REFERRAL AND CLINICAL GUIDELINES FOR LUNG CANCER

CRG Chair & Vice Chair	**Dr Shahedal Bari & Mr Manoj Purohit**
Issued:	**August 2009**
Reviewed:	**September 2011**
	May 2014
	June 2014(Chemotherapy/Radiotherapy)
	July 2017
	July 2019
	July 2021- still ongoing
	Oct 2024
Review Date	**July 2026(or earlier if new guidance is available) completed)**

Contributors April 2021- 24	**Dr John Howells (LTHTR)**	**Radiology**
	Dr Lipsita Patnaik (LTHTR)	**Pathology**
	Dr S Bari. Prof M. Munawar, Dr S. Mehdi	**Chest Physicians**
	Mr Manoj Purohit	**Surgical**
	Prof Ruth Board, Dr Amy Ford, Dr S.Lau, Dr R Portner. Dr A Mirza	**Oncology**

Index

Appendices

REFERRAL PROCESS

- Appointment Pathway
- Suspicious X-Ray Policy
- Clinical Assessment
- Fitness for Investigation/Treatment
- Bronchoscopy/PCNB/Mediastinoscopy/Interventional bronchoscopy Procedures
- Radiology Protocols
- Follow-Up Arrangements
- Histology/Cytology Protocols
- MDTM Arrangements
- Surgery
- Radiotherapy
- Chemotherapy

General Practitioner Information Arrangement

REFERRAL PROCESS

1. Central information point providing telephone, electronic and e-mail facilities

2. General Practice - Generic or Fast Track Lung Cancer Forms to be used

3. Hospital**:** In-house referrals from the Wards, Out-Patients or Casualty to be notified through the Central Referral System

APPOINTMENT PATHWAY - THE CASES OF SUSPECTED LUNG CANCER

1. Open Lung Cancer Referral Proforma

Mail to central referral point ⟶ Confirmation of receipt

Patient confirmation of appointment by letter or by telephone (Could be for CT scan first/through open access CT Scan) if clinic appointment within 48 Hours

⟶ GP informed by letter

Designated Lung Cancer Clinic with attending Lung Cancer Nurse

DNA's - Further appointment arranged for within Seven Days ⟶ GP informed within 24 hours

SUSPICIOUS X-RAY POLICY

The following procedure is to be undertaken when a report of a **routine** chest x-ray raises the possibility of lung cancer.

Radiology Department

1. Inform the patient's General Practitioner by fax/email or phone by the next working day of the unsuspected finding
2. Post the full confirmatory written report to the General Practitioner
3. Copy the report to the Chest Physician and the Chest Clinic and cancer data team if appropriate or organise CT scan as per local protocol.
4. In some cases, it will be appropriate to arrange urgent CT scan, before, or on the day of, chest clinic appointment

General Practitioner

The General Practitioner will initiate the referral under the **14 Day Rule.**

Chest Clinic

The Chest Clinic or cancer data team will number, and check referrals received against the copy x-ray reports.

FIRST CLINIC VISIT

1. Clinical Assessment

a) History including smoking habits, employment history (for suspected mesothelioma)

b) Examination - Height/Weight, clinical examination as appropriate

c) Performance Status

2. Investigations

a) Spirometry

b) Chest X-Ray/CT scan (may have had already)

c) Bloods - FBC/Serum Biochemistry/LFT's/Bone Profile/LDH

d) CT thorax/upper abdo to be arranged urgently or on same day (if not already done)

e) Full Lung Function Test, /PET/ Bronchoscopy/EBUS/CT guided biopsy to be arranged if appropriate

f) Send blood to NW GLH for ctDNA, if patient eligible ***(see appendix 15 for details)***

3. Patient Information

Provision of literature and contact arrangements by Lung Cancer Nurse

FITNESS FOR INVESTIGATION/TREATMENT

All patients should be considered for investigations to obtain histological or cytological confirmation of their disease.

Patients who after the initial assessment are deemed too seriously ill for further investigation should be discussed at the MDTM for registration and consideration for supportive care without a confirmatory histological diagnosis.

Patients who decline investigations or treatment should similarly be reviewed and a management strategy documented.

BRONCHOSCOPY/EBUS/Mini-probe/Sat Nav Bronch

1. Consent

Informed consent to be obtained by the Operator

2. Patient Information

Arrangements for the procedure to be explained by the Chest Clinic staff and with accompanying literature which should include a contact telephone number for any subsequent enquiries.

3. Follow-up

Follow-up arrangements to be initiated at the first visit for next results clinic after investigation for MDTM review.

CT Guided Lung Biopsy

1. **Suitability.** Most lung and mediastinal lesions (mediastinal lesions consider EBUS as appropriate) can be considered for CT Guided Lung biopsy However peripheral lesions >10mm are most suitable (to be discussed with the radiologist performing the test). As per local MDT protocols, PET scan can be done before biopsy.
2. **Fitness.** Resting hypoxia and impaired lung function (FEV1 < 1 litre, or <40%) are relative contraindications. Cognitive impairment which renders the patient uncooperative is a near absolute contraindication.
3. **Consent**. Outline consent should be obtained in the OPC, and written/electronic consent obtained by the operator on or before the day of procedure. Patient information literature should be given at the first opportunity.

REFERRAL GUIDELINES FOR IMAGING IN LUNG CANCER

CT Scan Referral

1. Requests received on a standard Staging CT request or by electronic referral.

2. Consultant Radiologist vets request to determine the appropriate protocol and level of urgency

3. Scans are booked on the next available urgent slot. Where possible and appropriate, scans will be performed on or before the day of clinic attendance. All scans are reported by a Consultant Radiologist or designated Registrar.

4. Where confirmed histology is available, a report should contain the following features:

    - Tumour site and maximum dimension
    - Multiplicity or satellite lesions
    - Evidence of pleural or fissural involvement
    - Evidence of pericardial involvement
    - Presence of associated pneumonitis or collapse
    - Presence of ipsilateral or contralateral lung nodules (T3/N3/M1a)
    - Evidence of mediastinal invasion, and comment on whether only mediastinal fat invaded
    - Proximity to the main carina or carina of the main bronchi
    - Location and short axis diameter of nodes
    - Evidence of distant metastasis

5. From this, a TNM stage will be offered, or alternative TNM stages dependent upon further investigation and a radiological tumour stage.

6. If there is a doubt as to histology no definite TNM stage is offered. A provisional TNM stage contingent upon histology may be offered if possible. In this instance, protocol indicating tumour stage should be confirmed at the MDT once histology is confirmed.

7. If reports identify a previously unsuspected lung cancer, a report should be faxed to the GP within 24 hours of the report being typed and a copy of the report sent to the MDT secretary.

8. Patient for curative intent/ radical treatment should have a recent scan (within 4 weeks) available for planning.

HISTOLOGICAL PATHWAYS FOR LUNG CANCER

The sample (cytology, biopsy or resected tumour) is reported as promptly as possible i.e., ideally a provisional working diagnosis provided within 48 hours for biopsies and cytology and 10 working days for resected specimens. It is recognised that if extended immunohistochemistry or external opinion is required it will take longer to report the resection specimens.

A report is then sent to the requesting clinician so that details of the specimen are available at the weekly MDT. In addition, a copy report of the resected specimen should be sent to the respective lung cancer nurse to facilitate further discussion at the MDT.

The vast majority of malignant tumours will be either small cell, squamous or adenocarcinoma and it is recognised that H and E staining alone will be sufficient to categorise some tumours appropriately. In difficult cases immunohistochemical and mucin staining may be required including a neuroendocrine panel (chromogranin, synaptophysin and CD56) as well as CK7, TTF1 and CK5/6. The reporting of resected tumours will be based on the Pathology Lung Cancer National Minimal Data Set (enclosed in appendix 6).
All non-small cell carcinoma cases should be assessed for PDL1 (at Blackpool Victoria Hospital) with DNA/RNA panels performed at the Manchester GLH if tumour nuclei content allows. In addition, ALK and ROS1 immunohistochemistry can be used for biopsy specimens to provide a faster result. Salvage/urgent genomic testing is performed at Blackpool Victoria Hospital. The decision for salvage testing is based upon low tumour volume or clinician request. Please see **Appendix 14** for the genomic testing flow chart. CtDNA should be used for appropriate patients based upon NHS Genomics advice.

POST INVESTIGATION FOLLOW-UP

1. <u>Bronchoscopy</u>

Follow-up appointment to be made at the first visit for the next results clinic, or appointment to be made subsequently when the MDTM/Histology/CT results are available.

2. <u>Staging CT scan</u>

Copies to Clinicians and Lung Cancer Nurses for urgent attention.

3. <u>PCNB/Pleural Biopsy /Bronchoscopy/EBUS/Mediastinoscopy/VAT Biopsy</u>

Appointment to be given to the patient after the procedure, post MDT for the next clinic or the Lung Cancer Nurse to be contacted to arrange further supervision.

4. <u>Histology/Cytology Report</u>

Copies to Clinicians, MDTs and Lung Cancer Nurses.

GENERAL PRACTITIONER COMMUNICATION

The General Practitioner must be informed by the end of the following working day of all patients who have been informed of their diagnosis of lung cancer.

1. Out-Patients

The General Practitioner/Surgery would be notified by telephone on the next working day that the patient had been informed of the diagnosis. The Clinician should ensure that a full report is available to the General Practitioner by the end of the following working day.

2. In-Patients

The medical team/Consultant office is responsible for telephone/E- confirmation of the patient information.

The record of date/time/author /telephone/email id information should be recorded in the patient's notes.

Multi-Disciplinary Team (MDT)

Once investigations have been completed all patients should be discussed at the weekly MDT meeting where individual treatment options will be determined. The completed MDT proforma would be an accepted referral letter for surgery/oncology/palliative care. All patients deemed suitable for radical treatment (surgery, radiotherapy or chemoradiation) should have a PET scan via the electronic referral form.

PET/CT SCANNING - REFERRAL STRATEGY

Clinical Indications in respiratory cancers

Following detailed discussion and taking into account current evidence base the following clinical indications were agreed.

1. Evaluation of solitary pulmonary nodules size >9mm
2. Staging of non-small cell lung cancer
3. Patients for radical intent treatment for staging or staging diagnostics

Patients meeting the above criteria are discussed in the local MDT. Referral should be made on the electronic request form, which must be fully completed, or it will be returned. This is in order to comply with IRMER regulations and the requesting process. Particular care should be taken in giving a full relevant clinical history and noting whether a patient is diabetic.

Brain scanning before radical treatment including surgery / radical radiotherapy

1.Do not offer dedicated brain imaging to people with clinical stage I NSCLC who have no neurological symptoms and are having treatment with curative intent.
2. Offer contrast-enhanced brain CT to people with clinical stage II NSCLC who are having treatment with curative intent. If CT shows suspected brain metastases, offer contrast-enhanced brain MRI.
3. Offer contrast-enhanced brain MRI for people with stage III NSCLC who are having treatment with curative intent.

Smoking Cessation:

Smoking cessation carries a number of benefits including improvements in response rate to treatment, reduced rates of toxicity and improved survival. Overview | Tobacco: preventing uptake, promoting quitting and treating dependence | Guidance | NICE

- Patients should be educated in the harms of smoking and encouraged to stop smoking.
- Patient (and family) are referred to smoking cessation services.
- Nicotine replacement therapy, varenicline and or bupropion are prescribed appropriately.

GUIDELINES ON INDICATIONS FOR SURGERY FOR LUNG CANCER

Surgery for stage I-IIIA should be considered if patient has the necessary respiratory reserve and is deemed medically fit for major surgery. There is a customised surgical referral form (Appendix 7) available (with bundle of information) for referral to cardiac.referral@bfwhospitals.nhs.uk

Based on the BTS Guidelines and NICE guidelines- See Links

https://thorax.bmj.com/content/thoraxjnl/56/2/89.full.pdf

Lung cancer: diagnosis and management (nice.org.uk)

FITNESS

a) Age:

i) Perioperative morbidity increases with advancing age. Elderly patients undergoing lung resection are more likely to require intensive perioperative support. Preoperatively, a careful assessment of co-morbidity needs to be made.

ii) Age over 80 alone is not a contraindication to lobectomy or wedge resection.

ii) Pneumonectomy is associated with a higher mortality risk in the elderly. Age should be a factor in deciding suitability for pneumonectomy.

b) Cardiovascular Fitness:

Previous MI – interval of 6 weeks + cardiological opinion
Previous CABG – no increased risk if asymptomatic
Previous CVA – Doppler for carotid artery stenosis
Murmur – ECHO
Angina or SOB due to cardiac disease – exercise test

c) Performance status:

WHO 0,1 or 2

The Medical and fitness optimisation checklist should be referred before referring for surgery (Appendix 9)

d) Further Assessment and Planning of Patients for Surgery (Based on NICE Guidance 2011,2019)

- Perform spirometry and Diffusion studies (TLCO,KCO) in all patients being considered for treatment with curative/radical intent.
- Offer patients surgery if they have an FEV1, TLCO within normal limits and good exercise tolerance.
- When considering surgery perform a segment count to predict postoperative lung function.

- Offer patients with predicted postoperative FEV_1 or T_LCO below the recommended limit of 30% the option of undergoing surgery if they accept the risks of dyspnoea and associated complications.
- Consider using shuttle walk testing (using a distance walked of more than 400 m as a cut-off for good function)or 6 Min walk test to assess fitness of patients with moderate to high risk of postoperative dyspnoea.
- Consider cardiopulmonary exercise testing(CPET) to measure VO_2 max and assess lung function in patients with moderate to high risk of postoperative dyspnoea, using more than 15 ml/kg/minute as a cut-off for good function.
- Offer patients with NSCLC who are medically fit and suitable for treatment with curative intent, lobectomy (either open or thoracoscopic) as the treatment of first choice. For patients with borderline fitness and smaller tumours (T1a–b, N0, M0), consider lung parenchymal-sparing operations (segmentectomy or wedge resection) if a complete resection can be achieved.
- Offer more extensive surgery (bronchoangioplastic surgery, bilobectomy, pneumonectomy) only when needed to obtain clear margins.
- Perform hilar and mediastinal lymph node sampling or en bloc resection for all patients undergoing surgery with curative intent.

e) <u>Special Situations:</u>

1. Advanced local disease: consider for surgery only if N0/N1

i) **Chest wall invasion:** Potentially operable if T3N0. Pain is a good predictor. CT 90% accurate. MRI may be indicated. High resolution Ultrasound is also a useful modality.

ii) **Adherence to vertebral column:** surgery may be contemplated in individual cases. MRI may be indicated.

iii) **Superior sulcus tumours:** Horner's syndrome, invasion of brachial plexus and subclavian vessels or vertebrae = inoperable. In this situation induction treatment with chemotherapy/immunotherapy and radiotherapy might be attempted to downsize the tumour with subsequent surgery as an option for very selected patients

2. N2 diseases: Surgery should be considered in all single station N2 patient, the selection should depend on the potential of curability and overall fitness of patient and consideration of immunotherapy.

3. Small cell lung cancer: for stage I only (T1N0, T2N0)

Following resection patients should be discussed at the MDT for consideration of adjuvant treatment (see under radiotherapy/chemotherapy section).

4. Reinvestigation and selection of patients for surgery after Neo adjuvant chemotherapy

A complete re-staging needs to be done as per protocol after Neo adjuvant chemotherapy and re-discuss in MDT. The modality for re-staging should be

individualised and plan agreed on before the start of Neo adjuvant chemotherapy to prevent delay.

5. **Oligometastasis**
   Fit patients with single curable metastasis/upto three and potentially curable local diseases should be considered for radical curative surgery.

L&SC Lung Network Second Opinion Guidance

Cardiothoracic Surgery

1) Internal (High risk Thoracic Surgery MDT at Blackpool Victoria Hospital)

It is felt that referral to Thoracic surgeons outside the network will rarely be necessary, as a full range of techniques and procedures are now available from the surgeons based at Blackpool Victoria Hospital. However, it is recognised that in difficult, complex or borderline fitness cases, the opinion of more than one surgeon may be valuable. Should a referring MDT feel that a particular patient requires discussion with a second surgeon, a referral should be made in writing on the High-risk thoracic surgery MDT form (Appendix 8) to the thoracic surgery nurse specialist at: cardiac.referral@bfwhospitals.nhs.uk

2) External

Referrals for Cardiothoracic surgical opinions outside the network should, it is envisaged, be only occasional, however should a referring MDT deem this necessary, then a referral should be made to the clinician of your choice. The external referral should be done only after the internal second opinion route has been explored. The core surgical member of the MDT should be aware about such referral, - for reference purposes this should be copied to the chair of the Lung NSSG/CRG together with a note of the outcome, if any. It is emphasised that the referring MDT retains clinical responsibility for the patient at all times.

INTERVENTIONAL BRONCHOSCOPY/THORACOSCOPY SERVICES

Among the many areas of respiratory medicine which have been revolutionised by technological advances, bronchoscopy is one of the most obvious examples. Parallel to the development of ever finer flexible bronchoscopes and working tools, there has been considerable expansion in the diagnostic and therapeutic techniques that can be practised via the bronchoscope, particularly in lung cancer. Diagnostic flexible EBUS bronchoscopy available in all centres of the network.

Therapeutic Flexible (Service available at Preston) and
Rigid Bronchoscopy (Service available at Thoracic surgery, Blackpool)

Tracheo-bronchial obstruction due to malignant processes can lead to recurrent pneumonia, respiratory insufficiency and death. Curative resection is not possible in the majority of cases, and treatment instead is focussed upon palliation. Techniques available for treatment of tracheobronchial obstruction include electrocautery, argon plasma coagulation, airway stents, laser therapy, cryotherapy, brachytherapy, balloon dilatation and photodynamic therapy. At Preston, we are able to offer majority of these techniques.

Endobronchial Electrocautery (Diathermy), Cryotherapy and Argon Plasma Coagulation (Service available at Preston)

Endobronchial Nd:Yag Laser debulking (Service available at Thoracic surgery, Blackpool)

Indications: These techniques are particularly useful when there is clear evidence of endobronchial disease, and the patient presents with one of the following:

1. Marked volume loss such as lobar or extensive lung collapse.
2. Stridor.
3. Worsening dyspnoea.
4. Post-obstructive pneumonia.
5. Haemoptysis caused by an accessible, visible lesion.

The following points are worth noting with regard to diathermy and argon plasma coagulation.

1. The more central the obstruction in the bronchus, the greater the likelihood of palliation. For more distal obstruction, benefit achieved is small. However, treatment of tracheal lesions carries a slightly greater risk.
2. These techniques are best considered after the more established treatment options have been looked at, such as surgery, radiotherapy and chemotherapy.
3. Diathermy is not indicated in the presence of massive haemoptysis, as adequate visualisation is essential to this technique, and in that situation surgical help with rigid bronchoscopy or interventional vascular radiology input would be needed.

Tracheobronchial Stenting (Service available at Preston and Thoracic surgery Blackpool)

The ultraflex (Nitinol, Alveolar) stent can be placed to relieve acute or sub-acute obstruction of the central airways, in patients who present with stridor, marked volume loss, increasing dyspnoea and post-obstructive pneumonia. This technique is useful essentially where the lesion is 'extrinsic' causing obstruction. Also, they are most effective where there is a relatively short segment of stenosis in the mid/lower trachea, right main and intermediate bronchi, and the left main bronchus (in rare situations where there is a combination of localised intrinsic and extrinsic obstruction, diathermy, laser debulking can be followed up with stenting).

Stenting can also be effective in the presence of a localised tracheo-oesophageal fistula, where double stenting may be required, that is tracheal followed by oesophageal stent.

Stent placement through the flexible bronchoscope is not possible when:

(a) There is a high tracheal lesion.
(b) The obstruction extends from the lower trachea into both main bronchi – where rigid bronchoscopy and an inverted Y stent is indicated.
(c) When the mucosa is involved by an extremely vascular, fragile process.

EBUS Transbronchial Needle Aspiration (TBNA) (Service available at Blackburn Blackpool, Lancaster , Preston and Barrow in Furness)

Over the last decade, EBUS TBNA has improved the diagnostic yield and extended the role of flexible bronchoscopy in the evaluation of mediastinal pathology and the diagnosis and staging of lung cancer.

Endobronchial ultrasound-guided transbronchial needle aspiration is a new technique which has largely superseded TBNA in majority of situations. This is a procedure using a dedicated bronchoscope with a convex ultrasound probe at the tip. Real time ultrasound images of mediastinal nodes are obtained, along with Doppler flow to differentiate blood vessels from the lymph nodes. Through a side port, a needle can be advanced into the lymph node and targeted samples can be obtained. With practice, this technique has a greater than 90% positive yield and samples can be aspirated from a variety of lymph nodes including sub-carinal, right paratracheal, left paratracheal, right hilar and left hilar regions. With the advantage of dynamic ultrasound guidance, larger samples are acquired, and the procedure carries a very low risk of bleeding.

Therefore, any patient with unexplained or malignant appearing mediastinal/ hilar adenopathy can be referred for this procedure. In addition, peribronchial lesions can be diagnosed and mediastinal staging can be completed.

Radial EBUS miniprobe guided biopsy-with or without Fluoroscopy and Navigation (Service available at Preston and BVH).

This technique utilises radial EBUS miniprobe guidance to sample parenchymal lung lesions which are not accessible via CT guided biopsy, VATS biopsy or second generation EBUS guided

TBNA, especially if the lesion is more than 2 cm in size and there is a 'CT Bronchus' sign (please discuss with your radiologist. The diagnostic yield ranges between 60% and 80%, and it is important to explain this to the patient prior to referral.

Indications:

1. Peri-bronchial disease-causing extrinsic compression.
2. Sub-mucosal disease.
3. Necrotic, haemorrhagic endobronchial lesions.
4. Mediastinal and/or hilar lymphadenopathy – to help diagnose malignant and benign lesions.

EBUS TBNA is particularly safe and carries a high yield for staging when the abnormality is in the sub-carinal, right para-tracheal or right hilar region.

Semi-Rigid Medical Thoracoscopy (Service available at Preston)

The technique involves a single incision of just over a centimetre in the mid-axillary line under local anaesthesia and standard sedation. It is performed in the Endoscopy Suite and the patient is usually required to stay overnight after the procedure.

Indications

1. Undiagnosed unilateral, exudative pleural effusion – drainage, pleural biopsy and if appropriate TALC pleurodesis can be performed in one sitting
2. Hydropneumothorax or pneumothorax when an underlying parietal pleural pathology is suspected.
3 Early cases of empyema.

All such patients should have normal clotting, liver and renal function, and a contrast enhanced CT scan of the thorax, besides a recent chest x-ray prior to the procedure.

Guidelines for Referrals (based on the Preston services)

1. If the indication for the procedure is obvious, as outlined above, please email a referral and arrange for the images to be uploaded to LTH PACS.
2. It is essential that the patient's clotting profile, renal and hepatic function are satisfactory. If the patient is on warfarin, this will need to be discontinued for about seven days before the procedure. The same applies to Clopidogrel.
3. In cases of therapeutic bronchoscopy, the patient and relatives need to be aware that the treatment is purely for palliation of symptoms/obstruction. Also, the risk of bleeding and other usual complications of bronchoscopy needs to be mentioned. Further details of the possible complications of the specific procedure will be outlined when the patient is seen.
4. The patient will often need to stay overnight after the procedure on the respiratory ward.
5. Patients referred for stenting will occasionally have to stay for a few days in the hospital, as the stents may have to be measured and ordered after the initial assessment, and the patient may require a further bronchoscopy after the stent is deployed.

Referral contact details

BTHT	ELHT	LTHTR	UHMBT
RESPIRATORY Tel: 01253 - 956706/955578 **T/B STENTING** Tel: 01253 951466	**ALL SERVICES** Tel: 01254 734338	**ALL SERVICES** Tel: 01772 522416 01772 522412 01772 522189	**ALL SERVICES** Tel: 01524 511979 01524 512249

Management and Investigation of Unilateral Pleural Effusions

- **Take a full history and perform a clinical examination**
  Clinical assessment can be used to identify transudative effusions which will not require sampling and can therefore be managed medically.

- **Perform pleural aspiration**
  Collect a 50 ml sample of the pleural fluid using a 21G (green) needle under US guidance. Note the colour and odour of the fluid; if it is turbid, collect an additional sample using an ABG syringe and analyse it immediately using the ABG machine.

- **Request appropriate analysis of the pleural fluid**
  Add 10 ml to two universal containers (for cytology and AAFB/gram stain/TB culture), 10 ml to each of anaerobic and aerobic blood culture bottles and the remainder to citrate (yellow, for glucose), gel (brown, for LDH/protein) tubes. If the fluid is frankly blood-stained, add 2 ml to an EDTA (red) tube to measure the haematocrit. Ensure the sample is analysed within 4 hours.

- **Apply Light's Criteria to the results received from the laboratory**
  The fluid is an exudate if $[protein]_p \div [protein]_s > 0.5$ or $[LDH]_p \div [LDH]_s > 0.6$

- **Interpret the results**
  - **pH < 7.2 with evidence of infection or positive gram stain**
    Empyema requiring prompt tube drainage; refer to the Respiratory team
  - **Transudate**
    Drain only if there is respiratory distress; treat the underlying cause.
  - **Exudate**
    Request a contrast-enhanced CT of the thorax optimised for pleural assessment and refer to the Respiratory Team.

RESPIRATORY PHYSICIANS

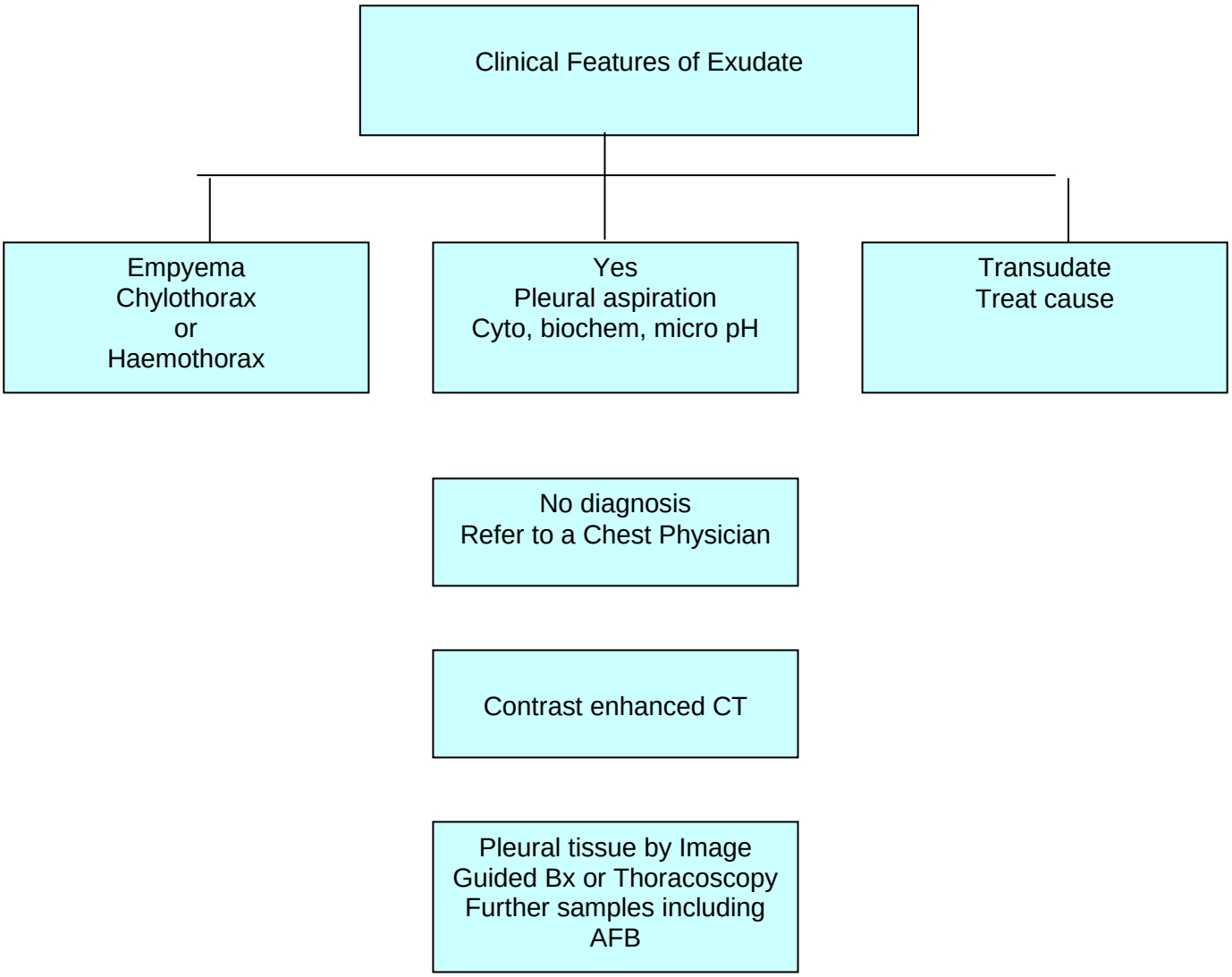
- **Discuss**
  The contrast-enhanced CT scan of the thorax should be reviewed ASAP with a radiologist or discussed in the next Chest Radiology meeting.

- **Direct as necessary for tissue diagnosis or case review**
  Thoracoscopy
  Direct visualisation of any pleural lesions. Sampling, drainage and talc poudrage performed in one sitting. Semi-rigid thoracoscopy (minimally invasive, under LA and sedation (Important note: Please try, if possible, to avoid complete therapeutic drainage of effusion prior to referral, as it can potentially cause adhesions and prevent safe access to the pleural cavity for thoracoscopy)

  Image guided Pleural biopsy- Ultrasound or CT guided- discuss with Consultant Radiologist

  VATS
  Requires GA and single lung ventilation- discuss with Cardio-thoracic Surgeon

Algorithm for investigation of Pleural Effusion



Guidelines for the Referral of Radiotherapy and Chemotherapy in Lung Cancer, Mesothelioma, and Thymoma.

Thymoma

Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (annalsofoncology.org)

WORKUP

Imaging and diagnostic tests

- Thymoma is the first diagnosis to consider when facing a mediastinal mass associated with autoimmune disease.
- The diagnosis of any thymic epithelial tumour relies on making the differential diagnosis with other anterior mediastinal tumours and non-malignant thymic lesions.
- Standard imaging for Thymic tumours is i.v. contrast-enhanced (CT) scan of the thorax
- MRI is recommended to differentiate thymic tumour from hyperplasia whenever CT scan is doubtful, or in case of cystic lesion.
- PET scan is generally not recommended to assess thymic masses.
- Therapeutic intervention is usually not required if the lesion is <30 mm, given a low risk of progression or thymic malignancy.
- Systematic immunological check-up is recommended, including complete blood cells count with reticulocytes and serum protein electrophoresis, as well as anti-acetylcholine receptor and anti-nuclear antibodies tests.

Need for a biopsy

- Pre-treatment biopsy is not required if the diagnosis of thymic epithelial tumour is highly suspected and upfront surgical resection is achievable.
- Biopsy is required in all other clinical situations; approaches may consist of percutaneous core-needle biopsy or incisional surgical biopsy through mediastinotomy or mini-thoracotomy.
- Fine-needle aspiration is not recommended

Diagnosis

- Thymic epithelial tumours are classified according to the WHO histopathological classification.
- Although designed for surgical resection specimen, the WHO classification may be used for small biopsies.
- Immunohistochemistry with anti-CD117/KIT and anti-CD5 antibodies is useful to establish the thymic primary nature of a mediastinal carcinoma.
- Each component of heterogeneous tumours may be quantified by 10% increments.
- Consultation with a second pathologist or referral of the case to a thymic tumour pathology panel is recommended whenever there is any diagnostic difficulty.
- Ontogenetic assessment should be carried out in case of familial thymic epithelial tumour, looking especially at MEN1.

Paraneoplastic syndromes associated with thymic neoplasms

Neurologic and neuromuscular	Myasthenia gravis, polymyositis, sensory neuropathy, stiff person syndrome, neuromyelitis optica, Isaacs syndrome (neuromyotonia), Lambert-Eaton myasthenic syndrome, hemichorea
Hematologic	Pure red cell aplasia, agranulocytosis, hemolytic anemia, pernicious anemia
Dermatologic	Alopecia areata, pemphigus, scleroderma, oral lichen planus, vitiligo
Endocrine	Addison's disease, Cushing syndrome, panhypopituitarism, thyroiditis
Miscellaneous	Acquired hypogammaglobulinemia, myocarditis, nephrotic syndrome, rheumatoid arthritis, sarcoidosis, hepatitis, gastrointestinal pseudoobstruction, ulcerative colitis

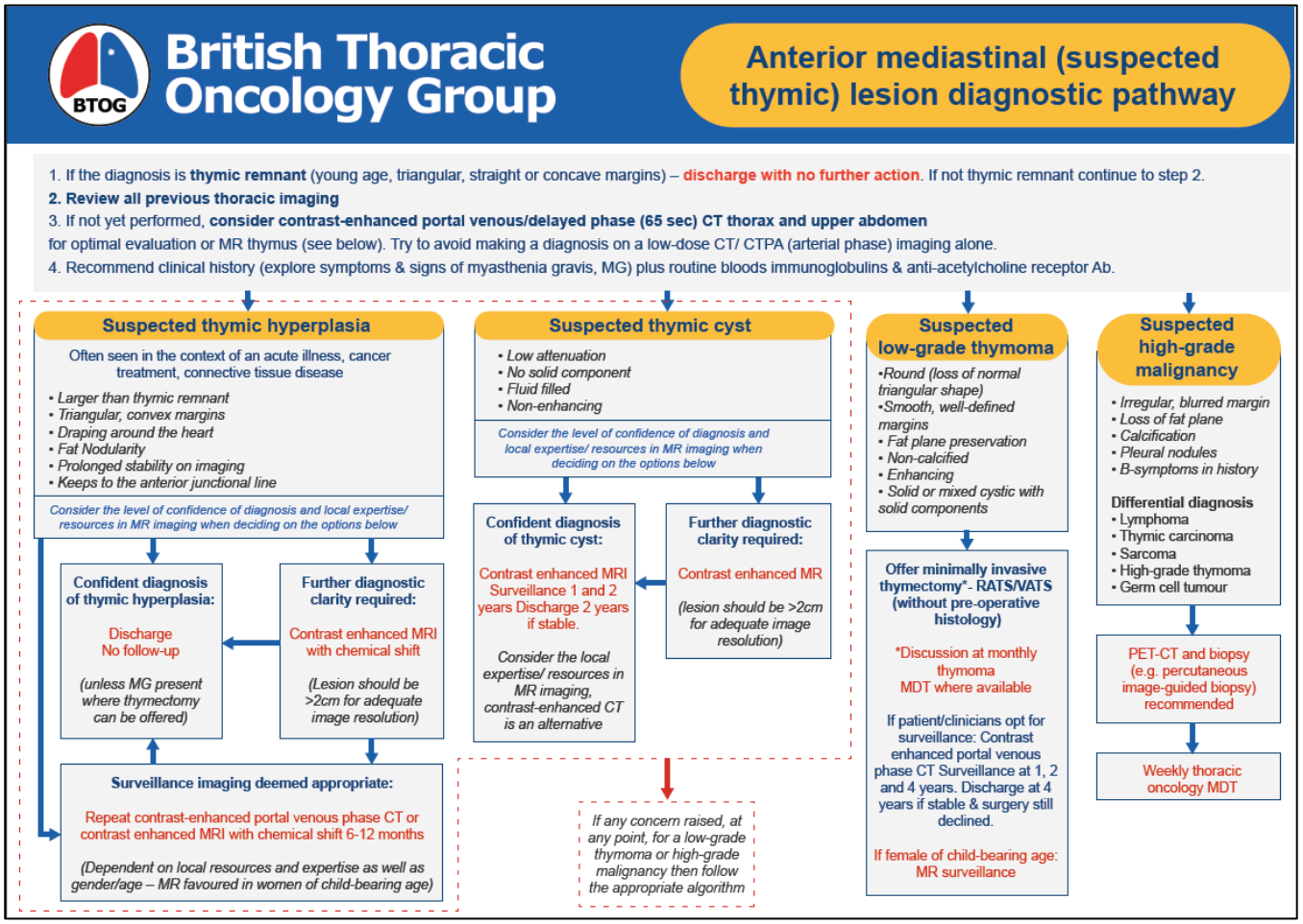
Classification of thymic epithelial tumors

Levine and Rosai*	Müller-Hermelink, et al¶	WHO$^{\Delta}$
Thymoma	Thymoma	Thymoma
Encapsulated	Medullary type	Type A
	Mixed type	Type AB
Malignant type I (invasive)	Predominantly cortical	Type B1
	Cortical type	Type B2
	Well-differentiated carcinoma	Type B3
Malignant type II	Thymic carcinoma	Thymic carcinoma (Type C thymoma)

Clinical staging of thymic epithelial tumors

Masaoka's clinical stage[1]
Stage I: Macroscopically completely encapsulated and microscopically no capsular invasion
Stage II: Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule
Stage III: Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, or lung)
Stage IVa: Pleural or pericardial dissemination
Stage IVb: Lymphogenous or hematogenous metastasis

BTOG Thymoma Pathway:



Tumors of the thymus TNM staging AJCC UICC 8th edition

Primary tumor (T)*¶	
T category	**T description**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
T1a	Tumor with no mediastinal pleura involvement
T1b	Tumor with direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	Tumor with direct invasion into any of the following: Lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with invasion into any of the following: Aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus
* Involvement must be microscopically confirmed in pathological staging, if possible. ¶ T categories are defined by "levels" of invasion; they reflect the highest degree of invasion regardless of how many other (lower-level) structures are invaded. T1, level 1 structures: thymus, anterior mediastinal fat, mediastinal pleura; T2, level 2 structures: pericardium; T3, level 3 structures: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, hilar pulmonary vessels; T4, level 4 structures: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus.	

Regional lymph nodes (N)Δ	
N category	**N description**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes
Δ Involvement must be microscopically confirmed in pathological staging, if possible.	
Distant metastasis (M)	
M category	**M description**
M0	No pleural, pericardial, or distant metastasis
M1	Pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

When T is...	And N is...	And M is...	Then the stage group is...
T1a,b	N0	M0	I
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IVA
Any T	N0, N1	M1a	IVA
Any T	N2	M0, M1a	IVB
Any T	Any N	M1b	IVB
◇ R0: no residual tumor; R-any: any type of resection (no residual tumor, microscopic residual tumor, or macroscopic residual tumor at the primary cancer site or regional nodal sites).			

Meneshian A, Giaccone G, Olivier KR. Clinical presentation and management of thymoma and thymic carcinoma. In: UpToDate, Post TW (James R Jett JR and others), UpToDate, Waltham, MA. (Accessed on November 21, 2021).

Masaoka-Koga staging and treatment recommendations:

Stage I Thymoma 100% 5-year survival	Surgery
IIA, IIB Thymoma 86-95% 5-year survival	Surgery OR Surgery with or without radiation therapy (PORT) in high-risk cases stage IIB (close surgical margins, WHO type B or, large tumour size)
Resectable III Thymoma 56-69% 5-year survival	Surgery + probably PORT
Potentially resectable III Thymoma Up to 50% 5-year survival	Neoadjuvant Chemotherapy followed by surgery (if operable) and radiation therapy OR Chemotherapy followed by radiation therapy (if it remains inoperable) Chemotherapy alone is not considered a curative option.
Resectable IVA Thymoma (limited pleural disease)	Surgery +/- PORT +/- chemotherapy OR Chemo followed by surgery +/-PORT
Thymoma: Unresectable stage III IVA (disseminated pleural disease) IVB	Chemotherapy followed by radiation therapy Chemotherapy alone Palliative RT BSC (if not fit for Chemo)
R0 resection	Observation for stage I or II Thymoma Consider for high risk IIB Thymoma Consider RT for stage III, IV Thymoma RT+Chemo for thymic carcinoma
R1 resection	RT for thymoma OR RT+/-chemo if thymic carcinoma
R2 resection	RT+/-Chemo for thymoma OR RT+/-chemo if thymic carcinoma
Relapse/Progression	Salvage surgery (isolated recurrence) RT Chemo. BSC

Risk assessment

- The management of autoimmune syndromes should be integrated in the oncological management.

Management of resectable disease

- The treatment strategy for thymic epithelial tumour is primarily based on whether the tumour may be resected upfront or not
- Complete respectability should be the aim; it is recommended to discuss indications for surgery in a multidisciplinary tumour board setting
- If complete resection is deemed to be achievable upfront, surgery represents the first step of the treatment

Surgery principles

- Standard approach is median sternotomy
- Complete thymectomy including the tumour, the residual thymus gland and perithymic fat, is preferred
- Thymomectomy alone—leaving residual thymic tissue and perithymic fat behind—is an option in stage I tumours in non-myasthenic patients
- If the tumour is widely extensive invasive (stage III/IV), en bloc removal of all affected structures, including lung parenchyma (usually through limited resection), pericardium, venous great vessels, nerves should be carried out
- Areas of uncertain margins are marked with clips to allow precise delivery of postoperative radiotherapy
- Phrenic nerve preservation does not affect OS but increases the risk of local recurrence.
- Frozen sections to assess tumour involvement of resection margins are not recommended.
- Minimally invasive surgery is an option for presumed stage I–II tumours
- The choice for minimally invasive resection should not jeopardise or change the principles that are deemed
  appropriate for an open approach, especially the achievement of complete resection that may ultimately Require switching to an open procedure.
- Minimally invasive surgery is not recommended for stage III tumours.
- There should be agreed protocol for lymph node managements for Thymic carcinoma (in process).

Systemic therapy Options:

First Line	Platinum based chemotherapy	PE or CAP as neoadjuvant, adjuvant, first line palliative. PE or Carboplatin paclitaxel for concurrent chemoradiation.	PE=Platinum etoposide. CAP=cyclophosphamide, Adriamycin, cisplatin.
Second Line	A wide range of chemotherapeutic agents has been used when disease progresses. They include Rechallenge with platinum-based regimen, Etoposide, ifosfamide, pemetrexed, octreotide, 5FU (FU) plus leucovorin, gemcitabine with or without capecitabine, and paclitaxel.	We do not offer immunotherapy to patients with thymoma or those with autoimmune disease due to concerns about irAEs	
Subject to Funding:	VEGF inhibitor therapy with sunitinib or lenvatinib		
Subject to Funding:	Immunotherapy for thymic carcinoma		

Radiotherapy protocols:

Indication	Dose fractionation
Postoperative	• 50Gy in 25 fractions • 60Gy in 30 fractions
Primary radiotherapy	• 60Gy in 30 fractions
Pre-operative radiotherapy	• 45Gy in 25 fractions
Palliative Radiotherapy, this is a radiosensitive disease	• As per lung cancer protocols

Follow-up

History, physical examination, and CT 6 months for 2 years, then annually for 5 years for thymic carcinoma.

Follow up for thymomas to continue upto 15 years.

MESOTHELIOMA

WORKUP

All Cases

- History and physical examination
- Thoracocentesis for cytology assessment
- Pleural biopsy for pathologic confirmation (e.g., VATS, CT/US -guided core biopsy, open biopsy)
- Pulmonary function tests
- Imaging-CT chest and abdomen with contrast, PET/CT
- Labs-FBC, LDH
- Clinicians should consider carrying out a Rockwood Clinical Frailty Scale Analysis and also a Charlson Co-morbidity Index (without including the malignancy in the Charlson Scale) for patients with ECOG PS 2 or worse.

Considerations

- Chest MRI
- Mediastinoscopy/EBUS and FNA for pathologic evaluation of mediastinal nodes
- VATS and/or laparoscopy if concern of contralateral or peritoneal disease
- Talc pleurodesis or indwelling pleural catheters if recurrent effusion
- Cardiac stress test (surgical evaluation)
-

TREATMENT RECOMMENDATIONS

I to IIIA epithelioid	Pleurectomy / decortication can be considered in very selected cases up to T3N1M0 epithelioid mesothelioma as of multimodality therapy. OR Chemo
IIIB or IV epithelioid OR sarcomatoid or biphasic type OR medically inoperable	Observation OR Chemo OR Palliative RT (e.g., chest wall, scar, skin, bone metastases) Or Ipilimumab + nivolumab immunotherapy (if funding available) for non-epithelioid mesothelioma. OR best supportive care (PS 3-4)

Stage	MST Epithelioid vs non-E	2-year survival Epithelioid vs non-E
IA	23.3 vs.19	48% vs.41%
IB	21.1 vs.15.5	46% vs.27%
II	21.6 vs.12.9	41% vs.25%
IIIA	15.4 vs.13.2	33% vs.22%
IIIB	16.6 vs.10.8	31% vs.14%
IV	10.7 vs.8.7	17% vs.15%

Overall survival according to overall stage

CHEMOTHERAPY FOR MESOTHELIOMA

		First Line	Second Line
Epitheloid	PS0-1	Platinum Pemetrexed	•Pemetrexed platinum if not used in first line or rechallenge following good durable response •Single agent immunotherapy with nivolumab or pembrolizumab (irrespective of PDL1 status) •Single agent chemotherapy with vinorelbine or gemcitabine •Cisplatin gemcitabine in selected patients •Motivated patients could be considered for clinical trials
	PS2	Single agent Vinorelbine or Gemcitabine	
Non Epitheloid	PS 0-1	•Pemetrexed and Platinum combination. •Nivolumab + Ipilimumab (nivolumab 3mg / kg 2 weekly and ipilimumab 1mg/kg 6 weekly, up to 2 years maximum duration). PS0-1 patients. [If funding available]	•Pemetrexed platinum if not used in first line or rechallenge following good durable response •Nivolumab + Ipilimumab (if not used first line) (nivolumab 3mg / kg 2 weekly and ipilimumab 1mg/kg 6 weekly, up to 2 years maximum duration). PS0-1 patients. (if funding is available. •Cisplatin gemcitabine in selected patients •single agent vinorelbine or gemcitabine •Motivated patients could be considered for clinical trials
	PS2	single agent vinorelbine or gemcitabine but priority is best supportive care.	

RADIOTHERAPY IN MESOTHELIOMA

Indication	Dose fractionation
Palliative chest wall pain	• As per lung cancer guidelines
Prophylactic radiotherapy	• This is not routinely used for biopsy sites. • Prophylactic radiotherapy may be offered to scar of Pleurectomy/ decortication

Follow up

Frequent follow up with CXR, CT chest, history, and physical examination indefinitely.

SMALL CELL LUNG CANCER

WORKUP

All Cases

- History and physical examination (including weight loss and performance status)
- Smoking cessation
- MRI brain
- PET/CT
- Labs- FBC, Electrolytes, LFTs, Ca, LDH, BUN, Creatinine
- Pathologic confirmation
- Clinicians should consider carrying out a Rockwood Clinical Frailty Scale Analysis and a Charlson Co-morbidity Index (without including the malignancy in the Charlson Scale) for patients with ECOG PS 2 or worse.
- (Pre-) Rehabilitation focusing on comorbidities, nutrition, exercise, and wellbeing is strongly encouraged.

Considerations

- Pathologic evaluation of mediastinal nodes only if T1-2 N0 and patient is surgical candidate.
- Thoracocentesis with cytology for pleural effusions
- Bone scan if PET unavailable and relevant symptoms
- SIADH in previously untreated patients: These patients should be managed actively in liaison with endocrinologists. Pharmacological options to correct low sodium include demeclocycline and tolvaptan. Ideally sodium should be $\geq$125 before starting chemotherapy.
- Pulmonary function tests.

Prognostic factors: Each adverse feature scores +1

1. LD vs ED
2. KP >60 vs ≤ 60
3. Serum Na (low vs normal)
4. Serum LDH (normal vs high)
5. Serum alk phos (normal vs high)

- Scores of 0 and 1 have better prognosis

TREATMENT RECOMMENDATIONS

Operable IA or IB (T1-T2a, N0, M0)	Surgery followed by chemotherapy and PCI OR (concurrent) ChemoRT followed by PCI OR surgery followed by ChemoRT followed by PCI
IA inoperable, IB inoperable, IIA, IIB, IIIA, IIIB. (Fit patients and radiotherapy volume feasible)	Concurrent ChemoRT followed by PCI
Unable to tolerate concurrent or tumour (radiotherapy) volume not suitable for concurrent	Sequential Chemo-RT followed by PCI
IV	Chemo followed by PCI and possible thoracic RT if good response to chemo. Chemo-IO +/- PCI
Unfit for Chemo	BSC, Palliative Radiotherapy, rarely radical radiotherapy is an option.
Recurrent disease	Chemo / Chemo-IO OR Palliative Radiotherapy Palliative Care

Staging	Median OS	5-y survival
Limited	20 months	20%
Extensive	12 months	1%

1.Limited Stage Disease, good Manchester Score (0/1) T1-4 N0-3 M0

- Stage 1 (T1-2a, N0, M0) may be considered for <u>surgical resection</u> (followed by adjuvant chemo- and radiotherapy).

- <u>Concurrent chemo-irradiation:</u> Fit patients with disease encompassable in radical radiotherapy portals should be offered concurrent chemoradiation with Cisplatin 80mg/m2 day1 and iv Etoposide 100-120mg/m2 day 1-3 x 4-6 cycles (oral Etoposide 200mg/m2 can be substituted for days 2-3). Radiotherapy will start ideally by cycle 2. Carboplatin can be substituted for cisplatin in case of renal impairment or poor tolerance to cisplatin.
    - A dose of 45Gy in 30 fractions twice daily over 3 weeks will be given to the involved areas. Alternatively, once daily radiotherapy to 60-66 Gy in 30-33 fr (with minimum over 50Gy in 25 fractions) can be utilised.
    - Prophylactic co-trimoxazole should be considered in concurrent chemoradiotherapy.
- <u>Sequential Chemo-irradiation:</u> Patients with initial disease volume too large to be treated with radical radiation should be reassessed after induction chemotherapy (as above) with platinum-based chemotherapy and could be offered sequential radiotherapy with a dose of 40Gy/15 fr; 55Gy/20fr; 66Gy/33fr or 45Gy/30Fr twice daily. A palliative radiotherapy dose (30Gy in 10 fr or

39Gy 13 fr may be employed if there is extensive residual disease that is not amenable to a more radical dose).

- PCI: For patients who have not progressed, with good PS (0-2) should be considered for prophylactic cranial irradiation (25Gy/10#). This may be withheld in patients over age 75.
    - The Premer Trial 2021 demonstrated the significant benefit of hippocampal sparing PCI IMRT, and this is suggested to be rapidly adopted in L&SC.
    - MRI brain surveillance can be utilised instead of PCI

2. **Limited stage, poor Manchester Score OR Extensive stage, good Manchester Score**

(Patients should receive primary prophylaxis with GCSF).

Chemo-IO: In PS 0-1 extensive stage patients. Combination chemotherapy with Carboplatin AUC5 day1 and Etoposide 100mg/m2 day 1-3 (oral Etoposide 200mg/m2 can be substituted for days 2-3) up to 4 cycles. Atezolizumab starts with cycle 1 chemo and continues as maintenance post chemo.

- Patients with brain metastases do not benefit from IO.

Chemotherapy alone: Combination chemotherapy with Carboplatin AUC5 day1 and Etoposide 100mg/m2 day 1-3 (oral Etoposide 200mg/m2 can be substituted for days 2-3) up to 6 cycles.

Thoracic consolidation radiotherapy (usually non radical dose) should be considered for these patients. Impower 133 trial did not utilise thoracic consolidation radiotherapy in chemo-IO arm.

- PCI should be considered in patients who have responded (PR or CR). This may be withheld in patients over age 75. The use of hippocampal avoidance techniques is recommended. MRI brain surveillance can be utilised instead of PCI.

3.Extensive Stage Disease, poor Manchester score

Treatment with single agent Carboplatin AUC5 could be considered as alternative to combination treatment initially. However, as soon as the performance status improves patients should be reassessed for use of combination chemotherapy.

- PCI is considered in patients who have responded (PR or CR). This may be withheld in patients over age 75 or of poor PS. The use of hippocampal avoidance techniques is recommended.
- Radiotherapy may also be used for symptom control e.g., lung, bone, brain skin metastases.

4.Second Line Chemotherapy

Patients who recur more than 3 months after completion of 1st line treatment should be considered chemosensitive and may be offered further chemotherapy with a platinum rechallenge, CAV or oral topotecan. Their overall prognosis is however poor and median survival is months.

- Radiotherapy may also be used for symptom control e.g., lung, bone, brain skin metastases.

Follow-up

First 2 years q 3 months

+2 years q 6 months

History and physical examination.

Blood tests only if clinically indicated

CT +/- brain imaging (MRI preferred) recommended at least 6 monthly

Guidelines for Radiotherapy and Chemotherapy in NON-SMALL CELL LUNG CANCER

Appropriate treatment choice for individual patients depends largely on the stage of disease at presentation, their performance status and presence of driver mutations / PDL1 status. Comorbidities should be optimised and prehabilitation considered particularly for patients whose disease is suitable for curative treatment. Investigations and actions to address these should be performed prior to referral to a surgeon or an oncologist.

Clinicians should consider carrying out a Rockwood Clinical Frailty Scale Analysis and also a Charlson Co-morbidity Index (without including the malignancy in the Charlson Scale) for patients with ECOG PS 2 or worse.

Work up:

All cases:

1-History and Examination (including weight loss and performance status)

2-smoking cessation assistance.

3-pulmonary function tests (including spirometry and transfer factor).

4-PET/CT.

5-Tissue diagnosis: CT-guided biopsy, bronchoscopic and EBUS directed biopsy, Bronchial lavage, Mediastinoscopy, VATS, or chamberlain for LN biopsy if indicated

6-MRI brain/ CT brain with contrast

7-Molecular markers (All specimens should be checked for biomarkers at diagnosis ideally via DNA and RNA NGS platforms.

Currently available tests are:

- DNA NGS: EGFR, BRAF, KRAS, MET
- RNA NGS: ALK, ROS1, RET, NTRK 1/2/3
- IHC: PDL1

The guidelines below do not deal with surgical issues:

Early / Locally Advanced Disease

Radical Radiotherapy

A] Chemoradiotherapy +/- Durvalumab IO

- Consider chemoradiotherapy for people with stage II or III NSCLC that are not suitable for or decline surgery.
- Vinorelbine/Cisplatin (or Carboplatin for patients unsuitable for Cisplatin) concurrent for NSCLC.
- Weekly Carboplatin Taxol x 6 for NSCLC is also utilised particularly in less fit patients.
- Consider co-trimoxazole in concurrent chemoradiotherapy.

--Durvalumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced unresectable NSCLC in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation only.
--For people with operable stage IIIa-N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider neoadjuvant and /or adjuvant therapy. However, we have not done neoadjuvant Chemoradiotherapy pre surgery at L&SC.

B] Radiotherapy alone

- For people with stage I-IIa (T1a-T2b, N0, M0) NSCLC who decline lobectomy or in whom it is contraindicated, offer radical radiotherapy with SABR (or sublobar resection).
- For people with stage I-IIa (T1a-T2b N0, M0) NSCLC who decline surgery or in whom any surgery is contraindicated, offer SABR. If SABR is contraindicated, offer either conventional or hypofractionated radiotherapy.
- For eligible people with stage IIIa NSCLC who cannot tolerate or who decline chemoradiotherapy (with or without surgery), consider radical radiotherapy (either conventional or hypofractionated).
- For eligible people with stage IIIb NSCLC who cannot tolerate or who decline chemoradiotherapy, consider radical radiotherapy (either conventional or hypofractionated).

If conventionally fractionated radical radiotherapy is used, offer either:

- 55 Gy in 20 fractions over 4 weeks **or**
- 60-66 Gy in 30-33 fractions over 6-6½ weeks.

C] Postoperative radiotherapy

Indications:

- Patients with incompletely resected disease
- Patients who are N2 and have had inadequate lymph node dissection / sampling. N2 disease per se is no longer an indication for adjuvant radiotherapy.

Post-operative radiotherapy (50Gy in 25# over 5 weeks) +/- adjuvant sequential / concurrent chemotherapy if their PS is good.

Concurrent chemoradiation to be considered only in the setting of positive margins / macroscopic residual disease.

D] Stereoablative Body Radiotherapy (SABR):

This involves high intensity radiotherapy to a small focal area of the lung.

Peripheral Tumours
- ITV ≥ 2.0cm from proximal bronchial tree (PBT), trachea, oesophagus, heart, great vessels, spinal cord,
brachial plexus, phrenic nerve, recurrent laryngeal nerve
- Dose 18Gy x 3# or 11Gy x 5#

Central Tumours
- Tumours which do not satisfy the criteria for peripheral tumours (as above) **and** are **not** ultra-central (as below)
- Dose 7.5Gy x 8#

Ultra-central Tumours should not be treated
- ITV < 1.0 cm from PBT **or**
- PTV directly contacting or overlapping the trachea, oesophagus, pulmonary vein or pulmonary artery

Early / Locally Advanced Disease

Systemic Therapy

A] Neoadjuvant chemotherapy

- Neoadjuvant chemotherapy is generally not advised outside the context of a clinical trial in Stage I and II patients.
- Selected Stage III patients may be suitable for chemotherapy x 2-4 cycles prior to considering surgical resection or radical radiotherapy. A cisplatin-based doublet such as cisplatin vinorelbine (or appropriate for histology is recommended). Carboplatin (AUC5) can be considered in place of cisplatin in patients in less fit patients and / or with poor renal function. Gemcitabine is a strong radiosensitiser and its use prior to radiotherapy must be approved by a clinical oncologist.

The patient fitness for possible surgery / radical radiotherapy should be assessed.

The restaging plan for surgery (post neoadjuvant chemotherapy) should be in place before starting neo adjuvant chemotherapy.

B] Adjuvant Systemic therapy

1] Adjuvant chemotherapy with Vinorelbine and Cisplatin x 4 cycles should be offered. Histology specific platinum doublet can be used.

Carboplatin (AUC5) can be considered in place of cisplatin in less fit patients or patients with poor renal function.

- Offer to fit patients with size over 4cm disease, Stage III and or Node +ve
- Consider in fit patients if they have: LVSI+ve, high grade, visceral pleural involvement, non-well differentiated neuroendocrine tumours.

2]Adjuvant osimertinib to be offered (if no contraindications) to EFGR sensistising mutation positive patients (exon 19 deletions or exon 21 L858R mutation) for 3 years either with or without prior chemotherapy.

3]Adjuvant atezolizumab (post adjuvant chemo) for completely resected stage II-IIIA NSCLC whose tumour express PDL1 >50% and whose disease has not progressed following platinum-based adjuvant chemotherapy.

C] Future Considerations:

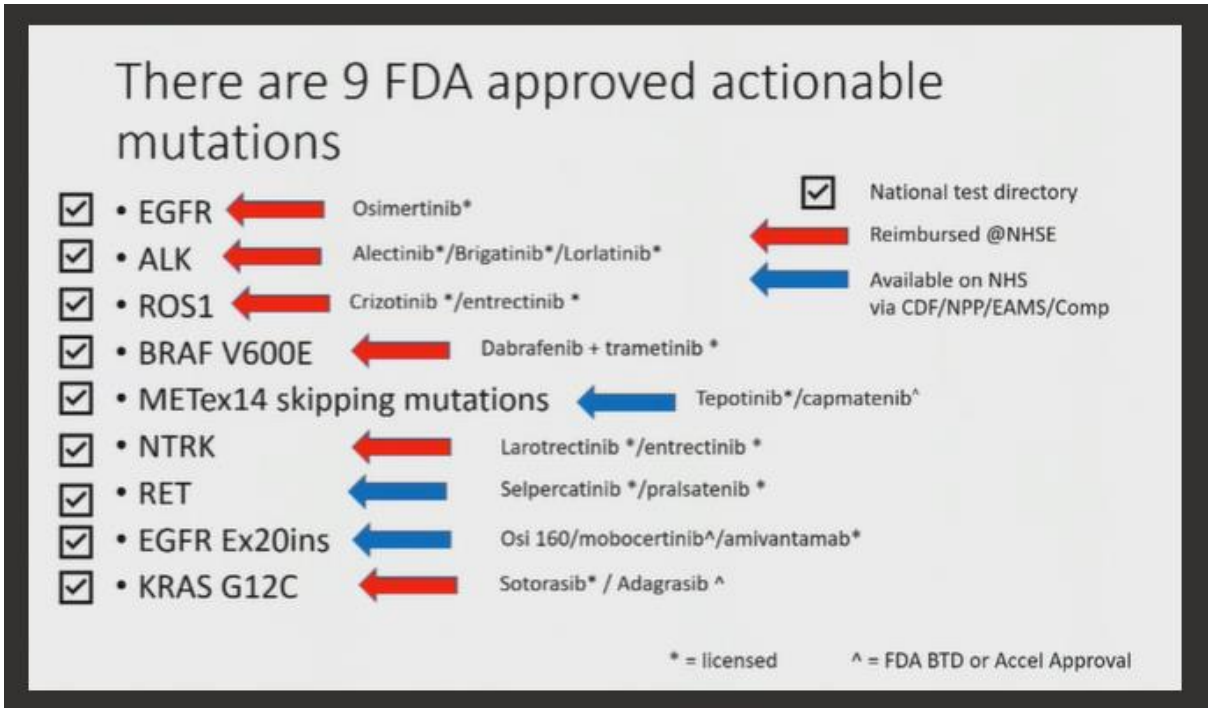
The use of (chemo)-immunotherapy with checkpoint inhibitors is actively explored in the neoadjuvant setting. This is to be reviewed as an interim measure as National Guidance evolves.

Advanced Disease

Patients with Stage III/IV disease unsuitable for radical treatment who have PS 0-2 should be considered for palliative systemic therapy. Further lines of therapy depend on previous response and duration of response to treatment, fitness, biomarkers and are at the discretion of the treating clinician.

(Pre-) Rehabilitation focusing on comorbidities, nutrition, exercise and wellbeing is strongly encouraged to be set up in each Trust. Clinicians should consider carrying out a Rockwood Clinical Frailty Scale Analysis and also a Charlson Co-morbidity Index (without including the malignancy in the Charlson Scale) for patients with ECOG PS 2 or worse.

A] Targeted therapy against driver mutations:



Riyaz Shah BTOG 2022

This is a fast-moving field that users need to stay up to date (beyond this guidance).

EGFR sensitising mutation positive such as Exon 19 deletion or L858R mutation:

- Preferred osimertinib first line.
- Other first options include: erlotinib, afatinib (for non-common mutations), gefitinib, dacomitinib

EGFR exon 20 insertion mutation positive

- First line: systemic therapy
- Second line: Amivantamab-vmjw or Mobocentric in trials or as available. Osimertinib can be used.

Kras G12c mutation positive:

- First line: systemic therapy
- Second line: sotorasib

ALK rearrangement positive:

- Available agents are: Brigatinib, Alectinib, Lorlatinib, Ceritinib. Useful occasionally: crizotinib

NICE:

- First Line: Brigatinb
- Second Line: Lorlatinib (Brigatinib post crizotinib)
- Third Line: Lorlatinib post Brigatinib post crizotinib

ROS1 rearrangement positive:

- Preferred First Line: crizotinib or entrectinib. Other recommended cetirinib
- Second Line: Lorlatinib or entrectinib

BRAF V600E mutation positive:

- Preferred First Line: Dabrafenib and trametinib

NTRK Fusion positive:

- Larotrectinib or Entrectinib

MET ex14 Skipping mutation

- Preferred First Line: Tepotinib or Capmatinib
- Can be useful: crizotinib

RET rearrangement positive:

- Preferred: selpercatinib or Pralsetinib
- Useful in certain circumstances: Cabozantinib or Vandetanib

B. Patients negative for actionable mutations.

Pre-amble on chemo:

- Chemotherapy for non-squamous histology should be a Platinum/Pemetrexed combination (or non-pemetrexed platinum regimen that is followed by maintenance pemetrexed). Patients with non-squamous histology who had at least stable disease after 4 cycles of platinum-based chemotherapy should be offered maintenance treatment with Pemetrexed every 3 weeks until disease progression.
- Chemotherapy for squamous cell carcinoma is carboplatin doublet with Gemcitabine, Taxane or Vinorelbine.
- Patients with PS 2 or worse (without actionable mutation) should have treatment tailored to their comorbidities and functional status. Single agent systemic therapy, best supportive / palliative care and palliative radiotherapy to be utilised appropriately.

B1] PDL-1 expression positive ≥50% and negative for actionable mutations and no contraindications to Immunotherapy. PS 0-1

Adenocarcinoma, Large cell carcinoma or NSCLC NOS:

First line Options include:

- Pembrolizumab single agent 2 years
- Platinum + pemetrexed + pembrolizumab. Maintenance Pemetrexed and pembrolizumab
- Atezolizumab single agent (also allowed if >10% tumour infiltration by immune cells and not subject to stopping rules at 2 years)
- (Chemotherapy alone if IO is contraindicated).

Second and subsequent Line therapy:

Patients with non-squamous histology who do not respond to, progress or relapse after 1st line chemotherapy and whose PS is 0-2 should be considered for 2nd line systemic therapy. Options include:

- Pemetrexed platinum regimen (if not previously received pemetrexed)
- Docetaxel 75mg/m2 every 3/52 for 4 cycles +/- Nintedanib or
- Pembrolizumab for maximum 2 years (if they have not previously received immunotherapy).
- Atezolizumab if no previous immunotherapy (also allowed if >10% tumour infiltration by immune cells and not subject to stopping rules at 2 years)

Squamous cell carcinoma, PDL1 >50%, PS 0-1

First Line options include:

- Pembrolizumab
- Carboplatin + Paclitaxel + Pembrolizumab with maintenance pembrolizimab to 2 years

- Atezolizumab (also allowed if >10% tumour infiltration by immune cells and not subject to stopping rules at 2 years)
- Non-pemetrexed platinum doublet (if immunotherapy is contraindicated)

Second and subsequent Line therapy:

- Platinum doublet chemotherapy (if chemo naïve) with gemcitabine, vinorelbine or taxane
- Docetaxel 75mg/m2 every 3/52
- Pembrolizumab for maximum 2 years (if they have not previously received immunotherapy).
- Atezolizumab if no previous immunotherapy (also allowed if >10% tumour infiltration by immune cells and not subject to stopping rules at 2 years)

B2] PDL-1 expression ≤50% and negative for actionable mutations and no contraindications to Immunotherapy. PS 0-1

Adenocarcinoma, Large cell carcinoma or NSCLC NOS:

First line Options include:

- Platinum + pemetrexed + pembrolizumab. Maintenance Pemetrexed and pembrolizumab.
- Carboplatin + Paclitaxel + Bevacizumab + Atezolizumab. Maintenance Bevacizumab and atezolizumab to maximum 2 years. (This regiment to be considered particularly for fit mutation positive patients who have exhausted targeted therapy, or fit patients with liver metastases). PDL-1 eligibility: 0-49%
- Chemotherapy without immunotherapy. Platinum/Pemetrexed combination (or non-pemetrexed platinum regimen that is followed by maintenance pemetrexed). Patients with non-squamous histology who had at least stable disease after 4 cycles of platinum-based chemotherapy should be offered maintenance treatment with Pemetrexed every 3 weeks until disease progression.

Second and subsequent Line therapy:

Options include:

- pemetrexed regimen (if not previously received pemetrexed),
- Docetaxel 75mg/m2 every 3/52 for 4 cycles +/- Nintedanib
- Chemotherapy with gemcitabine, vinorelbine or taxane either as single agent (or in combination with carboplatin depending on platinum free interval).
- Pembrolizumab for maximum 2 years (if they have not previously received immunotherapy). PDL1 ≥1%.
- Atezolizumab if no previous immunotherapy for maximum 2 years. PDL1 can be 0%.

- Nivolumab for maximum 2 years (if they have not previously received immunotherapy). PDL1 ≥1%.

Squamous cell carcinoma, PDL1 <50%, PS 0-1

First Line options include:

- Carboplatin + Paclitaxel + Pembrolizumab with maintenance pembrolizimab to 2 years
- Platinum doublet if immunotherapy is contraindicated. Chemotherapy for squamous cell carcinoma with Gemcitabine, Taxane or Vinorelbine and Carboplatin.

Second and subsequent Line therapy:

- Docetaxel 75mg/m2 every 3/52
- Chemotherapy with gemcitabine, vinorelbine or taxane either as single agent (or in combination with carboplatin depending on platinum free interval).
- Pembrolizumab for maximum 2 years (if they have not previously received immunotherapy). PDL1 ≥1%.
- Atezolizumab for maximum 2 years if no previous immunotherapy. PDL1 can be 0%.
- Nivolumab for maximum 2 years if no previous immunotherapy. PDL1 can be 0%.

Stage	IA	IB	IIA	IIB	IIIA	IIIB	IV
Clinical	76-92%	67%	60%	33-50%	17-34%	9-22%	1-20%
Pathological	81-92%	74%	65%	51-61%	34-40%	24-30%	1-20%

Overall survival at 5 years.

RADIOTHERAPY FOR NSCLC

Indication	Dose fractionation
Medically inoperable T1–3 (≤5 cm) N0: SABR	• 54Gy in 3 fractions over 5–8 days • 55Gy in 5 fractions over 10–14 days • 60Gy in 8 fractions over 10–20 days
Medically inoperable stage I and II	• 54Gy in 36 fractions treating thrice daily over 12 consecutive days continuous, hyperfractionated, accelerated radiotherapy (CHART) • 55Gy in 20 fractions
Concurrent Stage III	• 55Gy in 20 fractions over 4 weeks • 60-66Gy in 30-33 fractions over 6-6.5 weeks
Sequential stage III	• 55Gy in 20 fractions over 4 weeks • 60Gy-66Gy in 30-33 fractions over 6-6.5 weeks • 54Gy in 36 fractions treating thrice daily over 12 consecutive days (CHART)
Radiotherapy alone	• 54Gy in 36 fractions treating thrice daily over 12 consecutive days (CHART) • 66Gy in 33 fractions over 6.5 weeks • 55Gy in 20 fractions over 4 weeks
Pancoast tumours (T3–4 N0–1)	• 45Gy in 25 fractions over 5 weeks with chemotherapy such as cisplatin and etoposide followed by surgery
Palliative RT in patients with good PS	• 39Gy in 13 fractions over 2.5 weeks with cord dose limited to 36Gy • 36Gy in 6 fractions 48 hours apart over 2 weeks • 36Gy in 12 fractions over 2.5 weeks • 30Gy in 10 fractions over 2 weeks • 20Gy in 5 fractions over 1 week
Palliative RT in patients with poor PS	• 10Gy in 1 fraction • 20Gy in 5 fractions • 16-17Gy in 2 fractions over 8 days

Follow up:

Guidelines for Lung Cancer Follow Up Following Non-Surgical Oncology Treatment:

The pathways below were agreed by the Lung Oncologists across the Alliance in July 2024, to provide guidance for the follow up of lung cancer patients after treatment. A patient's individual circumstances should always be considered and follow up tailored as appropriate. For example, if a patient is not fit for further cancer treatment, or would not wish to pursue further treatment, the mode and frequency of imaging should be reviewed.

This document sets out the time points, from the completion of cancer treatments, when clinical review and imaging should take place.

Clinical reviews

Unless specified, clinical reviews can be carried out by **any** competent healthcare professional (HCP) including Oncologists, Respiratory physicians, nurses and allied health professionals. Reviews that need to be performed by the oncology team or that could be led by another HCP are specified. Consultant supervision of nurse/AHP delivered follow up may be by either Respiratory or Oncology teams, depending on service configuration at individual Trusts. Supervising Consultants should decide if they wish to maintain oversight of all imaging reports. This may depend on the experience and competencies of staff delivering patient review. It is recommended that time is allocated within consultant job plans for supervision of this workload.
Follow up could be telephone, virtual or face to face depending on patient preference and should involve a discussion of imaging results and review of any patient concerns or symptoms.

Imaging

The term 'CT scan' refers to a contrast CT scan of chest and abdomen. Pelvic CT can be included depending on the risk of metastasis.
Imaging outside of the proposed schedule can be requested based on clinical and radiological findings.
Imaging of the brain is discussed elsewhere.

Post radiotherapy with radical intent

Post SABR

Time since SABR	Investigation	Review
Year One		
6-8 weeks		Oncology team
3 months	CT scan	Any HCP
6 months	CT scan	Any HCP
12 months	CT scan	Any HCP
Year Two		
18 months	CT scan	Any HCP
24 months	CT scan	Any HCP
Year Three		
30 months	CT scan	Any HCP
36 months	CT scan	Any HCP
Year Four		
48 months	CT scan	Any HCP
Year Five		
60 months	CT scan	Any HCP

Post chemo-radiotherapy (without adjuvant IO)/Post radical radiotherapy:

Time since XRT	Investigation	Review
Year One		
6-8 weeks		Oncology team
3 months	CT scan	Any HCP
6 months	CT scan	Any HCP
12 months	CT scan	Any HCP
Year Two		
18 months	CT scan	Any HCP
24 months	CT scan	Any HCP
Year Three		
30 months	CT scan	Any HCP
36 months	CT scan	Any HCP
Year Four		
48 months	CT scan	Any HCP
Year Five		
60 months	CT scan	Any HCP

Post chemo-radiotherapy, followed by adjuvant immunotherapy

Time since XRT	Investigation	Review
Year One whilst receiving adjuvant IO		
Clinic review every 1-2 cycles, whilst on adjuvant IO, with CT scans at 3, 6, and 12 months post XRT. Reviews can be a mixture of medical, Any HCP depending on local service configuration and patient factors.		
Year Two		
15 months	Clinical review with a particular focus for late IO side effects	Any HCP
18 months	CT scan	Any HCP
24 months	CT scan	Any HCP
Year Three		
30 months	CT scan	Any HCP
36 months	CT scan	Any HCP
Year Four		
48 months	CT scan	Any HCP
Year Five		
60 months	CT scan	Any HCP

<u>Post Surgery and Adjuvant treatments</u>

Post-surgery and 3 months of adjuvant chemotherapy

Time since surgery	Investigation	Review
Year One		
First 3 months	Adjuvant chemo	Oncology team before each cycle
3 months		Oncology
6 months	CT scan	Any HCP
12 months	CT scan	Any HCP

Year Two		
18 months	CT scan	Any HCP
24 months	CT scan	Any HCP
Year Three		
36 months	CT scan	Any HCP
Year Four		
48 months	CT scan	Any HCP
Year Five		
60 months	CT scan	Any HCP

Post-surgery and 3 months of adjuvant chemotherapy, then 12 months of adjuvant immunotherapy

Time since surgery	Investigation	Review
Year One		
First 3 months	Adjuvant chemo	Oncology team
3-15 months	Clinic review every 1-2 cycles, whilst on adjuvant IO, with CT scans at 6 and 12 months post-surgery. Reviews by can be a mixture of medical, nurse/AHP depending on local service configuration and patient factors.	
Year Two		
15 months	Clinical review with a particular focus for any late IO side effects	Any HCP
18 months	CT scan	Any HCP
24 months	CT scan	Any HCP
Year Three		
36 months	CT scan	Any HCP
Year Four		
48 months	CT scan	Any HCP
Year Five		
60 months	CT scan	Any HCP

Post-surgery, after 3 cycles of neoadjuvant chemo-immunotherapy:

Time since surgery	Investigation	Review
Year One		
3 months	Clinical review with a particular focus for any late IO side effects	Any HCP
6 months	CT scan	Any HCP
12 months	CT scan	Any HCP
Year Two		
18 months	CT scan	Any HCP
24 months	CT scan	Any HCP

Year Three		
36 months	CT scan	Any HCP
Year Four		
48 months	CT scan	Any HCP
Year Five		
60 months	CT scan	Any HCP

Post-surgery and 36 months of adjuvant oral TKI:

Time since surgery	**Investigation**	**Review**
Year One Adjuvant oral TKI (+/- 3 months of adjuvant chemo prior to TKI) Clinic review every 1-3 cycles		
All stages	3 monthly CT (consider omitting month 9 CT is patient well and no concerns)	Oncology team. Reviews can be a mixture of medical and Any HCP depending on local service configuration and patient factors.
Year Two Adjuvant oral TKI Clinic review every 1-3 cycles		
18 months	CT scan	Oncology team
24 months	CT scan	Oncology team
Year Three Adjuvant oral TKI Clinic review every 1-3 cycles		
30 month	CT scan	Oncology team
36 month	CT scan	Oncology team
Year Four		
42 month	CT scan	Any HCP
48 month	CT scan	Any HCP
Year Five		
54 month	CT scan	Any HCP
60 month	CT Scan	Any HCP
Year 6-8	Annual CT scan	Any HCP

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Stage Grouping for the 8th Edition of the TNM Classification for Lung Cancer

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

References

1. Rami-Porta R, Bolejack V, Giroux DJ et al. The IASLC Lung Cancer Staging Project: the new database to inform the 8th edition of the TNM classification of lung cancer. *J Thorac Oncol* 2014; 9: 1618-1624.
2. Rami-Porta R, Bolejack V, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 990-1003.
3. Asamura H, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 1675-1684.
4. Eberhardt WEE, Mitchell A, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the M descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 1515-1522.
5. Goldstraw P, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2015; 11: 39-51.
6. Nicholson AG, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 300-311.
7. Travis WD, Asamura H, Bankier A et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016; 11: 1204-1223.

UICC TNM 8, which should be used for all tumours diagnosed after 1 January 2018.

Primary tumour (T)

TX Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy

T0 No evidence of primary tumour

Tis Carcinoma in situ; Tis (AIS) for adenocarcinoma in situ, Tis (SCIS) for squamous cell carcinoma in situ

T1 Tumour 30 mm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus[a]

- T1mi Minimally invasive adenocarcinoma[b]
- T1a Tumour 10 mm or less in greatest dimension[a]
- T1b Tumour more than 10 mm but not more than 20 mm in greatest dimension[a]
- T1c Tumour more than 20 mm but not more than 30 mm in greatest dimension[a]

T2 Tumours more than 30 mm but not more than 50 mm in greatest dimension; or tumours with any of the following features:

- involves the main bronchus
- invades the visceral pleura
- associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the whole lung.

T2 tumours with these features are classified as T2a if 40 mm or less, or cannot be determined, or T2b if more than 40 mm but not more than 50 mm[c]

- T2a Tumour more than 30 mm but not more than 40 mm in greatest dimension
- T2b Tumour more than 40 mm but not more than 50 mm in greatest dimension

T3 Tumour more than 50 mm but not more than 70 mm in greatest dimension, or one that directly invades one of the following: parietal pleura (PL3), chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or associated separate tumour nodule(s) (intra-pulmonary metastases) in the same lobe as the primary

T4 Tumour more than 70 mm or one of any size that directly invades one of the following: diaphragm, mediastinum, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, vertebra; or separate tumour nodule(s) (intra-pulmonary metastases) in a different ipsilateral lobe to that of the primary

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional node involvement

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar nodes and/or intrapulmonary nodes (node stations 10–14), including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal node(s) (node stations 1–9)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular nodes

Distant metastasis (M)

M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion[d]
M1b	Single extrathoracic metastasis in a single organ and involvement of a single distant (non-regional) lymph node[e]
M1c	Multiple extrathoracic metastases in one or several organs

*Small cell carcinomas:	Staging via TNM 8 is now recommended, especially for those with limited disease
*Carcinoid tumours:	Staging via TNM 8 is now recommended for all cases

[a]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

[b]Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension in any one focus.

[c]T2 tumours with these features are classified as T2a if 4 cm or less, or if size cannot be determined, and T2b if greater than 4 cm but not larger than 5 cm.

[d]Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements on clinical judgement dictate that the effusion is not related to tumour, the effusion should be excluded as a staging descriptor.

[e]This includes involvement of a single non-regional node.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Stage Grouping for the 8th Edition of the TNM Classification for Lung Cancer

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

References

1. Rami-Porta R, Bolejack V, Giroux DJ et al. The IASLC Lung Cancer Staging Project: the new database to inform the 8th edition of the TNM classification of lung cancer. *J Thorac Oncol* 2014; 9: 1618-1624.
2. Rami-Porta R, Bolejack V, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 990 - 1003.
3. Asamura H, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 1675-1684.
4. Eberhardt WEE, Mitchell A, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the M descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 1515-1522.
5. Goldstraw P, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2015; 11: 39-51.
6. Nicholson AG, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 300-311.
7. Travis WD, Asamura H, Bankier A et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016; 11: 1204-1223.

Performance Status

KP			**WHO**
100		Normal, no complaints, no evidence of disease	0
90		Able to carry on normal activity; minor signs or symptoms of disease	
80		Normal activity with effort, some signs and symptoms of disease	1
70		Cares for self but unable to carry on normal activity or do work	
60		Requires occasional assistance but is able to care for most personal needs	2
50		Requires considerable assistance and frequent medical care	
40		Disabled; requires special care and assistance	3
30		Severely disabled; hospitalisation indicated; death no imminent	
20		Very ill; hospitalisation and active supportive care necessary	4
10		Moribund	
0		Dead	

Appendix 4

Small Cell Lung Cancer Staging

Small Cell Lung Cancer Staging should be done according to the TNM staging
The description of limited/extensive stage disease not in use anymore

Limited stage – disease confined to one hemithorax (can include ipsilateral SCF and contralateral hilar nodes but excludes pleural effusion)

Extensive stage – disease beyond one hemithorax

Prognostic factors

- LD vs ED
- KP >60 vs ≤ 60
- Serum Na (low vs normal)
- Serum LDH (normal vs high)
- Serum alk phos (normal vs high)
- Each adverse features scores +1

Scores of 0 and 1 have better prognosis

Appendix 5

Calculation of predicted post-operative FEV1 (ppoFEV1)

$$\text{ppoFEV1} = \text{pre FEV1} \times \frac{(19 - \text{segments to be removed})}{19}$$

If any obstructed segments:

$$\text{ppoFEV1} = \text{pre FEV1} \times \frac{(19 - a) - b)}{19 - a}$$

a = no of obstructed segments
b = no of obstructed segments to be resected

Right upper lobe	= 3	Left upper lobe	= 3
Middle lobe	= 2	Lingula	= 2
Right lower lobe	= 5	Left lower lobe	= 4

Appendix 6

Dataset for Lung Cancer Histopathology reports (3rd edition)

Histopathology reporting proforma for lung cancer resection specimens

Surname	Forenames	Date of birth	Sex
Hospital	Hospital no	NHS/CHI no	
Date of receipt	Date of reporting	Report no	
Pathologist	Surgeon/physician	Lab no	

Previous treatment (neoadjuvant chemotherapy/radiotherapy) Yes ϒ No ϒ

Specimen type

Right lung	ϒ	VATS	ϒ
Left lung	ϒ	VATS converted to open	ϒ
		Open	ϒ
Single wedge resection	ϒ	Pneumonectomy (extra-pericardial)	ϒ
Multiple wedge resections	ϒ	Pneumonectomy (intra-pericardial)	ϒ
Segmentectomy	ϒ		
Lobectomy/bi-lobectomy	ϒ	Other ϒ (specify) ……..……..……..	

Other surgical procedures

Sleeve resection ϒ Other (e.g., chest wall) ……..….....

Macroscopic features

Main bronchus within 20 mm of carina (T3) (if known) ϒ

Main bronchus more than 20 mm from carina (T2) ϒ

Location of tumour: ……..….....

Hilar/endobronchial/central ϒ

Right upper lobe	ϒ	Right middle lobe	ϒ	Right lower lobe	ϒ
Left upper lobe	ϒ	Left lower lobe	ϒ	Not assessable	ϒ

Tumour size…….mm (maximum dimension) Not assessable ϒ

(T1a =<20 mm; T1b 21–≥30 mm; T2a 31–≤50 mm; T2b 51–≤70 mm; T3 >70 mm).

Distance of tumour (or stapled margin if completion lobectomy) from bronchial or medial resection margin: ….....….mm

Extent of atelectasis/obstructive pneumonia: None/less than the two categories below ϒ

Involving hilar region but not whole lung (T2) ϒ

Involving whole lung (T3) ϒ

Microscopic features

Histological type

Squamous cell carcinoma ϒ Large cell undifferentiated ϒ Small cell carcinoma ϒ

Adenocarcinoma ϒ

Adenocarcinoma-in-situ ϒ

Minimally invasive adenocarcinoma (invasive component less than 5 mm) ϒ

Predominant pattern …….…. (lepidic, acinar, papillary, micropapillary, solid)

Mucinous ϒ

Non-mucinous ϒ

Mixed mucinous/non-mucinous (>10% of each) ϒ

Combined tumours ϒ (specify …….....)

Other tumour ϒ (specify, e.g., carcinoid, etc. ……)

Local invasion

Visceral pleura (T2) ϒ

Parietal pleura/chest wall (T3) ϒ

Mediastinal pleura (T3) ϒ

Pericardium (T3) ϒ

Diaphragm (T3) ϒ

Great vessel (aorta, central pulmonary artery or vein) (T4) ϒ

Atrium, heart (T4) ϒ

Malignant pleural effusion (M1a) ϒ

Satellite nodules

Satellite tumour nodules in same lobe (T3) ϒ

Satellite tumour nodules in different ipsilateral lobe (T4) ϒ

Satellite tumour nodules in contralateral lobe (M1a) ϒ

Pleural invasion

PL0 (no pleural involvement) ϒ

PL1 (breaching of the outer layer of the visceral pleura but no extension to the pleural surface) ϒ

PL2 (breaching of the outer layer of the visceral pleura **and** extension to the pleural surface) ϒ

PL3 (involvement of the parietal pleura) ϒ

Lymph node spread

Ipsilateral hilar/intrapulmonary (node stations 10–14)	Submitted ϒ	Involved (N1) ϒ
Ipsilateral mediastinal (node stations 1–9)	Submitted ϒ	Involved (N2) ϒ
Contralateral mediastinal, hilar nodes	Submitted ϒ	Involved (N3) ϒ
Ipsilateral or contralateral scalene or supraclavicular nodes	Submitted ϒ	Involved (N3) ϒ

Margins

Bronchial	Clear ϒ	Involved ϒ	N/A ϒ
Mediastinal	Clear ϒ	Involved ϒ	N/A ϒ
Vascular	Clear ϒ	Involved ϒ	N/A ϒ
Chest Wall	Clear ϒ	Involved ϒ	N/A ϒ

Other pathology (non-core)

Emphysema	No ϒ	Yes ϒ	Specify degree(mild/moderate/severe)
Interstitial fibrosis	No ϒ	Yes ϒ	State cause (if known) ……..
Other ϒ	Details: ……..		

Metastases

Unknown (MX) ϒ Absent (M0) ϒ Present (M1a) ϒ (M1b) ϒ

Details: ……

Ancillary data

Epidermal growth factor mutation Yes ϒ No ϒ Not assessed ϒ

Other genetic data (specify) ……

Summary of pathological staging

(Select highest stage from above data; for synchronous primaries, use protocol above;
use prefix ‘y’ for resection during or following treatment and ‘r’ for recurrence after treatment)

…pT ……..pN ……pM ……

Complete resection at all margins Yes ϒ No ϒ

SNOMED code:

Comments ……

Signature .....……
Date ……../……../……...

Appendix 7

Blackpool Teaching Hospitals NHS
NHS Foundation Trust

Thoracic Surgery Referral Form

Please email the form to: Cardiac.Referral@bfwhospitals.nhs.uk **Date Email/Fax……**

NHS No:	Consultant:
Hosp. No DOB:	Key Worker (Local Nurse Specialist)
Name: Address: Patient Tel No:	62 day Cancer Treatment Target Date: MDT Date Accepted/Referred Surgeon in MDT Mr. Bittar/ Mr. Duncan/Mr. Purohit/ Mr. Zacharias/NONE

Presenting Symptoms:

Incidental…… …… Chest Pain SOB

Cough Hemoptysis Bone Pain Wt. Loss

Other……

Performance Status (Tick as appropriate): 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

Exercise Tolerance……Limited by……..

CT Scan: ☐ STAGING T N M Date:

Site of Nodule/Tumour (Circle as appropriate)

Right – RUL RML RLL Left- LUL LLL Other Important Findings…….. ……..

PET CT Scan: ☐ STAGING T N M Date:

CT Scan **Head** (Large central Tumours,T4 tumours,N2 diseases, Possible pneumonectomy) : ☐

Histological Diagnosis: If Histology available report must be attached

State method used for tissue sample: Date:

Previous Medical History

IHD Y ☐ N ☐…… **Previous Malignancy**1……..

CVA Y ☐ N ☐,,,,,,,,,,,,,,,,,,…… 2……

Asbestos exposure Y ☐ N ☐ PVD Y ☐ N ☐

Lung Function Test:FEV1- L % ,RATIO FEV1/FVC TLCO KCO

All patients for lung resection must have Full Lung Function Tests included with referral.

Smoking history

Current smoker: ☐ Ex-smoker: ☐ Never smoked: ☐ Year Stopped: Number per day: Pack year:

Antiplatelet/Anticoagulation Medication:

Other Medication

Has the patient been informed of this referral? YES ☐ NO ☐

Other relevant information**:(e.g., Specific MDT discussion, i.e., assessment only/wedge only/biopsy/Lymph nodes etc)**

Authors: Mr M Purohit, Consultant Cardiothoracic Surgeon / Bernie McAlea, Thoracic Specialist Nurse
V2.31/01/2017

Appendix 8

Blackpool Teaching Hospitals NHS
NHS Foundation Trust

High Risk Lung Cancer Surgical MDT Referral for 2nd opinion at BVH

Please email to Cardiac.Referral@bfwhospitals.nhs.uk

NHS NO	Consultant
H No DOB	Lung Ca Nurse specialist
Name Address Pt Tel no	Surgeon Present in MDT AD/MP/MNB/JZ Date of MDT CT/PET/MRI/Bone Scan
Site Right U,M,L Left U,L	Date of Breach
Final Staging T N M Any Important Invasion-	Important Bronchoscopy finding
Histology Obtained by	Cardiac History
Lung Function FEV1 L (%) DLCO FEV1/FVC KCO	Other Comorbidities 1 2 3 4
Performance Status 0 1 2 3 4	Smoking History:- Current Ex Never
<u>The Question for the High Risk MDT</u> <u>(Reason for referral)</u> 1. 2.	
Alternative Treatment 1. 2.	

Authors: Mr M Purohit, Consultant Cardiothoracic Surgeon / Bernie McAlea, Thoracic Specialist Nurse
V1.23/02/2016

Appendix 9

Optimisation

Blackpool Teaching Hospitals NHS
NHS Foundation Trust

National Optimal Lung Cancer Pathway

Medical and Fitness Optimisation Checklist

Please action this checklist as soon as a decision has been made that the patient may be suitable for surgery.

Condition	Action	Checked
Anaemia	IV Iron	☐
Active cardiac condition	Refer to Cardiologist	☐
Stroke/TIA/CVA	Waiting time of 4-6 weeks before surgery	☐
Atrial Fibrillation	Needs to be controlled	☐
Hypertension	Needs to be controlled	☐
Active Haematological or coagulation issues	To be reviewed by Haematologist	☐
Diabetes	Needs to be reviewed and controlled	☐
Smoking Cessation	Needs to be actioned	☐
Excess Alcohol Consumption	Needs to be reviewed and controlled	☐
Incidental finding on scans	Requires clarification	☐
Medications		
Cytotoxic/Chemotherapy	Wait 4-6 weeks before surgery	☐
Antiplatelet	Do not stop without date and surgical input	☐
Anticoagulation	Inform team but no further action	☐

This checklist is for internal use only. It is not an exhaustive list and should be based upon clinical judgement.

Appendix 10

Staging Cards

Please click on the below PDF document to access:

Staging cards.pdf

https://thorax.bmj.com/content/thoraxjnl/56/2/89.full.pdf

Appendix 11

"Routine post-Surgery Follow-up"

Authors: J Thekkudan, M Purohit

Consensus Follow-up plan for Lancashire and South Cumbria region:

Time since surgery	Investigation
1st year	
~ 4 weeks	CXR
3 months	CXR
6 months	CT scan[1]
9 months	CXR
12 months	CT scan[1]
2nd year	
18 months	CT scan[1]
24 months	CT scan[1]
3rd year	CT scan[1]
4th year	CT scan[1]
5th year	CT scan[1]

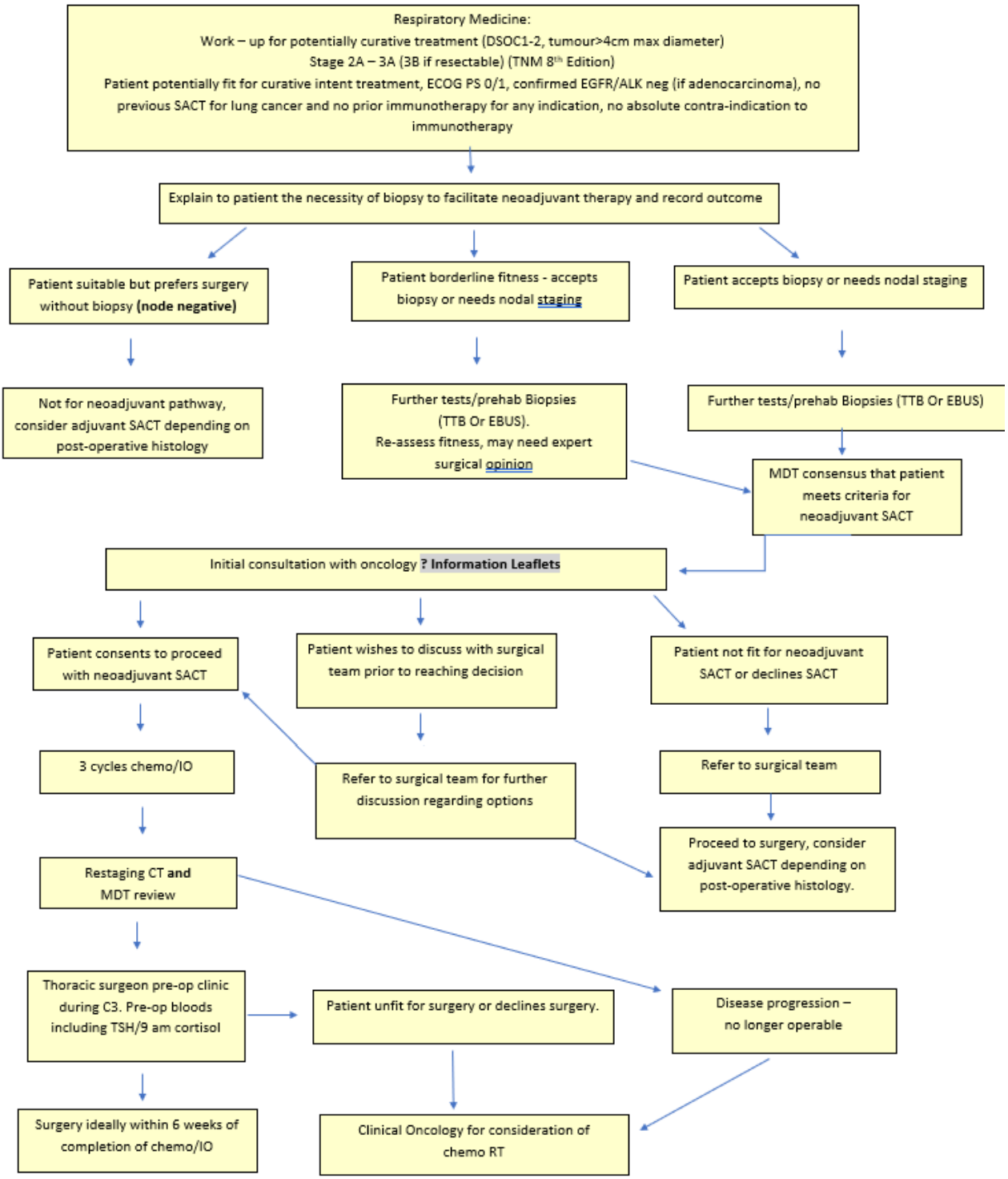
1. CT scan[1] = contrast CT chest/upper abdomen (including adrenals)

Discharge if no signs of recurrence at 5 years

Patient advice to contact if signs/symptoms of recurrence

V1.0 January 2022

Neoadjuvant Treatment for Lung Cancer Pathway



Issued:
Review Date:

Cardiovascular Fitness Guidance

1.5 Assessing people with non-small-cell lung cancer for treatment with curative intent

Cardiovascular function

1.5.2 Avoid surgery within 30 days of myocardial infarction. [2011]

1.5.3 Seek a cardiology review in people with an active cardiac condition, or 3 or more

Lung cancer: diagnosis and management (NG122)

Page 15 of 51

risk factors, or poor cardiac functional capacity. [2011]

1.5.4 Offer surgery without further investigations to people with 2 or fewer risk factors and good cardiac functional capacity. [2011]

1.5.5 Optimise any primary cardiac treatment and begin secondary prophylaxis for coronary disease as soon as possible. [2011]

1.5.6 Continue anti-ischaemic treatment in the perioperative period, including aspirin, statins and beta-blockers. [2011]

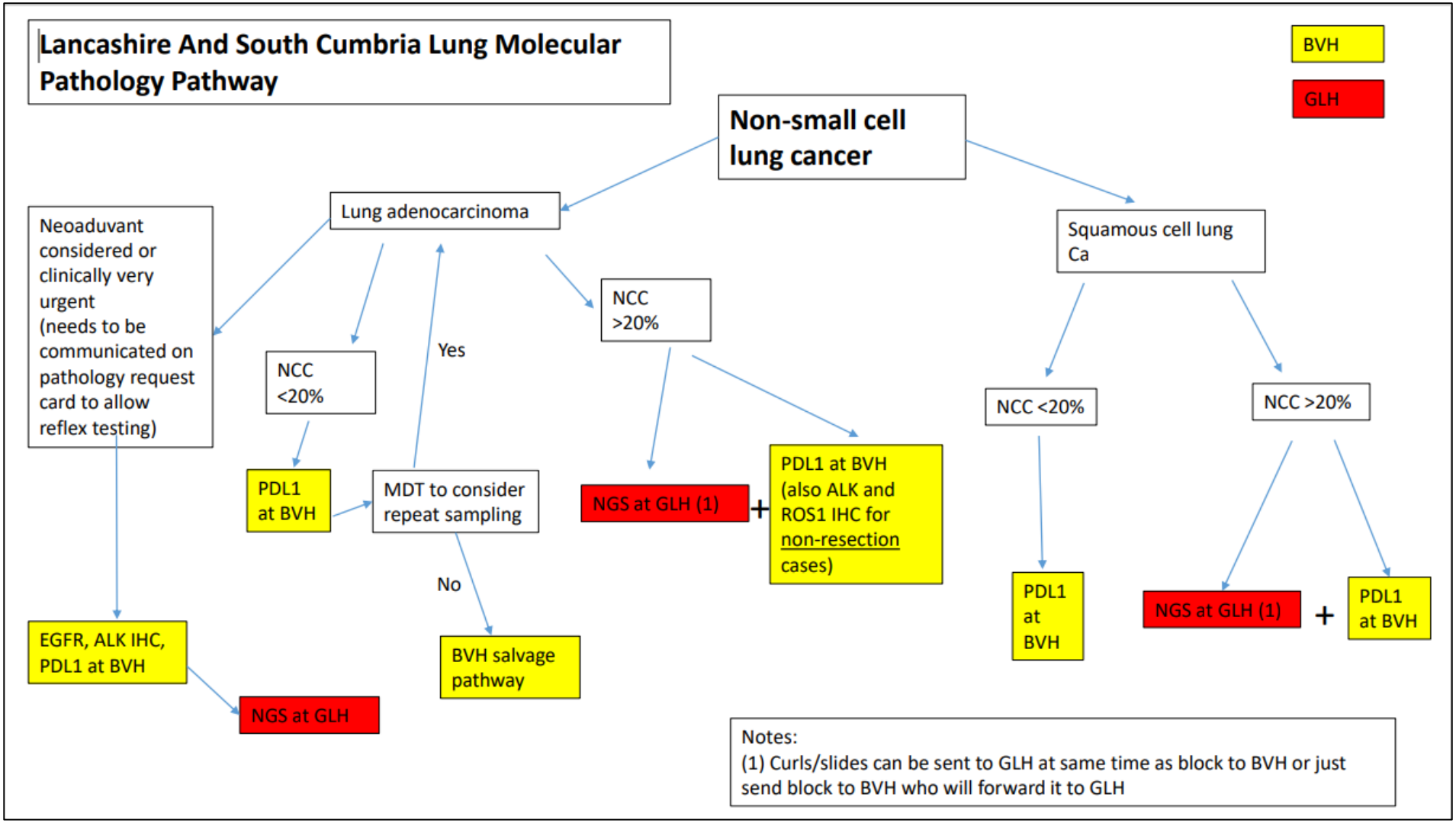
1.5.7 For people with coronary stents, discuss perioperative anti-platelet treatment with a cardiologist. [2011]

1.5.8 Consider revascularisation (percutaneous intervention or coronary artery bypass grafting) before surgery for people with chronic stable angina and conventional indications for revascularisation. [2011]

The Links
2.1.2. Risk assessment for cardiovascular morbidity Clinical assessment and risk stratification
BTS Guidelines on the Radical Management of Patients with Lung Cancer.pdf

1.5 Assessing people with non-small-cell lung cancer for treatment with curative intent
Lung cancer: diagnosis and management

Appendix 14


Lancashire And South Cumbria Lung Molecular Pathology Pathway
BVH
GLH
Non-small cell lung cancer
Lung adenocarcinoma
Squamous cell lung Ca
Neoaduvant considered or clinically very urgent (needs to be communicated on pathology request card to allow reflex testing)
NCC <20%
NCC >20%
Yes
PDL1 at BVH
MDT to consider repeat sampling
NGS at GLH (1)
+
PDL1 at BVH (also ALK and ROS1 IHC for non-resection cases)
NCC <20%
NCC >20%
PDL1 at BVH
NGS at GLH (1)
+
PDL1 at BVH
No
EGFR, ALK IHC, PDL1 at BVH
BVH salvage pathway
NGS at GLH
Notes:
(1) Curls/slides can be sent to GLH at same time as block to BVH or just send block to BVH who will forward it to GLH

NHS
North West
NHS Genomic Laboratory Hub

Lung Circulating Tumour test FAQ Document

This document covers frequently asked questions for the ctDNA test available for radiologically suspected stage 3 / 4 lung cancer patients in England.

Contents

1. Ordering and Receiving Blood Collection Kits

- **How do we order the Blood Collection Kits (BCK)?**
    - NHS Trusts will need to complete a BCK Order Form (found within the document pack provided), detailing the number of kits required and where the kits need to be sent, including a contact name.

- **What is the minimum and maximum number of kits we can order at one time?**
    - A minimum of 10 kits per order and a maximum of 50.

- **How long does it take for the kits to be delivered after placing an order?**
    - Please allow 3 working days for the kits to arrive.

- **Who should we contact for issues related to kit orders?**
    - mft.northwest.ctdna@nhs.net

2. Test Patient Eligibility Criteria

- **What is the exact eligibility criteria for patients to participate in this pilot?**
    - Patients with a radiologically suspected stage III/IV Lung cancer, likely unsuitable for curative intent surgery or radical radiotherapy and an ECOG PS 0-3.
    - Additionally, patients with a confirmed new histological diagnosis of NSCLC, previously untreated for advanced disease where diagnostic molecular testing has failed, and an alternative option would be to re-biopsy.
- **Are there any additional clinical criteria beyond that can be considered for testing patients?**
    - Within the current commissioned service provision there is no further eligibility criteria that can be considered however, we will notify all Trusts if criteria changes.
    -
- **Is written patient consent required for the test?**
    - There is no signed consent required from the patient. Informed consent is taken following a verbal explanation of the test.

- **When should bloods be taken?**
    - Ideally the blood draw should be done at the earliest opportunity, normally this is in the patients first outpatient consultation. This ensures the test report is ready for timely treatment decisions and can be discussed at your local Genomic Tumour Advisory Board (GTAB).
    - Blood samples should arrive in the laboratory within 7 days of venepuncture. Blood samples taken on a Friday should be posted on the day, using the Royal Mail pre-paid blood collection kit, to ensure samples arrive in the laboratory Monday/Tuesday the following week.
    -

3. Blood Collection Protocol

- **Where can we find detailed instructions for blood collection and handling?**
    - Please refer to the ‘Instructions for Use’ document within the document pack provided.

- **Who do we contact if there are issues or questions regarding blood collection procedures?**
    - mft.northwest.ctdna@nhs.net

- **How should the blood samples be packaged and labelled before shipping?**
    - Please refer to the ‘Instructions for Use’ document within the document pack provided.

4. Test Requisition Form

- **What specific information is required on the test requisition form?**
    - Please refer to section 5 of the ‘Standard Operating Procedure’ document provided within the document pack.

- **Are there any mandatory fields that must be completed on the form?**
    - Please note mandatory fields are:
        - DOB

- Sex
- Has the patient had any type of transplant
- If yes, please state type(s)
- Sample collection date (dd/mm/yyyy)
- Suspected lung cancer
- Stage

- **Who should we contact if there is missing or unclear information on the form?**
  - mft.northwest.ctdna@nhs.net

5. Shipping

- **What are the shipping requirements for the blood samples?**
  - Please refer to section 5 of the 'Standard Operating Procedure' document provided within the document pack.
- **How should the samples be packaged to ensure compliance and safety?**
  - Please refer to the 'Instructions for Use' document within the document pack provided.
- **How do we track the shipment of the samples?**
  - Record locally the Royal Mail Tracking number on the postage label to enable tracking during transit.

- **What should we do if the samples do not arrive at the NW GLH within the specified time frame?**
  - The BCK should arrive within 48 hours using the pre-paid Royal Mail Track24 service. Please send samples as soon as they are taken. Samples must arrive in the lab within 7 days of venepuncture, to ensure the sample integrity meets the requirements for processing.

6. Results and Turnaround Time

- **How will the test results be communicated to us?**
  - Results will be sent securely to the emails provided on the test request form via NHS.net or hospital email (.nhs.uk).

- **What is the typical turnaround time for receiving the results?**
  - Results are usually available within 14 calendar days of the sample being received at the laboratory.

- **Who will receive the results?**
  - The referring clinician/department
  - The regional GLH hub
  - Lead oncologist

  Names that are provided on the test request form.

- **Where should the results be stored?**
    - Results need to be incorporated into Trusts electronic patient record (EPR) alongside other molecular results received by the Genomic Laboratory Hub (GLH) and made available to the clinical and pathology teams.

- **What should we do if there is a delay, or we do not receive the results within the expected time frame?**

    - Reach out to mft.northwest.ctdna@nhs.net, if you have any concerns.

- **Who should determine if a result is informative or not?**
    - It's recommended that all results are either reviewed by your local GTAB or a lung oncologist colleague experienced in the interpretation of ctDNA results. This will help inform the answers to whether the result is informative and the level of confidence.

7. General Queries

- **Can the SOP be customized for local use, and if so, to what extent?**

    - The 'Standard Operating Procedure' document is not to be altered locally and should only be updated by the NW GLH team.

- **What additional support or resources are available to assist us with this pilot?**

    - Test kits will be provided to your Trust upon request. The pilot team will also provide you with a package of documents providing you with the information required. If you require any further support, please reach out to mft.northwest.ctdna@nhs.net for requests.

- **How can we provide feedback or report issues encountered during the pilot phase?**

    - Please reach out to mft.northwest.ctdna@nhs.net, with any feedback or issues.

- **What is the cost of the test?**
    - Up to 10,000 tests have been commissioned by NHS England for Trusts across England for 24/25. Therefore, no individual cost per test will be incurred by a requesting Trust.

8. Contact Information

- **Is there a specific contact person or department for different types of queries (e.g., kit orders, test requisition forms, shipping issues)?**

    - Please refer to the 'Standard Operating Procedure' document provided within the document pack, for this information.
- **Are there any alternative methods of contact besides email for urgent inquiries?**

    - Our pilot team email address (mft.northwest.ctdna@nhs.net), is the only route for contact currently. However, we will be sure to let you know if any alternate forms of contact are made available.