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Time to diagnosis key in improving lung cancer outcomes

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SPECIAL REPORT

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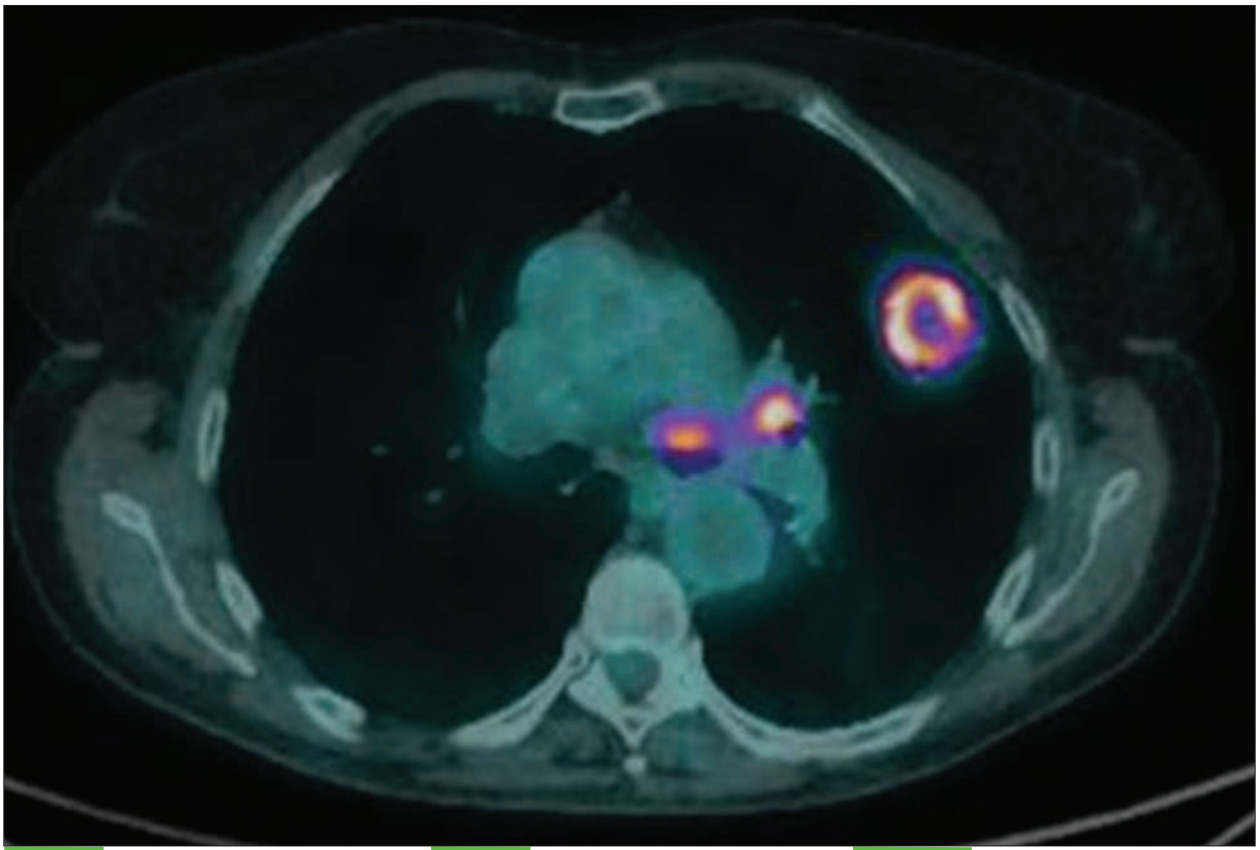


How should patients be assessed?

OUTCOMES FOR PATIENTS WITH LUNG CANCER ARE IMPROVING: THE LATEST FIGURES FROM THE International Cancer Benchmarking Partnership showed that the five-year survival in the UK had improved from 10% to 14.5%. However, the UK still lags behind other comparable countries, where five-year survival figures are around 20% or more.[1]

Presentation via an emergency route remains a problem; data collected by the National Cancer Registration and Analysis Service showed that 33% of patients were diagnosed following an emergency presentation in 2016. Although this is an improvement from 39% in 2006 it is still too high.[2] These patients have much poorer outcomes than those who are diagnosed by other routes with only 16% surviving a year and more than a third dying within a month.[3]

Prevention of lung cancer is a priority and smoking cessation advice should be integrated into the process.

How can time to diagnosis be improved?

DIAGNOSIS

One of the main reasons lung cancer is difficult to diagnose early is that there are often no symptoms related to the cancer until it has spread.

A study using primary care data showed that patients with lung cancer did interact with GPs in the 12 months prior to diagnosis suggesting that there were potential missed opportunities to diagnose them earlier.[4] At an individual GP level, lung cancer is rare; each GP may see only one new case per annum.[5] Efforts must therefore be made to identify those patients at risk, perhaps using risk prediction tools or software prompts.

Although risk prediction models have been developed to try to aid earlier identification of patients with lung cancer these are not widely used.[6,7] QCancer® has been integrated into some primary care computer systems and provides both overall cancer risk for the individual and risks for specific cancers, including lung cancer.

NICE updated its guidelines on recognition and referral for cancer in 2015 but did not make any »

What are the management options?

Table 1

NICE criteria for investigation and referral for suspected lung cancer[8]

Direct referral using a suspected cancer pathway referral for an appointment within two weeks:
- Chest X-ray findings that suggest lung cancer or
- Aged 40 and over with unexplained haemoptysis

Offer an urgent chest X-ray (to be performed within two weeks) to assess for lung cancer in people aged 40 and over if they have two or more of the following unexplained symptoms, or if they have ever smoked and have one or more of the following unexplained symptoms:
- Cough
- Fatigue
- Shortness of breath
- Chest pain
- Weight loss
- Loss of appetite

Consider an urgent chest X-ray (to be performed within two weeks) to assess for lung cancer in people aged 40 and over with any of the following:
- Persistent or recurrent chest infection
- Finger clubbing
- Supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- Chest signs consistent with lung cancer
- Thrombocytosis

Safety netting recommendations:
- Ensure results of investigations are reviewed and acted upon
- Be aware of the possibility of false-negative chest X-rays
- Consider review of people at increased risk of cancer over an agreed timeframe or a patient-initiated review if there are persistent, worsening or new symptoms

recommendations about using multivariable models. Table 1, above, shows the recommendations for lung cancer; it is important to remember that NICE also includes safety netting recommendations about false-negative chest X-rays and ongoing or new symptoms.[8]

LUNG CANCER SCREENING

The two largest randomised controlled trials of low radiation dose computed tomography (LDCT) screening have shown a reduction in lung cancer mortality.

The National Lung Screening Trial (NLST) which randomised 53,454 people in the United States to three annual screens with LDCT or chest radiography[9] showed a 20% reduction in lung cancer mortality in the LDCT arm after six years.

The NEderlands-Leuvens Longkanker Screenings ONderzoek (NELSON) trial, is the largest European randomised trial with 15,422 subjects. Although publication of the full results is still awaited, interim results showed a 26% reduction in lung cancer specific mortality in men and 39-61% in women. Furthermore, two smaller European trials also showed a reduction in lung cancer mortality with extended follow-up.

The Multicentric Italian Lung Detection (MILD) trial demonstrated a 39% reduction in lung cancer mortality at ten years and the German Lung Cancer Screening Intervention (LUSI) showed a 26% reduction in mortality at 8.8 years' follow-up.[10,11]

Screening for lung cancer has been endorsed in the United States since 2015 but most European countries were, until recently, awaiting the publication of the NELSON results before making final recommendations.

NHS England is funding ten pilot projects on lung health checks that include a low-dose CT for eligible people.[12] The intention is for this to be rolled out nationally. In addition, there are almost as many people who will undergo LDCT as part of further pilots or research trials. In this respect, England is some way ahead of other parts of Europe.

FASTER DIAGNOSIS AND OPTIMAL PATHWAYS

There is mounting evidence that time to diagnosis is important in lung cancer. This may be because performance status (a measure of fitness) deteriorates rapidly in some patients and this is one of the strongest predictors of survival, as strong as cancer stage.

Timed lung cancer pathways have been adopted in England and the National Optimal Lung Cancer Pathway (NOLCP) is a major national priority. This shows how the time to treatment can be reduced to 49 days, as there is increasing evidence that faster pathways improve outcomes (see figure 1, p23).[13-15] Key points include urgent reporting of chest X-rays suspicious for lung cancer, with CT completed the same day or within 72 hours, and subsequent review in the fast track lung cancer clinic. CT should be carried out with administration of contrast and include the lower neck, chest, liver and adrenals. The NOLCP effectively provides GPs with access to CT through locally agreed protocols.

This procedure should also be performed in patients in whom the chest radiograph is normal but there is a high suspicion of underlying malignancy. Studies have indicated that around 20-25% of patients with confirmed lung cancer may have a chest X-ray reported as normal.[16-18] This figure may be higher for early stage lung cancers.

Positron emission tomography-computed tomography (PET-CT) is an important staging investigation and is recommended in those patients who are deemed suitable for treatment with curative intent. It is useful in assessing mediastinal nodal involvement and has a key role in detecting metastatic disease, with a sensitivity of 93% and specificity of 96%. Small studies have suggested that PET-CT detects unsuspected metastases in 6-36% of cases.[19-21]

The brain is a common site for metastases in lung cancer and the incidence of brain metastases is reported to be around 10-20% at the time of diagnosis.[22-24] NICE updated the 2011 guidance in 2019 (NG122) to include recommendations to image the brain in all patients with stage II or IIIA non-small cell lung cancer (NSCLC) who are suitable for treatment with curative intent and in all those who present with clinical features suggestive of intracranial pathology.[25]

In most patients potentially suitable for treatment, a tissue diagnosis is required to guide further management. Minimally invasive techniques (for example, endoscopic procedures) are generally preferred first, particularly in those with advanced disease.

Consideration should be given to the yield of the procedure so that the sample is of sufficient size and quality to allow immunohistochemical and molecular characterisation, while also minimising risk and accommodating patient preference.

The key objectives in the investigation of patients with lung cancer are to establish an accurate diagnosis, determine the cancer stage, assess the individual's fitness and determine patient preference. These factors will determine which treatment is likely to be beneficial to the patient.

The NHS England Lung Cancer Clinical Expert Group has produced diagnostic standards of care bundles to guide evidence-based management and reduce variation in practice.[26] An example is shown in figure 2, p24.

MANAGEMENT

Non-small cell lung cancer

Surgery: Surgery remains the preferred treatment in early stage NSCLC, with the greatest chance of cure. Resection rates in the UK have been increasing, from around 9% in 2006 to 18% in 2018. Increasing numbers of patients are suitable for surgical resection as minimally invasive surgical techniques such as video-assisted and robotic techniques are becoming more widely available. Postoperative systemic treatment is indicated for later stage disease (any tumour ≥ 4 cm, or any nodal disease).

Radiotherapy: The updated NICE guidance recommends that patients with early stage NSCLC (stage I-IIA) who choose not to have surgery, or are not good surgical candidates, should be offered radical radiotherapy in the form of stereotactic ablative radiotherapy (SABR). SABR uses multiple beams of radiotherapy delivered from different angles, allowing higher doses to be focused on the tumour, while the surrounding healthy tissues receive a lower dose.

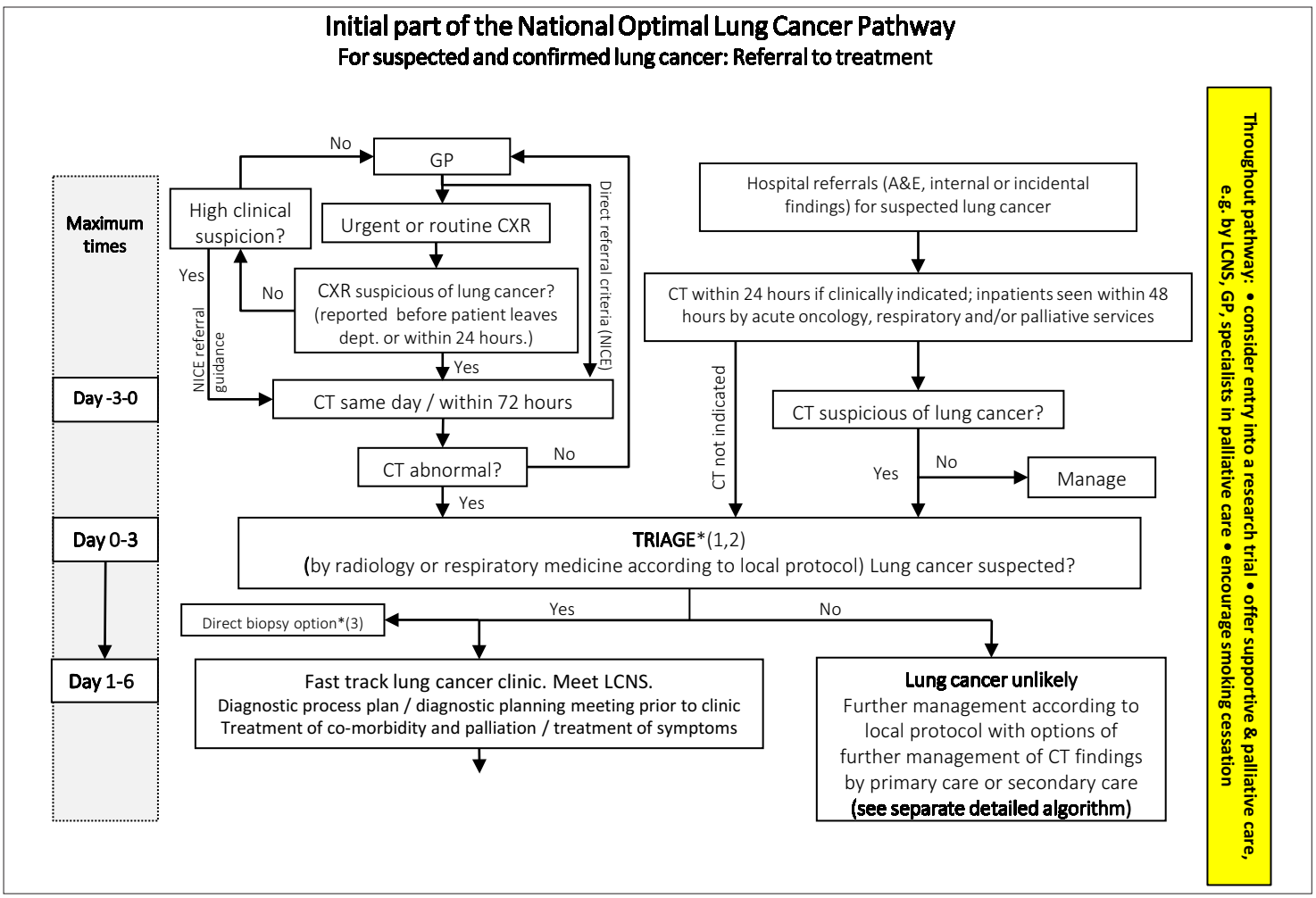
Small studies suggest SABR may be comparable with surgery in selected patients.[27] If SABR is contraindicated, either conventional or hyperfractionated radiotherapy should be offered, but outcomes are better following surgery or SABR.

Continuous hyperfractionated accelerated radiation therapy (CHART) is offered, where available, as it has been shown to confer a survival benefit compared with conventional radical radiotherapy.[28,29] It offers a similar radiation dose but is given over 12 consecutive days rather than the six weeks a conventional regimen takes to complete.

Palliative radiotherapy has a place in the treatment of thoracic symptoms (for example haemoptysis) and bone metastases.

Systemic treatment: As with many other cancers, this is a rapidly changing area as more drugs are licensed either as monotherapy or in various combinations. NICE has adopted a regular review process of its systemic therapy algorithm to reflect this. »

FIGURE 1
Initial part of the National Optimal Lung Cancer Pathway. For suspected and confirmed lung cancer: referral to treatment



Where possible, conventional cytotoxic chemotherapy is replaced by biologic treatment with specific mutations/rearrangements targeted, currently three in the UK (EGFR, EML4-ALK, ROS-1), for adenocarcinoma. Immune checkpoint inhibitors are also recommended either alone or in combination with chemotherapy depending on the presence of the immune marker programmed death ligand 1 (PD-L1) on tumour cells for both adenocarcinoma without targetable mutation and squamous cell carcinoma.

Combination therapy: The 2019 update of the NICE lung cancer guideline recommends considering the use of combination chemoradiotherapy followed by surgery for patients with operable stage IIIA disease.

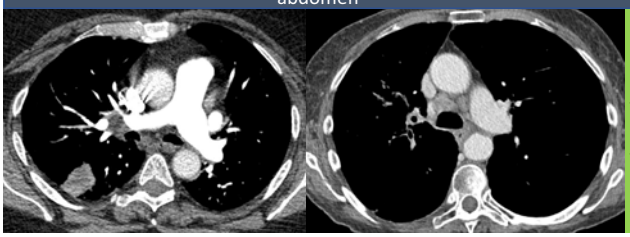
This is a new recommendation and not one that is currently offered widely or outside specialist centres and is only suitable for a small sub-set of patients.

FIGURE 2
NHS England: Lung Cancer Diagnostic Standard of Care Bundle 2 (DSOC2)

DSOC 2: Lesion with mediastinal / hilar lymphadenopathy without distant metastases on staging CT

NHS England

Assess contrast-enhanced CT of lower neck, thorax and upper abdomen



Broadly assess for fitness for treatment

Proceed with this standard of care where patients are thought to be fit enough for, and willing to undergo, investigations and treatment. Patients who are unfit for, or unwilling to undergo investigations and treatment, should be discussed at the MDT meeting to explore further options including supportive care.

Notes and guidance

Staging EBUS ± EUS should be performed where there are enlarged nodes, including isolated N1 hilar nodes and where there is FDG avidity in normal sized nodes. PET-CT has a significant false negative rate, so sampling of normal sized, PET negative nodes is recommended when nodal appearances are not typically benign on CT or endosonography.

Where staging EBUS ± EUS is performed there should be a systematic examination of mediastinal and hilar lymph nodes beginning with N3 stations, followed by N2 and finally N1. Any accessible lymph node based on CT (≥10mm), PET-CT (FDG avidity above the mediastinal blood pool) or sonographic assessment, is sampled.

A specialist supportive/palliative care review should be routinely offered to all patients for whom the MDT treatment decision is 'best supportive care' and/or uncontrolled symptoms.

Commence prehabilitation / optimisation at first assessment – Ensure the pillars of prehabilitation are covered:
Offer smoking cessation | **Encourage physical activity** | **Prevent and manage malnutrition**

Refer to Lung Cancer Nurse Specialist | **Consider participation in research**

Diagnostic and staging tests

Request Diagnostic and Staging Bundle:

- ! **PET-CT** (complete within 5 days); **pre-book** staging EBUS ± EUS . Review PET-CT **avoiding full MDT discussion** and proceed as below. Where PET-CT upstages the tumour to M1 see DSOC 4
- ! Proceed with staging **EBUS ± EUS** where no SCN seen.
- ! **US guided nodal biopsy** where CT or PET-CT show enlarged or FDG avid supraclavicular nodes (SCN)
- ! **Biopsy of the primary lesion** where nodes negative on EBUS ± EUS
- ! Reflex predictive biomarker testing is preferred
- ! Contrast-enhanced CT brain for suspected stage II (or if known small cell).
- ! Contrast-enhanced MR brain for suspected stage III

Physiology tests (request simultaneously)

Request Fitness assessment:

- ! Spirometry and transfer factor
- ! Consider one or more of: Shuttle walk*, or CPEX*
- ! ECG
- ! Consider perfusion scan if pneumonectomy

Request echocardiogram if*:

- ! Heart murmur
- ! Abnormal ECG
- ! Known ischaemic heart disease / valvular disease
- ! Possibility of pneumonectomy

Assessment by a cardiologist may be required

*May be omitted if surgery not an option

Dataset for MDT discussion:
PET-CT and CT or MR brain results
Bronchoscopy / EBUS ± EUS / other pathology
Performance status, FEV_1 and DLCO
Additional fitness tests as required

Lung Cancer Diagnostic Standard of Care Bundle 2 (DSOC 2)

Small cell lung cancer

Small cell lung cancer (SCLC), because of its aggressive nature, tends not to be curable at presentation. Patients with very early disease (tumours < 3 cm and no nodal spread) may be considered for surgery, with adjuvant chemotherapy.

Patients who have a good performance status and disease that could be encompassed within a radiotherapy field may be offered chemoradiotherapy (either concurrent or sequential). This can result in long survival and even cure in some patients.

However, the majority of patients present with extensive disease, where the priority is to commence chemotherapy as soon as possible. The recommendation is that all patients with SCLC should be seen by an oncologist within one week of the decision to commence treatment.

Patients with SCLC and good performance status (0-2) who respond to initial treatment are offered prophylactic cranial irradiation. The addition of immunotherapy has been shown to improve outcomes.

ENHANCED SUPPORTIVE CARE

All patients with advanced stage lung cancer should be offered enhanced supportive care. This addresses the prevention and management of adverse events from cancer and its treatment.

Early involvement of the palliative care team not only improves quality of life, but has been shown to have a survival benefit of up to two months.[30]

Current smokers should be offered smoking cessation support. It is of particular significance in those undergoing treatment with curative intent, as it reduces the risk of post-operative and systemic treatment-related complications and in addition reduces the chance of cancer recurrence.[31,32]

CONCLUSIONS

In order to improve outcomes for patients with lung cancer, the focus must continue to be on early detection and faster diagnosis.

For GPs this means identifying those patients at high risk. In secondary care, expediting investigations to allow

key points

SELECTED BY

Selected by Dr Phillip Bland
Former GP, Dalton-in Furness, UK

Although the five-year survival in the UK has improved from 10% to 14.5%, the UK still lags behind other comparable countries, where five-year survival figures are around 20% or more. Presentation via an emergency route remains a problem: 33% of patients were diagnosed following an emergency presentation in 2016. These patients have much poorer outcomes than those who are diagnosed by other routes with only 16% surviving a year and more than a third dying within a month.

NICE recommends urgent referral via a suspected cancer referral pathway to the two week wait service if: chest X-ray findings suggest lung cancer or if patients aged 40 and over have unexplained haemoptysis. However, studies have indicated that around 20-25% of patients with confirmed lung cancer may have a chest X-ray reported as normal and this figure may be higher for early stage lung cancers. Therefore, the National Optimal Lung Cancer Pathway (NOLCP) recommends that where there is a high suspicion of underlying malignancy (but the chest X-ray is normal), GPs should refer patients directly for a CT scan.

There is mounting evidence that time to diagnosis is important in lung cancer. This may be because performance status (a measure of fitness) deteriorates rapidly in some patients and this is one of the strongest predictors of survival. The NOLCP recommends urgent reporting of chest X-rays suspicious for lung cancer, with CT scanning completed the same day or within 72 hours, followed by review in the fast track lung cancer clinic. CT should be carried out with administration of contrast and include the lower neck, chest, liver and adrenals.

Positron emission tomography-computed tomography is an important staging investigation and is recommended in those patients who are deemed suitable for treatment with curative intent. It is useful in assessing mediastinal nodal involvement and has a key role in detecting metastatic disease. NICE recommends brain imaging in all patients with stage II or IIIA non-small-cell lung cancer (NSCLC) who are suitable for treatment with curative intent and in all those who present with clinical features suggestive of intracranial pathology. In most patients who are potentially suitable for treatment, a tissue diagnosis is required to guide further management.

Surgery remains the preferred treatment in early stage NSCLC and gives the greatest chance of cure. Patients with early stage NSCLC who choose not to have surgery, or are not good surgical candidates, should be offered radical radiotherapy in the form of stereotactic ablative radiotherapy. Small cell lung cancer SCLC is usually incurable at presentation although patients with very early disease may be considered for surgery with adjuvant chemotherapy. For the majority of patients with extensive disease the priority is to commence chemotherapy as soon as possible.

prompt treatment by using the NOLCP will help achieve the new faster diagnosis standard, to be implemented in April 2020. This states that most people with suspected cancer should receive a definitive diagnosis or have cancer ruled out within 28 days of referral from a GP or screening.

Timely presentation, prompt recognition of the risk of lung cancer and referral will enhance the impact of faster diagnosis on outcomes.

Competing interests

Professor David Baldwin has received an honorarium from AstraZeneca for help with an international CT screening standard. The other authors have no competing interests

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Useful information

Roy Castle Foundation
Information for healthcare professionals
www.roycastle.org/for-healthcare-professionals

Cancer Research UK
Lung cancer pathway
www.cancerresearchuk.org/health-professional/diagnosis/accelerate-coordinate-evaluate-ace-programme/ace-findings-and-resources#info-gallery-id-4_slide-0

NHS England
Targeted lung health checks
www.england.nhs.uk/wp-content/uploads/2019/02/targeted-lung-health-checks-standard-protocol-v1.pdf

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