Management of Early-Stage Resected Non-Small Cell Lung Cancer: Consensus Statement of the Lung cancer Consortium

Ahmed Allehebi (Oncology Department King Faisal Specialist Hospital & Research Center – Jeddah, Saudi Arabia),
Khaled Al Kattan (Dean College of Medicine, Al Faisal University, King Faisal Specialist Hospital & Research Center – Riyadh, Saudi Arabia)
Mashael Al Rujaib (Radiology Department, King Faisal Specialist Hospital & Research Center – Riyadh, Saudi Arabia)
Fouad Al Dayel (Pathology Department, King Faisal Specialist Hospital & Research Center – Riyadh, Saudi Arabia)
Edward Black (Thoracic surgery, SSMC-Mayo Partnership, Khalifa University, UAE)
Mervat Mahrous (Oncology Department, Prince Sultan Military Medical City, Riyadh)
Muath AlNassar (Oncology Department, Kuwait Cancer Control Center)
Hamed Al Hussaini (Oncology Department King Faisal Specialist Hospital & Research Center – Riyadh, Saudi Arabia)
Abdullah Al Twairgi (Oncology department, King Fahad Medical City, Riyadh)
Nafisa Abdelhafeiz (Oncology Department, King Abdulaziz Medical City, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia)
Ameen Al Omair (Radiation oncology, King Faisal Specialist Hospital & Research Center – Riyadh, Saudi Arabia)
Salem Al Shehri (Radiation Oncology, King Abdulaziz Medical City,
King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia)
Humaid O. Al-Shamsi (Department of Oncology and Innovation and Research Center, Burjeel cancer institute Abu Dhabi, College of Oncology Society – Dubai, College of Medicine, University of Sharjah, UAE)
Abdul Rahman Jazieh (College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, Cincinnati Cancer Advisors, Cincinnati, OH, USA)

Corresponding Author:

Ahmed Allehebi, M.B.B.S
King Faisal Specialist Hospital & Research Center
Jeddah, Saudi Arabia
Ahmed.aonl@gmail.com

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Abstract

Background
Management of early-stage non-small cell lung cancer (ES-NSCLC) has evolved over the last few years especially in terms of work-up and the use of systemic therapy. This consensus statement was developed to present updated guidelines for the management of this disease.

Methods
Multidisciplinary team (MDT) of lung cancer experts convened to discuss a set of pertinent questions with importance relevance to the management of ES-NSCLC. ES-NSCLC includes stages I, II and resected stage III. The experts included consultants in chest imaging, thoracic surgery, radiation oncology, and medical oncology. Questions were discussed in virtual meetings and then a written manuscript with supporting evidence was drafted, reviewed, and approved by the team members.

Results
The Consensus Statement included 9 questions addressing work-up and management of ES-NSCLC. Background information and literature review were presented for each question followed by specific recommendations to address the questions by oncology providers. The Statement was endorsed by various oncology societies in the Gulf region.

Conclusion:
The Consensus Statement serves as a guide for thoracic MDT members in the management of ES-NSCLC. Adaptation of these to the local setting is dictated usually by available resources and expertise, however, all efforts should be excreted to provide the optimal care to all patients whenever possible.

1. Introduction

A small percentage of lung cancers are upfront-resectable, of which stage I comprises around 26% and stage II around 9%***(1).*** The main modality of treatment for early-stage non-small cell lung cancer (ES-NSCLC) is surgery and over the past few decades, the main post-operative treatment strategy is adjuvant chemotherapy. It is well known that adjuvant chemotherapy is mainly indicated for stage IIA (formerly Stage IB) ***(2)*** and beyond with certain indications for systemic chemotherapy in stage IIA. The most important indications being tumor size >4 cm ***(3,4)***. Stage III NSCLC constitutes a heterogenous group of diseases where different treatment modalities should be considered using a multidisciplinary team (MDT) approach ***(5)***, however, when upfront surgery is done for stage III NSCLC then adjuvant chemotherapy should be considered here as well ***(3,4)***. The overall benefit of adjuvant chemotherapy would be around 5% only for stages II and III ***(3).*** However, despite the use of chemotherapy the risk of disease recurrence or death ranges from 45% to 76% in stages I and III respectively ***(3).*** It is worth noting that the main site of disease recurrence is the brain, almost 40% ***(6)***

In a certain subtype of NSCLC, mainly adenocarcinoma, there are well-recognized cancer driver mutations that can be targeted and treated effectively in the metastatic setting with the use of various Tyrosine Kinase Inhibitors (TKIs), most notably Osimertinib, which are effective in the metastatic setting on NSCLC (adenocarcinoma) with significant improvement in overall survival (OS) ***(7).*** However, the main genetic mutations that confer response to Epidermal Growth Factor receptors (EGFR) include Exon 19 deletions (EX19del) and Exon 21 Leu858Arg point insertion (***7).***

Recently, new evidence is arising from the use of the adjuvant TKI (Osimertinib) in the setting of upfront-resectable NSCLC; stages IIA (formerly IB), II and IIIA where the previously mentioned EGFR mutations are associated with significant Disease-Free Survival benefit (8).

Due to the recent advances in the management of this disease, a need arose to have a guiding statement to help incorporate these advances into practice.

2. Methods:

A multidisciplinary team was formed with the following specialties to develop these consensus guidelines: pulmonary medicine, imaging, thoracic surgery, radiation oncology and medical oncology. The team listed the most pertinent issues that impacted the management of ES-NSCLC recently and phrased them in questions format. Once the final list of questions is finalized, the team members reviewed the most updated guidelines for each discipline and extracted the following recommendations related to the ES-NSCLC). The team had reviewed the literature included international guidelines accordingly (9,10)
Multiple meetings were held with the group members to discuss the recommendations. The manuscript has been generated and approved by all the group members to ensure final feedback was included in each discipline with the final version of the guidelines being approved by the whole team.

The MD experts in the panel used the following evidence level to grade their recommendations

Evidence levels

The following evidence levels (EL) were adopted for the consensus recommendations:

- (EL-1) High Level: well, conducted phase III randomized studies or well-done meta-analyses.
- (EL-2) Intermediate Level: good phase II data or phase III trials with limitations.
- (EL-3) Low Level: observational or retrospectives studies or expert opinions.

Consensus Statement and Recommendations

3. Recommendations:

3.1 Patient assessment

3.1.1 Initial patient assessment:

1 Each patient should undergo a history and physical examination. Document smoking history, performance status, weight loss and other comorbidities.
2 The following laboratory work should be done: Complete Blood count with differentials, liver function tests, renal function tests, electrolytes, calcium, serum albumin, magnesium and phosphorus.
3 Two-view chest x-ray (EL3). Contrast enhanced CT (Computed tomography) scan of the chest (EL1)

3.1.2. Diagnosis

1 Obtain adequate tissue specimen for diagnostic markers. (EL-1)
2 A multi-disciplinary team (MDT) approach is recommended for the work up and staging according to the availability and expertise (EL-2)
3 Procedure risk and possible treatment options should be taken into consideration before deciding on the best procedure / biopsy site to pursue.
4 The preferred initial site for biopsy is the one that could simultaneously lead to the exact underlying pathology and the highest stage of the disease.
5 Minimally invasive procedures including bronchoscopy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endobronchial ultrasound-guided fine needle aspiration (EUS-FNA), and transthoracic needle biopsy (TTNB) carry lower risk for major complications and are preferred (Muthu *et al.*, 2019) over more invasive procedures. (EL-2)

Question I.

What are the required imaging studies to determine lung cancer stage and resectability?

The role of imaging is indispensable in early detection, diagnosis and staging of lung cancer. Computed tomography (CT) of the chest is the recommended modality of choice for staging lung cancer and to determine its resectability. The use of low-dose CT without contrast to screen for lung cancer has been increasing, with increasing detection of pre-cancerous lesions such as atypical adenomatous hyperplasia (AAH) and non-invasive carcinomas presenting as ground glass nodules or minimally carcinomas presenting with part-solid nodules where the slid component is smaller than 5 mm. However, when a lung nodule is suspected of being lung cancer with a solid component that is 5 mm or larger, CT chest with contrast would be considered more appropriate than CT chest without contrast for staging.

3.1.3 Staging

It is very critical to determine the exact staging of the disease especially in case of stage IIIA NSCLC.

3.1.3.1 Imaging studies:

1. CT chest (from thoracic inlet till upper abdomen) with IV contrast is more appropriate than CT chest without IV contrast. 11
    a. FDG/PET CT:
    All patients should have FDG-PET/CT (from skull base to mid-thigh).
2. Multiphase abdomen CT with IV contrast is recommended only in the absence of FDG PET/ CT, or in the presence of clinical signs or symptoms referable to the abdomen. 12-17
3. Brain imaging
    i. Head MRI without and with IV contrast is usually appropriate in any patient with clinical stage II, III, or IV NSCLC, even in the absence of neurologic symptoms. 18, 19 (table 1)
    ii. Head MRI without and with IV contrast is optional in patients with clinical stage IB NSCLC without neurologic symptoms. 20, 21
    iii. Head MRI without and with IV contrast is recommended in all NSCLC patients exhibiting neurologic symptoms, regardless of stage. 21
    iv. CT of head without and with IV contrast is appropriate to detect brain metastasis if MR brain is not performed or in the presence of neurologic symptoms/ clinical signs. 18
4. Other imaging studies
    i. Respiratory dynamic (RD) MR of the chest is recommended when invasion of the chest wall and or diaphragm is equivocal on CT chest with contrast. 22

ii. MR of the superior sulcus is recommended in the presence of neurologic symptoms/ signs referable to the brachial plexus or when invasion of the brachial plexus/ vertebrae is suspected on CT chest.22-25
iii. CINE MR of the chest/ heart is recommended when invasion of the cardiovascular structures is equivocal on CT chest with contrast.26
iv. Chemical shift MR of the adrenal glands is appropriate when adrenal lesion/s remain equivocal following CT and FDG/PET (if performed). 27
v. Bone scan may be appropriate to detect bone metastasis in the absence of FDG/PET CT. 28

Table 1
Subtypes of localized / early-stage NSCLC (as per AJCC 8th edition)

Overall stage	TNM subtype	Description
Stage IB	T2a N0 M0	Tumor >3 cm but ≤4 cm in greatest dimension
Stage IIA	T2b N0 M0	Tumor >4 cm but ≤5 cm in greatest dimension
Stage IIB	T1a to c N1 M0	T1a; Tumor ≤1cm in greatest dimension T1b; Tumor <1 but ≤2 cm in greatest dimension T1c; Tumor >2 but ≤3 cm in greatest dimension N1; Metastasis in ipsilateral peribranchial and/or ipsilateral hilar LNs and intrapulmonary nodes including involvement by direct extension
	T2a N1 M0 T2 any tumor >3 cm but ≤5 cm with any of the following: ▪ Involves main bronchus regardless of distance from the carina but without involvement of the carina ▪ Invades visceral pleura ▪ Associated with atelectasis or obstructive pneumonitis that extends to the hilar	T2a: Tumor >3 cm but ≤4 cm in greatest dimension N1; Metastasis in ipsilateral peribranchial and/or ipsilateral hilar LNs and intrapulmonary nodes including involvement by direct extension

	region, involving part or all of the lung	
	T2b N1 M0	T2b: Tumor >4 cm but ≤5 cm in greatest dimension N1; Metastasis in ipsilateral peribranchial and/or ipsilateral hilar LNs and intrapulmonary nodes including involvement by direct extension
	T3 N0 M0	T3; Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest well (including parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium.
Stage IIIA	T1a to c N2 M0	T1a; Tumor ≤1cm in greatest dimension T1b; Tumor <1 but ≤2 cm in greatest dimension T1c; Tumor >2 but ≤3 cm in greatest dimension N2; Metastasis in ipsilateral mediastinal and/or subcarinal LNs
	T2a to b N2 M0	T2a: Tumor >3 cm but ≤4cm in greatest dimension T2b: Tumor >4 cm but ≤5 cm in greatest dimension N2; Metastasis in ipsilateral mediastinal and/or subcarinal LNs
	T3 N1 M0	>5 - 7 cm parietal pleura or pericardium, chest wall, phrenic nerve, or separate nodule in the same lobe & ipsilateral peribronchial and/or hilar or intrapulmonary LN
	T4 N0 M0	>7 cm invading mediastinum, heart, vertebra, diaphragm, esophagus, carina and ipsilateral separate nodule in different lobe No LN
	T4 N1 M0	>7 cm, invading mediastinum, heart, vertebra, diaphragm, esophagus, carina and ipsilateral separate nodule in different lobe Ipsilateral peribronchial and/or hilar or intrapulmonary LN

Question II:
What is the required pathologic work-up of lung cancer?

Deciding the best diagnostic tool for early lung cancer is best determined by a multidisciplinary lung cancer team. The goal is to select the least invasive diagnostic tool with high tissue yield.

3.2.1 Pathologic work up:

1 Obtain adequate tissue specimen for diagnostic and molecular predictive markers. Tissue management plan by pathologist is important.

2 Confirm histopathological diagnosis of lung cancer and determine the histological subtypes of non-small cell lung cancer i.e. adenocarcinoma vs squamous cell carcinoma vs. large cell carcinoma using most recent WHO classification of lung cancer (WHO 2021).

3 Utilization of proper immunohistochemistry staining (panel includes CK 5/6, CK 7, CK 20, TTF 1, P63, P40, Napsin A) to minimize the diagnosis of lung cancer not- otherwise-specified (NOS). One marker for adenocarcinoma (TTF 1, Napsin A) and one marker for squamous cell carcinoma (P60, P40) can be sufficient for classification.

4 Significant limitation in molecular testing is tissue adequacy. Reflex slide sectioning for diagnostic and predictive markers is one way to maximize tissue utilization.

5 The ADAURA Trial is shifting the molecular testing of lung cancer from advanced/metastatic to early-stage lung cancer.

6 To maximize molecular profiling of early lung cancer, it is advised to utilize next generation sequencing (NGS) panels to test for multiple genes. It is also good to consider RNA-based NGS to maximize detection of fusion mutations.

7 For early lung cancer, if NGS is not available, the most important predictive marker to test is EGFR mutations using real-time PCR or Sanger sequencing techniques. Both techniques are focused assays with faster TAT than NGS. (29,30,31)

- Testing can be performed on diagnostic biopsy or resected specimen.
- Exon 19 deletions and L858R point mutation in exon 21 are the most common mutations. Both respond to EGFR TKI therapy.

3.2.2 Mediastinal staging:

1. Endosonographic FNA (fine needle aspiration) is the preferred modality for mediastinal sampling since it is minimally invasive requiring only moderate conscious sedation.
2. EBUS-TBNA is the preferred first-step procedure for sampling suspected nodal metastases in the lung, hilum and mediastinum
3. Combination of EBUS/EUS, if available, increases the sensitivity and may decrease the frequency of unnecessary surgical procedures.
4. The lymph node of the highest stage should be biopsied first i.e. N3 followed by N2 and then N1 to prevent falsely upstaging the tumor.
5. Representative lymph node aspirate containing adequate numbers of lymphocytes does not always exclude metastases.
6. Perform staging cervical mediastinoscopy for negative EBUS/EUS if high suspicion of mediastinal node involvement i.e. N2/N3 on imaging.
7. VATS (video-assisted thoracoscopic surgery) is preferred for sampling aortopulmonary lymph nodes.
8. Determine precise TNM staging using 8th edition.

Question III
How to determine if patient is operable or not, resectable or not?

3.3.1 Assessment of resectability:

Surgery for lung cancer should be performed by surgeons who perform lung cancer surgery as the prominent part of their practice and who participate regularly in the lung MDT. (32)

Prior to surgery the surgeon must ensure adequate physiological assessment to confirm that the patient has the capacity to recover to an acceptable performance status afterwards for their activities of daily living and for completion of therapy if multimodal therapy is (likely) required. Surgery should not prevent a patient from completing adjuvant therapy.

Scans used for the preoperative anatomical planning must be less than 60 days old at the time of surgery. Planning should be for an oncological resection. There is very little role for non-anatomical or wedge resections due to the high rates of local recurrence and reduced survival compared to anatomical/ oncological resections.

Oncological operations require lymphadenectomy or systematic sampling to include intra-lobar, inter-lobar, hilar and mediastinal lymph nodes. (33) A minimum of three mediastinal lymph-node zones must be harvested. (34) Survival is related to the lymph-node stage and the ratio of lymph-nodes with metastases to the total number of lymph-nodes removed. (35) The tumor must be microscopically free from the resection margins. For small non-palpable lesions that do not easily fall within segmental anatomy consider peri-operative marking (coils, dye, isotope etc). (36)

In order to provide oncological operations adequately the type of the incision or approach (uniportal/multiportal VATS for example) must not compromise the resection. Therefore, if it appears that the lymph-nodes will be difficult to remove by video-assisted thoracoscopic surgery (VATS) then early elective conversion to an open thoracotomy is preferable. Muscle sparing approaches and muscle flap harvesting (for pneumonectomy) must all be considered.

For patients with early-stage disease, a VATS lobectomy is usually the preferred operation. It reduces post-operative pain and complications and facilitates completion of adjuvant therapy. (35) It must include complete resection of the tumor and the lymph-nodes, all individually labelled as per the IASLC lymph-node map. (36)

For most patients a lobectomy will be the preferred resection. Even for large or central tumors a sleeve resection is preferred over pneumonectomy. Sub-lobar resections may preserve physiological performance and can provide an equivalent oncological result to lobectomy. In order for segmental resections to provide this level of benefit the tumor must be peripheral, have clear segmental margins > the diameter of the tumor, the tumor be <2 cm in size, preferably of ground glass or part solid on the CT scan and if available confirmed to have <5% micro-papillary histology. (32,39) Adjuncts such as marking and 3D-planning are useful perioperative tools.

For tumors invading the chest wall an en-bloc resection is required. For large central tumors, if surgery is uncertain consider an opinion from an experienced surgical center. The role neo-adjuvant therapy is discussed below.

When a single excisable mediastinal node/zone is identified incidentally intraoperatively then continue with the surgery provided that no more than a lobectomy will be required to achieve complete resection. Otherwise close the patient and refer for neo-adjuvant therapy before restaging prior to resection. (40)

Pathology results must be discussed in the lung MDT.

Question IV
What are the indications of surgical resection in stage III NSCLC?

Stage III NSCLC represents a wide range of different T and N stages where surgical resection varies between resectable with curative intension and un-resectable.
Accordingly, there are difficulties in standardizing the surgical management of these patients and they represent a variable survival outcome (12%-41%) (Table-1) [48,51]
The surgeon decision should be supported by the Multidisciplinary Tumor Board (MTB) and accurate radiological and pathological staging including mediastinal LN is essential [51].
N2 sampling versus lymphadenectomy remains controversial and it is usually dictated by the surgeon training and experience [51]
In terms of operation type, sleeve resection is preferred, if possible, to reserve lung function (52)
Finally, minimally invasive approach showed better post-operative recovery and may have oncological advantages (52,53)

Stage III includes 3 subgroups of A, B and C.

3.4.1 Surgical indications of stage IIIA:

i T3N1M0:

1. These cases should be planned for curative resection (T 5-7 cm) with attention being paid to dissecting out the N1 stations completely and N2 sampling.
2. For cases with T3 invasion like chest wall invasion, en bloc resection with lymph node clearance and chest wall reconstruction when necessary is advised (55,56,57).
3. Complete resection of the ribs involved with a rib above and a rib below is preferable

ii T4 N0 M0 and T4 N1 M0:

1 In cases that T4 is related to **size (>7 cm)**, resection should be planned with clear margins. That may include pneumonectomy after confirming that N2 stations are negative (56).

2. In cases that T4 is related to **Ipsilateral metastatic nodule in another lobe**: In these cases, resection should occur for the primary tumor with the addition of a sub-lobar resection to the metastatic nodule (56). If pneumonectomy is indicated, it can be performed in the absence of N2 disease, in selected cases and use of radiofrequency ablation may be considered for the metastatic nodule.
3. In cases that T4 is related to **invasion**: These include a variety of anatomical structures, the least technically challenging being the diaphragm. In this situation, resection is advised if margins are negative, preferably en bloc, and reconstruction of the diaphragm (57,58). For other anatomical structures such as vertebra and mediastinal vessels. *Most of these cases*

are deemed inoperable after thorough nodal staging, however. A few case series have been reported in highly selected patients showing a survival benefit (21,27,28). These cases may require neoadjuvant therapy followed by thorough workup and assessment to ensure that if surgical resection is offered should be curative [59,60].

4 In cases that T4 carina (anatomical location) should also be assessed for curative carinal resection with or without neoadjuvant therapy.

iii **T1-T2 N2 M0:**

1 In general, surgery for N2 disease with curative intent is not provided unless there is only clinically staged limited nodal disease.
2 Neoadjuvant concurrent chemoradiation should be considered as definitive therapy for clinically and bulky N2(61).
3 If the patient was successfully down-staged, surgical resection should be reconsidered if pneumonectomy is unlikely to be indicated(62).
4 Patients with persistent large (>3 cm) N2, or patients with tumor extending to multi-station N2 disease should not undergo surgery (63,64,65).
5 Occult N2 disease that is discovered intraoperatively **(or occult N2 that is positive on frozen section)** should undergo the planned operation (avoiding pneumonectomy if possible) and follow through with adjuvant chemo/radiotherapy after recovery.
6 Patients with bulky unresectable N2, or patients with multi-station N2 disease should not undergo surgery (65). Patients should go for neo adjuvant therapy and surgical resection is offered for those with down staging (rare and selective high-performance patients)
7 Regarding the use of ***Neoadjuvant therapy*** prior to surgery for Stage III lung cancer with N2 disease:

7.1 Multiple studies with differing regimes have shown a benefit for neoadjuvant chemo- or chemoradiotherapy (preferred) prior to surgical resection for stage III lung cancer. (66,67).

7.2 In advanced centers full does of radiotherapy should be administrated to maximize the benefit even if he is likely to be proceeded with surgery) (68).

7.3 The timing of surgery post neoadjuvant chemotherapy is generally 4-6 weeks after the last dose of chemotherapy. However, the timing of radiotherapy prior to surgery is quite controversial and is subject to logistic constraints and clearly increases the risk of intra and post-operative events

as well as the technical difficulty of the surgery. We recommend 4-6 weeks after last does of Radiotherapy (69).

8 Patients should be ***restaged*** after completing neoadjuvant therapy with PET-CT and consider re-biopsy of their mediastinal lymph nodes. This can be done by EBUS, Mediastinoscopy, VATS or prior to resection. Patients that demonstrate radiological and pathological downstaging after neoadjuvant therapy have the best survival benefit(70,71,72).

9 Pneumonectomy for resectable single station N2 disease after neoadjuvant therapy has been shown in early data to be associated with a high operative mortality rate and is *generally not recommended*(73). New data is emerging showing survival benefit in selected cases(74). It is yet unclear what role pneumonectomy has for N2 disease after neoadjuvant therapy currently.

10 Targeted therapy is currently being indicated as post-operative therapy in selected cases and will be discussed in another section.

Question V
What is the role of neoadjuvant therapy?

The role of neoadjuvant or induction chemotherapy in non-metastatic NSCLC carries several theoretical advantages including locoregional cytoreduction, control of distant micrometastases, and a higher preoperative chemotherapy compliance compared with chemotherapy compliance after surgery. The main potential disadvantages were treatment-associated toxicities and a delay in the surgical procedure, and cases may turn unresectable after being resectable although at present, these drawbacks are considered barely relevant (81).

The Spanish Lung Cancer Group led the NATCH (Neo-adjuvant Versus Adjuvant Taxol/Carbo Hope)(82) trial which included 624 patients with stages IA (size >2 cm), IB, II, T3N1 NSCLC. Although a trend for improved 5-year disease-free survival rates with neoadjuvant therapy was observed (38.3% with neoadjuvant chemotherapy, 36.6% with adjuvant chemotherapy, and 34.1% with surgery alone), there were no statistical differences ($p = 0.71$) among the three arms; it is noteworthy that the majority of patients had stage I disease. In this trial, in the subgroup of patients with stage II-T3N1, the 5-year disease-free survival rates favored the neoadjuvant arm (36.6% in the neoadjuvant group, 31% in the adjuvant arm, and 25% in the surgery group).

The CHEST (Chemotherapy for Early Stages Trial) (83) has reported surprisingly different findings. A significant advantage for induction chemotherapy was found with regard to progression-free survival (HR 0.70, $p = 0.003$) and overall survival (HR 0.63, $p = 0.02$). The study was positive in its primary end point (progression-free survival). However, the benefit of induction chemotherapy in progression-free survival was limited only to the subgroup of patients with stages IIB or IIIA disease (and the majority, 92%, were IIB).

Meta-analyses from data of randomized trials addressing the role of neoadjuvant chemotherapy in early-stage NSCLC are of interest. Berghmans *et al*. (84) reported data from six randomized

trials, published between 1990 and 2003, including 590 patients. The addition of neoadjuvant chemotherapy to surgery was associated with a non-significant improvement in overall survival (HR 0.65, CI, 0.41-1.04).

CheckMate 816 study (85) which is a Phase III study was presented at ASCO 2021 by Jonathan Spicer. The study included 358 pts and were randomized to Nivolumab + chemotherapy versus chemotherapy alone as induction therapy followed by surgery within six weeks followed by adjuvant therapy. The study met the primary end point as pCR ($p < 0.0001$) and resulted in more minimally invasive surgery and fewer pneumonectomies. Although the study and data are not mature to draw final conclusions, these findings are promising.

3.5.1 Role of neoadjuvant chemotherapy recommendations:

1 Current standard of care and the evidence are favoring upfront surgery followed by adjuvant therapy in stage Ib-IIIA.

2 Neo adjuvant chemotherapy can be used in more advanced disease (T3N1, and patients with multiple N1 regions and isn't feasible for surgery) and for those in whom may not be suitable candidate for adjuvant chemotherapy. Such decision should be made based on MDT discussion

3 Concurrent neoadjuvant chemotherapy and radiation also benefit patients with superior sulcus tumors that are T3 to T4 and N0 to N1, which are a special clinical type of NSCLC (86).

4 Overall, neoadjuvant approaches are less well studied than adjuvant strategies and the majority of neoadjuvant trials have closed early or have been small in size. The level of evidence is low. However, Further study and proof-of-concept data are needed.

Question VI
What are the indications of adjuvant chemotherapy?

For patients with completely resected stage II and IIIA disease, adjuvant chemotherapy using cisplatin-based regimen was associated with improved survival. This was demonstrated in the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis that included five largest trials with approximately 4600 patients with completely resected non-small cell lung cancer (NSCLC) (87). In median follow-up of 5.2 years, adjuvant cisplatin-based chemotherapy was associated with a significant decreased risk of death of 5.4 percent at 5 years compared with no chemotherapy (HR 0.89, 95% CI 0.82-0.96). Among patients with stage II and IIIA disease, the effect on survival reached statistical significance (for stage II HR 0.83, 95% CI 0.73-0.95, for stage IIIA HR 0.83, 95% CI 0.72-0.94). Adjuvant chemotherapy for patients with stage IA disease was associated with worsened survival (HR 1.40, 95% CI 0.95-2.06) (87). There was a nonsignificant trend toward

improved survival in patients with stage IB disease receiving adjuvant chemotherapy (HR 0.93, 95% CI 0.78-1.10). Adjuvant chemotherapy may be considered for high-risk stage IB disease, including tumor size >4 cm, lymphovascular invasion, visceral pleural involvement, high-grade tumor, and sub-lobar resection (88,89).

3.6.1 Recommendations on adjuvant chemotherapy:

3.6.1.1 Indications of adjuvant chemotherapy:

1. Adjuvant chemotherapy should be offered for patients with resected stage II and III NSCLC.
2. Adjuvant chemotherapy can be considered for patients with high-risk stage IB disease, including tumor size >4 cm, poor differentiation, visceral pleural invasion, lymphovascular invasion, and sublobar resection
3. For patients with stage IA disease, adjuvant chemotherapy is not recommended

3.6.1.2 Choice of adjuvant chemotherapy:

Cisplatin-based doublet chemotherapy should be used for patients receiving adjuvant therapy. This is based on data from LACE meta-analysis which demonstrated improved survival with cisplatin-based regimens (87).

The optimal cisplatin-based regimen has not been determined in randomized trials. For those with non-squamous histology, cisplatin can be paired with pemetrexed due to better tolerability (90,91). Cisplatin with vinorelbine, docetaxel, or gemcitabine is an appropriate option for patients with squamous histology. There was no benefit from adding bevacizumab to cisplatin-based regimens (92).

Carboplatin-based regimens can be used for patients with comorbidities such as baseline hearing loss or significant existing neuropathy or for those who cannot tolerate cisplatin-based doublet (89).

A multidisciplinary team meeting (MDT) should make the decision about adjuvant chemotherapy, taking into account pre-existing comorbidities, time from surgery and postoperative recovery.

The period between surgery and the start of chemotherapy was limited to 6 to 8 weeks in most studies; however, comparative outcome of patients treated after a longer interval post-resection has been documented.

In Randomized studies, the chemotherapy delivered for total of 4 cycles

1. Cisplatin-based doublet is preferred for patients receiving adjuvant chemotherapy.
2. Bevacizumab is not indicated in the adjuvant setting

3 Carboplatin-based regimens can be considered for patients with significant comorbidity or those who cannot tolerate cisplatin-based doublet
4 Adjuvant chemotherapy is given for total of 4 cycles and better to start within 8 weeks of surgery

Question VII
What is the role of TKIs in EGFRmut resected NSCLC?

The role of EGFR testing is well recognized in the setting of metastatic NSCLC (Adenocarcinoma) as it is considered as part of the routinely ordered molecular tests in such setting since it will confer a therapeutic option for these patients which has been confirmed in multiple studies that involve medications such as Osimertinib (93,94), Gefitinib (95), Erlotinib (96).

Based on the trials done in the metastatic setting, the use of EGFR TKI was tested in the resected NSCLC (adenocarcinoma) with positive EGFR mutation (97,98). In one trial Gefitinib was used (CTONG 1104)(5), where the EGFR status was tested after resection of the mass and based on the EGFR status the patients were randomized to either Gefitinib vs chemotherapy and this trial showed good disease free survival but no overall survival benefit(5). Also, there were other trials that were done in the same setting which did not yield to any significant overall survival benefit (98).

However, in reference to the previous studies that looked at the use of EGFR TKI in the adjuvant setting (97,99), a new study entertained the use of Osimertinib which is a potent EGFR TKI with high penetrance to the brain (99) which is a notorious site that represent a pattern of treatment failure in the adjuvant setting (99). The ADAUR trial (99) examined the efficacy of giving Osimertinib (whether after chemo or directly after surgery) in which Osimertinib was given to the patients who had positive EGFR mutation (ex19del or L858R) vs placebo and that trial showed significant benefit in terms of disease free survival in all resected stages (Stage IB – IIIA). It is worth noting that this trial was unblinded early secondary to the significant benefit that was shown in this trial (99). Hence, EGFR testing should be done in all resected NSCLC (adenocarcinoma) as there is the option the use of osimertinib as per the ADAURA trial (99).

3.7.1 Recommendations on Role of adjuvant Osimertinib

1 All resected stage IB-IIIA NSCLC should be tested for EGFR mutations (ex19del / L858R point mutation)
2 Osimertinib should be considered in all resected NSCLC (adenocarcinoma) with as follows:
i Resected (R0) NSCLC (Adenocarcinoma) in the following stages: stage IB, II, IIIA
ii Starting either;

a- 10 weeks after surgery without adjuvant chemo
b- 26 weeks after surgery with adjuvant chemo
iii Targetable mutations for adjuvant osimertinib are:
ex19del or L858R mutation
iv Osimertinib 80 mg po daily for 3 years

Question VIII

Is there a role for adjuvant radiation therapy?

The role of adjuvant radiotherapy is limited in early-stage NSCLC. Adjuvant radiotherapy is detrimental in completely resected early-stage NSCLC. (100) Postoperative external beam radiotherapy (EBRT) or brachytherapy (intraoperative radiotherapy) can be considered for limited resections in high-risk patients to improve local control. (101) In case of positive surgical margin post resection of early-stage lung cancer adjuvant radiotherapy should be considered if re-resection is not feasible, and target can be precisely identified. Adjuvant radiotherapy in this setting should provide feasibility, safety, ability to define the location of the margin considering patients overall health and respiratory status. Adjuvant radiotherapy is usually administered to bronchial stump and hilum. (102)

3.8.1 Recommendations on adjuvant radiation therapy:

1 Post-operative adjuvant radiotherapy is not recommended after complete resection of Stage I or II NSCLC.
2 Patients with positive bronchial resection margins, postoperative adjuvant radiotherapy will decrease the chance of local recurrence.

Question IX.
What are the management options of unresected early-stage NSCLC?

Surgery has been and continue to be the standard of care for patients with ES-NSCLC). For medically inoperable patient, the alternative local ablative therapy includes stereotactic body radiation therapy (SBRT) or thermal therapy for instance radiofrequency ablation (RFA) and cryoablation.

SBRT is a non-invasive method which considered the standard of care for medically inoperable ES-NSCLC (100). The introduction of SBRT has improved population-based survivals (101, 102). Local control rates were reported in prospective, multi-institutional studies to be more than 90% with minimum risk of severe toxicity (103, 104). An attempt to compare SBRT with surgery in patients with operable early-stage non-small-cell lung cancer was made in phase 3 randomized control trial, however, and unfortunately was aborted because of low accrual (105).

Thermal ablation is another alternative curative invasive method. Percutaneous RFA resulted in a 2-year local control rates of approximately 64% in smaller tumors i.e <3 cm with acceptable morbidity (106).
Thermal ablation including that using RFA is an appropriate alternative to SBRT when SBRT is not feasible.
However, the local tumor control rate (LCR) at 1, 2, 3, and 5 years for RFA was significantly lower than that for SBRT (107).

3.9.1 Recommendations on Management options of Unresected ES-NSCLC:

1 SBRT is a non-invasive method which considered the standard of care for medically inoperable ES-NSCLC (100). The introduction of SBRT has improved population-based survivals (101, 102). Local control rates were reported in prospective, multi-institutional studies to be more than 90% with minimum risk of severe toxicity (103, 104). An attempt to compare SBRT with surgery in patients with operable early-stage non-small-cell lung cancer was made in phase 3 randomized control trial, however, and unfortunately was aborted because of low accrual (105).

2 Thermal ablation is another alternative curative invasive method. Percutaneous RFA resulted in a 2-year local control rates of approximately 64% in smaller tumors i.e >3 cm with acceptable morbidity (106).

3 Thermal ablation including that using RFA is an appropriate alternative to SBRT when SBRT is not feasible.

4 However, the local tumor control rate (LCR) at 1, 2, 3, and 5 years for RFA was significantly lower than that for SBRT (107).

Discussion:

A multidisciplinary team approach is critical in the management of lung cancer at all stages now with all the new advances and in the treatment algorithm that we have in the field of oncology.

It is worth noting, that the discovery of driver's mutations in lung cancer (NSCLC – adenocarcinoma variant) had changed the perspective of our treatment paradigm in the metastatic setting as we rely ion Next Generation Sequencing on all upfront metastatic NSCLC (adenocarcinoma) and should there be any evidence of +ve driver mutations then a targetable therapy is advisable in that setting.

Recently, there has been significant advances in the management of early-stage NSCLC especially in the setting of active driver's mutation, as the presence of EGFR mutation in a resected lung cancer would make the option of Osimertinib (3rd generation TKI) a viable option with or without chemotherapy. Hence, it is vital to check all upfront resected NSCLC (adenocarcinoma) for the presence of EGFR mutations as Osimertinib should be considered as part of the adjuvant treatment in such circumstances.

The rationale for upfront chemotherapy as part of a neoadjuvant treatment strategy is not standard especially with the risk of toxicities and delays in a curative intent surgery, however, neoadjuvant chemo can be exercised with caution in patients with advanced NSCLC (stage III) rather than stages I – II based on the provided evidence that we have so far.

In conclusion, the management of ES-NSCLC requires a closer focus and attention in particular after the new advances which could potentially change the outcome of this deadly disease drastically. However, the main issue now relies in establishing a widespread campaign to ensure the proper education of health care providers as well as the public to pursuit lung cancer screening program according to the standard of care as this will help up to pick up early onset lung cancer.

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