention. The committee noted a number of factors posited in the evidence base that might affect outcomes; lobectomy vs pneumonectomy, bulky vs non-bulky N2, single vs multiple station N2, performance score and age, for example, but chose not to make recommendations about these due to a lack of randomised evidence explicitly investigating these factors. They also considered making recommendations specifying what constitutes operability but the same limitations in the evidence base applied (technical resectability had been established via MDT assessment in the underpinning RCTs and little further detail had been provided). The committee did, however, recommend that centres undertaking multi-modality treatment including surgery submit data to the NCLA and LCCOP. It is hoped that this will prove a valuable source of information on the effectiveness of surgical interventions in this patient group as well as prognostic factors that are associated with better outcomes.

The committee acknowledged the statistical uncertainty in outcomes reported in the individual trials but noted that the health economic model, which took into account the joint uncertainty in a number of survival outcomes, found an 89% probability that CRS would generate more life years than CR for the average patient. When the most uncertain survival outcome, the probability of survival at study endpoint (there was only an 86% probability that this outcome favoured CRS over CR) was set equal, the model still found an 77% probability that CRS would generate more life years than CR (although this sensitivity analysis moved the ICER to £40,000/QALY, the committee took into account the full range of sensitivity analyses and concluded that the true ICER for CRS vs CR is likely to be much lower than this). The model found a 79% probability that CS is not cost-effective compared to CR (and no plausible sensitivity analyses changed that conclusion), with a base case ICER of >£70,000/QALY gained, but the committee chose not to explicitly make recommendations against this option, again because of the acknowledged uncertainties in the evidence base and heterogeneity in the patient population. It is understood that not all patients having planned CRS will undergo surgery following completion of CR (a 17% drop-out rate [pooled data from Pless 2015, Eberhardt 2015 and Albain 2009] was included in the economic model).

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The surgical arms of the economic model accounted for dropouts following initial treatment, which was appropriate as the survival outcomes used in the NMAs were reported on an intention-to-treat basis. It also took into account adverse events of grade 3+ and quality of life decrements from surgery. Following receipt of the consultation comments highlighting additional data available in Albain et al 2009 that had not been included, we conducted a separate NMA for the proportion of first events that are deaths, which found a higher odds ratio in both surgical arms versus CR. These data made a negligible difference to the health economic analysis, however, as PFS time, PPS time and probability of survival at 5 years (the most important outcomes for generating life years and QALYs) remained unchanged. A note of the committee's discussion has been added to Evidence Review C.

In light of the uncertainty in overall survival and the different risks and benefits associated with each of the treatments, the committee made a recommendation encouraging clinicians to discuss these explicitly with patients in whom chemoradiotherapy and surgery might be considered.

Some stakeholders referenced narrative reviews or publications based on audit/activity data showing that tri-modality therapy is used infrequently in this patient group. The committee were aware of this but concluded based on the analyses conducted for this guideline that it is likely to represent an effective and cost-effective use of NHS resources compared with bi-modality alternatives in people who are fit for surgery and hoped that these recommendations would encourage in increase in uptake. In recognition of the complexity of delivering tri-modality therapy and the lack of expertise at some centres, they also made a recommendation that MDTs offering CRS should have expertise in combined therapy and all of its components.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*

[i] Koshiaris C, Aveyard P, Oke J, Ryan R, Szatkowski L, Stevens R, Farley A. Smoking cessation and survival in lung, upper aero-digestive tract and bladder cancer: cohort study. *British Journal of Cancer* October 2017; 117, 1224-1232

[ii] Walker M, et al. Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. Cancer, Epidemiology, Biomarkers & Prevention 2006; 15(12): 2370-2377

[iii] RCP, *Hiding in Plain Sight,* 2018, 224

[iv] Farley A, Koshiaris C, Oke J, Ryan R, Szatkowski L, Stevens R, Aveyard P. Physician support of smoking cessation after diagnosis of lung, bladder, or upper aerodigestive tract cancer. Ann Fam Med. September 2017; 15(5) 443-450

[v] West R. Stop smoking services: increased chances of quitting. NCSCT Briefing #8. 2012: http://www.ncsct.co.uk/usr/pub/Briefing%208.pdf

[vi] Shahab L. Cost-effectiveness of pharmacotherapy for smoking cessation. NCSCT Briefing #7. 2012: http://www.ncsct.co.uk/usr/pub/B7_Cost-effectiveness_pharmacotherapy.pdf

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[vii] Shahab L. Effectiveness and cost-effectiveness of programmes to help smokers to stop and prevent smoking uptake at local level. NCSCT 2015: http://www.ncsct.co.uk/usr/pub/NCSCT%20briefing-effectiveness%20of%20local%20cessation%20and%20prevention.pdf

[viii] Hu X, Hay JW. First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective. *Lung Cancer* September 2018; 123: 166-171