# STAGE III:
# NSCLC Consensus
## 第三期非小細胞肺癌專家共識

# STAGE III:
## NSCLC Consensus

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# Prologue

In Taiwan, non-small cell lung cancer (NSCLC) comprises more than 90% of all lung cancer cases, and around 16% of patients with NSCLC have stage III disease at diagnosis. Stage III NSCLC is a very heterogeneous disease that encompasses patients with resected, potentially resectable, and unresectable tumors.

Chemoradiotherapy is one of the major parts of treatment for all stage III patients, regardless of whether they undergo surgery or immunotherapy. For patients with resectable tumors, our typical approach is to administer induction chemoradiation, restage the tumor, and then operate. Patients with unresectable tumors, based on the updated NCCN guideline, receive definitive chemoradiation in conjunction with durvalumab, the first immunotherapy drug for stage III NSCLC, which has the potential to make a huge impact on patient survival.

Both the staging and optimal treatment of stage III NSCLC require the joint work of a multidisciplinary team of expert physicians within the tumor committee. To improve the care of patients with stage III NSCLC in Taiwan, the Taiwan Lung Cancer Society has invited different specialists in the diagnosis and treatment of this disease to issue this consensus. Our hope is that this will help standardize the management of stage III NSCLC and ultimately improve patient care.

Yuh-Min Chen 陳育民

***Professor Yuh-Min Chen MD, PhD***

President of Taiwan Lung Cancer Society

Stage III non-small cell lung cancer (NSCLC) describes a heterogeneous population, with disease presentation ranging from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky, nodal disease. To provide an overview of the epidemiology of stage III NSCLC in Taiwan, the results of the national cancer registry in consecutive years, the Kindle study, and the latest observation trial of stage III NSCLC in Taiwan have been collected in this consensus.

Development of a treatment plan for a patient with stage III NSCLC depends upon multiple factors, including an assessment of the patient's overall medical condition, tumor stage, etc. These are discussed in the second chapter.

Surgery has long been the preferred local treatment for patients with resectable disease. For select patients, multimodality therapy involving systemic and radiation therapies in addition to surgery improves treatment outcomes compared to surgery alone. For patients with unresectable disease, concurrent chemoradiation is the preferred treatment. Research into different chemotherapy agents, targeted therapies, radiation fractionation schedules, intensity-modulated radiotherapy, and proton therapy has shown promise to improve treatment outcomes and quality of life. More recently, the results of the PACIFIC trial established the role of immunotherapy in locally advanced inoperable stage III NSCLC in the consolidation setting. Clinical trials evaluating other immunotherapeutic agents are currently ongoing. The array of treatment approaches for locally advanced NSCLC is large and constantly evolving.

Furthermore, considering stage III NSCLC includes a highly heterogeneous group of patients, multidisciplinary team care might have benefits for those patients, and its implementation could improve patient survival.

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# I.Introduction

# Epidemiology data of stage III non-small cell lung cancer in Taiwan in the cancer registry

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Stage III non-small cell lung cancer (NSCLC) is a heterogeneous disease for which optimal treatment continues to pose a clinical challenge.

In Western countries, NSCLC comprises more than 80% of all lung cancers, and one third of patients with NSCLC have stage III disease at diagnosis[1]. Median overall survival (OS) for stage III NSCLC was less than 2 years, with an expected 5-year survival of only 15%[1].

From data collected between 2010 to 2015, lung cancer TNM (tumor, node, and metastases) staging was performed according to the 7$^{th}$ edition of the American Joint Committee on Cancer (AJCC) staging system. NSCLC comprises 92.5% of all lung cancers, and approximately 16 to 17% of patients with NSCLC have clinical stage III disease at diagnosis.

Among clinical stage III NSCLC patients, the following data were obtained: prevalence of stage IIIA and stage IIIB, 47.8% and 52.2%; Male vs. Female, 72.8% vs. 27.2%; median age, 69 (59, 77) years; Right lung vs. Left lung, 60.8% vs. 38.9%; adenocarcinoma vs. SCC vs. other NSCLC, 47.4% vs. 39.5% vs. 13.2%; EGFR mutation test not done vs. mutant vs. wild type, 55.4% vs. 19.0% vs. 22.7%; never smoker vs. smoker vs. ex-smokers, 35.8% vs. 32.2% vs. 32.0%; ECOG PS, 0-1 vs. 2-4, 73.4% vs. 16.0%.(Table 1)

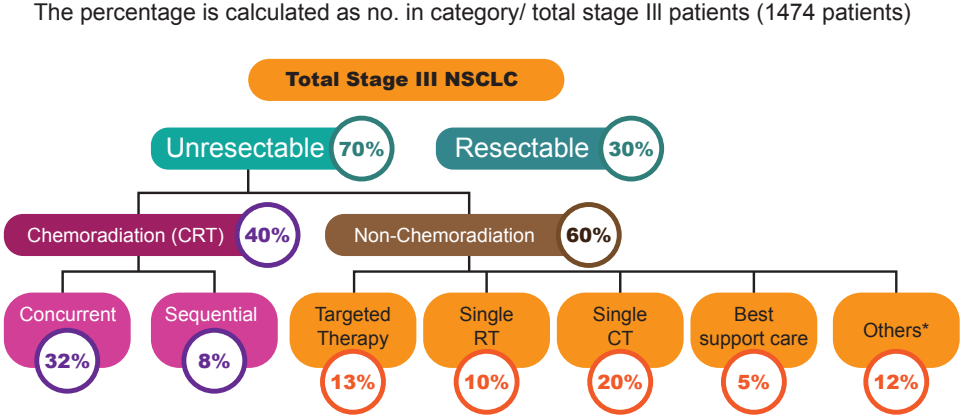
| stage | n | % |
|---|---|---|
| 3A | 3786 | 47.8 |
| 3B | 4142 | 52.2 |
| Year of diagnosis | | |
| 2010 | 1386 | 17.5 |
| 2011 | 1305 | 16.5 |
| 2012 | 1345 | 17.0 |
| 2013 | 1310 | 16.5 |
| 2014 | 1301 | 16.4 |
| 2015 | 1281 | 16.2 |
| Sex | | |
| M | 5775 | 72.8 |
| F | 2153 | 27.2 |
| Age at diagnosis, years | | |
| ≤50 | 694 | 8.8 |
| 51-70 | 3615 | 45.6 |
| >70 | 3619 | 45.6 |
| Median (IQR) | 69 (59,77) | |
| Laterality | | |
| Right | 4817 | 60.8 |
| Left | 3086 | 38.9 |
| Missing | 25 | .3 |
| Histology | | |
| AD | 3754 | 47.4 |
| Squamous | 3131 | 39.5 |
| Other NSCLC | 1043 | 13.2 |

| During 2011-2015 | | |
|---|---|---|
| EGFR mutation | | |
| No detection | 3626 | 55.4% |
| mutation | 1244 | 19.0% |
| wild type | 1485 | 22.7% |
| Detection cannot be interpreted | 20 | .3% |
| unknown | 267 | 2.5% |
| Smoking status | | |
| non-smoker | 2303 | 35.8% |
| smoker | 2067 | 32.2% |
| quit smoking | 2059 | 32.0% |
| ECOG score | | |
| 0 | 1883 | 28.8% |
| 1 | 2920 | 44.6% |
| 2 | 655 | 10.0% |
| 3 | 237 | 3.6% |
| 4 | 157 | 2.4% |
| 5 | 4 | .1% |
| unknown | 686 | 10.5% |

Table 1. Patient demographics and clinical characteristics

Treatment methods were heterogeneous and included surgery, radiotherapy, chemotherapy, targeted therapy, and/or a combination of the above.

For example, in 2014, 30% of patients received surgery, and the remaining 70% received other treatments.(Figure 1)




Data from Cancer registry annual report, 2014
* Others includes RT seq. targeted therapy, refuse to be treated, no treatment and other treatments

Figure 1:The Treatment for Stage III NSCLC in Taiwan (year 2014)

If stages IIIA and IIIB were divided into more detailed subgroups, the more complicated conditions would be T4, N2, and other conditions that would require the patients to use different modes of treatment.

For clinical stage IIIA, surgery is one of the main treatment choices. (Table 2)

| Treatment approaches | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Group | | Surgery only[1,3] | neoadjuvant Tx[1,3] | adjuvant Tx [1,3] | CCRT only [1] | EGFR(+)/ TKI | seq CTRT[1] | CT or RT only[1] | Others[2] | Total |
| cT4 N0 | n | 55 | 37 | 73 | 114 | 41 | 24 | 138 | 13 | 495 |
| | % | 11.1 | 7.5 | 14.7 | 23 | 8.3 | 4.8 | 27.9 | 2.6 | 100 |
| cT3-4N1 | n | 54 | 42 | 146 | 133 | 32 | 38 | 166 | 9 | 620 |
| | % | 8.7 | 6.8 | 23.5 | 21.5 | 5.2 | 6.1 | 26.8 | 1.5 | 100 |
| cT1-3N2 | n | 244 | 262 | 563 | 383 | 132 | 100 | 527 | 23 | 2234 |
| | % | 10.9 | 11.7 | 25.2 | 17.1 | 5.9 | 4.5 | 23.6 | 1.0 | 100 |
| Total | n | 353 | 341 | 782 | 630 | 205 | 162 | 831 | 45 | 3349 |

1 contain EGFR(-)/TKI
2 no Tx, other treatments and EGFR (-)/TKI only
3 Lobectomy or pneumonectomy

Table 2:Treatment approaches for clinical IIIA NSCLC(2010-2015)

For clinical stage IIIB, chemoradiotherapy is used more often in stage IIIA patients.(Table 3)

| Treatment approaches | | | | | | |
|---|---|---|---|---|---|---|
| Group | | neoadjuvant Tx[1] | CCRY only | seq CTRT | Others | Total |
| cT1-4N3 | n | 91 | 814 | 148 | 1574 | 2627 |
| | % | 3.5 | 31 | 5.6 | 59.9 | 100 |
| cT4N2 | n | 58 | 404 | 96 | 567 | 1125 |
| | % | 5.2 | 35.9 | 8.5 | 50.4 | 100 |

1 contain EGFR(-)/TKI

Table 3:Treatment approaches for clinical IIIB NSCLC(2010-2015)

Among stage IIIB lung adenocarcinoma patients, EGFR-TKIs are one of the treatment choices. (Table 4)

| Treatment approaches | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| EGFR status | | OP, neoadjuvant, adj Tx | CCRT or seqCTRT | CT or RT only | TKI RT or CT | TKI only | TKI+ CCRT, seq CTRT | TKI+ Other Tx | No Tx | Total |
| Wild type | n | 86 | 264 | 283 | 0 | 0 | 0 | 0 | 12 | 645 |
| | % | 13.3 | 40.9 | 43.9 | 0 | 0 | 0 | 0 | 1.9 | 100 |
| Mutation | n | 45 | 49 | 32 | 91 | 324 | 25 | 37 | 3 | 606 |
| | % | 7.4 | 8.1 | 5.3 | 15 | 53.5 | 4.1 | 6.1 | 0.5 | 100 |
| Total | | 131 | 313 | 315 | 91 | 324 | 25 | 37 | 15 | 1251 |

TKI+Other Tx: TKI+OP, TKI+OP+CT, TKI+OP+RT and TKI+OP+RT+CT

Table 4:Treatment approaches for clinical IIIB,AD NSCLC(2011-2015)

In terms of survival outcomes, patient conditions are complicated by the use of different treatment methods among heterogeneous patients. Comparisons that are more complicated would emerge, as an increasing number of different treatments appear, such as immunotherapy after CCRT.

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# Taiwan real world data for stage III NSCLC-KINDLE study

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The KINDLE study is a multicenter, multi-country, longitudinal cohort of patients with primary stage III non-small cell lung cancer (NSCLC). This study was conducted as a retrospective review of established patient medical records. Between January 1, 2013, and December 31, 2017, patients diagnosed with primary stage III NSCLC were recruited, and patients with a follow-up period of less than 9 months were excluded. This study enrolled a total of 3151 patients across 19 countries, including 200 patients in Taiwan. The baseline characteristics of the patients in Taiwan are summarized in Table 1. Median patient age was 64.2 (range 56.0 - 73.0) years; there were 71 female patients (35.5%) and 129 male patients (64.5%). Eight (4.0%) patients had a history of asbestos exposure, and 103 (51.5%) patients had a history of tobacco smoking. The most common histologic type was adenocarcinoma (61.0%), followed by squamous cell carcinoma (29.0%) and large cell carcinoma (1.0%). Ninety (45.0%) patients had stage IIIA, and 116 (58%) patients had good performance status (Eastern Cooperative Oncology Group [ECOG] 0-1).

| Characteristic | No. of patients (%),N = 200 |
|---|---|
| Median (range), (years) | 64 (56-73) |
| Sex | |
| Female | 71 (35.5%) |
| Male | 129 (64.5%) |
| Asbestos exposure | |
| Yes | 8 (4.0%) |
| No | 99 (49.5%) |
| Unknown | 93 (46.5%) |

| | |
|---|---|
| Tobacco smoking | |
| Current smoker | 28 (14.0%) |
| Ex-smoker | 75 (37.5%) |
| Never smoker | 93 (46.5%) |
| Unknown | 4 (2.0%) |
| Histology | |
| Adenocarcinoma | 122 (61.0%) |
| Squamous cell carcinoma | 58 (29.0%) |
| Large cell carcinoma | 2 (1.0%) |
| Other unspecified | 13 (6.5%) |
| Mixed | 1 (0.5%) |
| Unknown | 4 (2.0%) |
| Stage | |
| IIIA | 90 (45.0%) |
| IIIB | 110 (55.0%) |
| Performance status | |
| ECOG 0-1 | 116 (58.0%) |
| ECOG ≥2 | 16 (8.0%) |
| Unknown | 68 (34.0%) |

ECOG, Eastern Cooperative Oncology Group.

Table 1. Patient characteristics

The median follow-up period of patients from Taiwan was 21.2 months. Event-free survival (EFS) and overall survival (OS) were 10.3 months (interquartile range, 8.8-11.8) and 24.8 months (interquartile range, 21.3-27.4), respectively (Figures 1A and 1B). The survival rates of different subgroups were then analyzed. First, patients were classified according to stage. Median EFS and OS were similar between patients with stage IIIA and stage IIIB NSCLC (Figures 2A and 2B). Second, patients were classified by tumor resectability. Median EFS was 13.4 months (interquartile range, 11.6-18.4) in patients with resectable disease, which was significantly longer than those with unresectable disease (8.6 months, interquartile range, 7.2-10.7; p=0.014, Figure 3). Similarly, median OS was 33.9 months (interquartile range, 29.5-45.1) in patients with resectable disease, which was also significantly longer than those with unresectable disease (20.5 months, interquartile range, 17.9-24.6; p<0.001, Figure 3). Moreover, when subgroup analysis by resectability was performed based on different stages, both the EFS and OS were similar between patients with stage IIIA and IIIB NSCLC in both the resectable and unresectable groups (Table 2). These data indicate that resectability is a more important prognostic factor than stage among patients with stage III NSCLC.

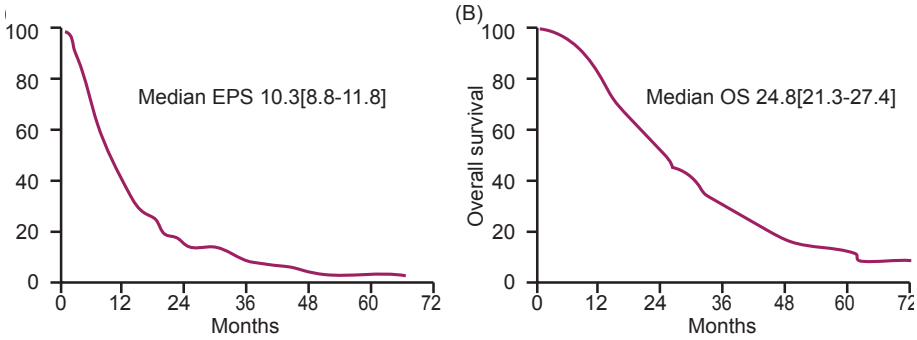


Figure 1. Event-free survival (A) and overall survival (B) of patients from Taiwan in the KINDLE study. EFS, event-free survival; OS, overall survival.

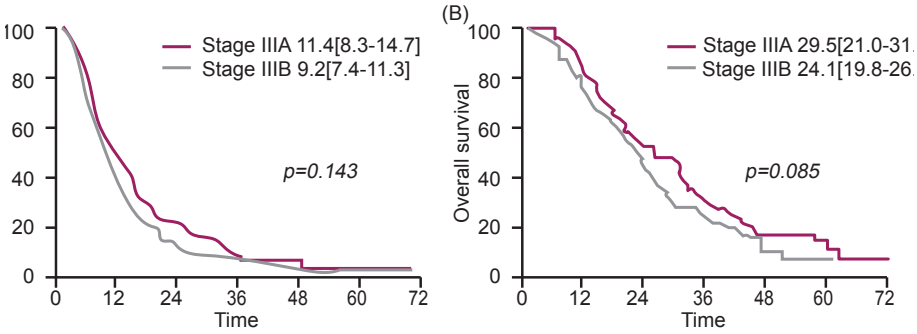


Figure 2. Event-free survival (A) and overall survival (B) of patients with stage IIIA and IIIB disease.

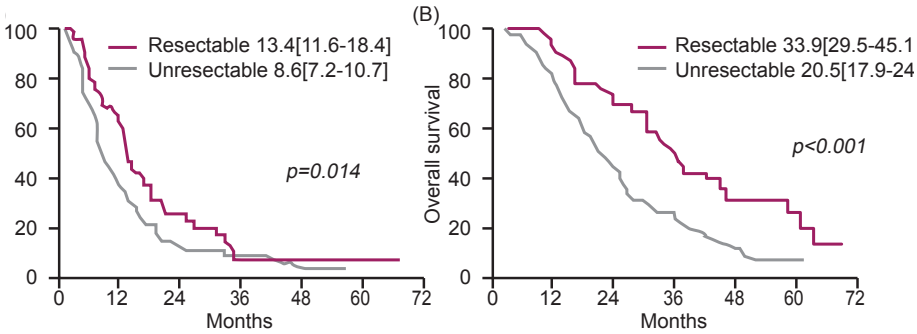


Figure 3. Event-free survival (A) and overall survival (B) of patients with resectable and unresectable disease.

| | Resectable (n=56) | Unresectable (n=125) | P value |
|---|---|---|---|
| Event-free survival | 13.4 [11.6-18.4] | 8.6 [7.2-10.7] | 0.014 |
| Stage IIIA | 13.7 [11.3-18.5] | 7.3 [5.0-14.3] | |
| Stage IIIB | 15.9 [4.2-NR] | 8.6 [6.8-10.9] | |
| Overall survival | 33.9 [29.5-45.1] | 20.5 [17.9-24.6] | <0.001 |
| Stage IIIA | 34.4 [26.0-45.0] | 17.9 [12.4-22.6] | |
| Stage IIIB | 28.9 [14.6-29.7] | 21.5 [15.0-24.4] | |

NR, not reached.

Table 2. Event-free survival and overall survival among non-small cell lung cancer patients stratified by resectability

All 55 patients with resectable disease received curative-intent treatment, including 53 (96.4%) who underwent surgery and 2 (3.6%) who received chemoradiotherapy (CRT)-based therapy. The EFS of patients who underwent surgery was 14.7 months (interquartile range, 12.7-18.5), which was significantly longer than that of patients receiving CRT-based therapy (7.5 months, interquartile range, 4.2-10.9) (Table 4). However, median OS was 34.9 months (interquartile range, 29.0-56.6) in patients receiving surgery, which did not reach statistical difference as compare to that of patients receiving CRT-based therapy (25.5 months, interquartile range, 14.8-36.2) (Table 3). Among 116 patients with unresectable disease, 38 (32.8%) received curative-intent CRT-based therapy and 78 (67.2%) received systemic therapy. Both the EFS and OS were similar between unresectable patients receiving different treatment modalities (Table 4).

| | Surgery-based therapy (n=53) | CRT-based therapy (n=2) | P value |
|---|---|---|---|
| Event-free survival | 14.7 [12.7-18.5] | 7.5 [4.2-10.8] | 0.028 |
| Overall survival | 34.9 [29.0-56.6] | 25.5 [14.8-36.2] | 0.339 |

CRT, chemoradiotherapy.

Table 3. Event-free survival and overall survival among patients with resectable non-small cell lung cancer by treatment modality

| | CRT-based therapy (n=38) | Systemic therapy (n=78) | P value |
|---|---|---|---|
| Event-free survival | 6.3 [5.3-7.9] | 9.0 [7.4-11.8] | 0.112 |
| Overall survival | 19.5 [16.3-23.7] | 19.4 [15.5-24.8] | 0.827 |

CRT, chemoradiotherapy.

Table 4. Event-free survival and overall survival among unresectable non-small cell lung cancer patients by treatment modality

In summary, the KINDLE study showed that resectability is the major prognostic factor in Taiwan patients with stage III NSCLC. Although surgery could provide a better EFS in patients with resectable disease, the overall survival was similar among patients receiving different treatment modalities. Moreover, differences in baseline characteristics (e.g., Tumor-Node-Metastasis stage, EGFR status, subsequent therapy) have not yet been completely considered in the current data, which is a limitation of the study. Further analysis is warranted and will be performed in the future.

# II.Staging and assessment

# How do we sub-stage stage III non-small cell lung cancer to improve decision making?

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Stage III non-small cell lung cancer (NSCLC) includes a highly heterogeneous group of patients with differences in the extent and localization of disease. Many aspects of the treatment of stage III disease are controversial[1]. When stage III NSCLC is sub-staged prior to decision making, the classification of tumors as resectable or unresectable is the most important concern[2,3].

When patients with stage III disease undergo primary surgical resection, there is a proposed definition of a surgically complete resection. In the majority of patients where stage III disease is confirmed by initial staging investigations, it is still important to classify them at baseline as[4,5]:

- Resectable
- Potentially resectable with an increased risk for incomplete resection
- Unresectable

An important component of the sub-staging evaluation is an assessment of the mediastinal lymph nodes. Absence of tumor involvement of the mediastinal lymph nodes remains one of the most important factors in selecting patients for surgical intervention.

Surgical resection is a key component of the treatment of patients with stage III N0 or N1 NSCLC if complete resection is technically feasible and the patient' s overall condition is satisfactory[6,7]. Complete resection is pathologically defined by the confirmation of negative surgical margins in the resected specimen, including the highest mediastinal node negativity at the time of surgical

resection and/or mediastinal lymph node dissection[8]. The majority of patients in stage III; however, will be found to have stage defining extensions (e.g. N2 or N3) in the initial imaging and invasive staging investigations[9,10]. The optimal treatment of patients with stage III NSCLC with mediastinal involvement (N2 or N3) has not been clearly defined and many aspects of therapy remain controversial. A multidisciplinary approach that includes input from medical oncology, radiation oncology, and thoracic surgery is indicated prior to treatment[4,5]. Key factors influencing the treatment planning include the extent of the primary tumor and nodal disease, the ability to achieve complete surgical resection if indicated, and the patient' s overall condition and preferences. Furthermore, this multidisciplinary approach should classify the patient upfront as either clearly potentially resectable, potentially resectable as part of an intermediate group, or definitely unresectable[4,5]. In the intermediate group, resection is deemed to have an underlying increased risk of an incomplete resection. Here, tumors of the superior sulcus (Pancoast) and specific centrally located tumors (T3/T4 involvement) can typically be identified[7,11]. Evaluating and predicting these parameters upfront is key for adequate planning of the definitive local treatment without treatment interruptions (either surgery, a neoadjuvant chemotherapy or chemoradiotherapy approach, as defined by an initial combination chemotherapy given before any definitive local therapy, such as surgery or primary definitive radiation/chemoradiotherapy), because of its complexity and the risk that an incorrect decision may result in an unsuccessful outcome. This could lead to palliative treatment (e.g. an incomplete resection after preoperative concurrent chemotherapy and radiotherapy to a dose of 45 Gy).

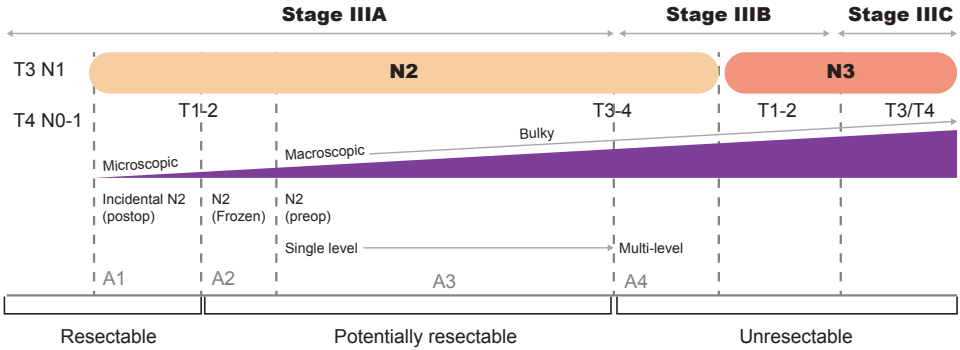


Figure 1: Spectrum of stage III with different tumor and nodal status.

A schematic diagram showing the heterogeneity of stage III NSCLC with different presentations and subgroups (stage IIIA/B/C) depending on the tumor and nodal status, which can be categorized into resectable, potentially resectable, and unresectable disease. A1-A4 depicts Robinson classification for stage IIIA disease. The red triangle represents the spectrum of nodal involvement ranging from incidental/microscopic to macroscopic, then increasing levels of disease bulk, from single level to multi-level nodal involvement (adapted from 2019 ATORG consensus on optimal management of stage III NSCLC [4]).

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# Optimal diagnostic work-up for stage III non-small cell lung cancer patients

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The initial radiographic imaging evaluation of patients with stage III non-small-cell lung cancer (NSCLC) should include positron emission tomography-computed tomography (PET-CT) scan or chest/abdomen/pelvis CT scan plus whole-body bone scan, combined with contrast-enhanced brain CT or MRI. PET-CT scan for pretreatment staging is ideal.

### *PET- CT scan*

The diagnostic impact of whole-body PET-CT scan for initial stage III diseases has been investigated in several randomized trials[1-3]. This can be used to exclude extra cranial and extra thoracic metastasis prior to deciding on the methods of local treatment with a curative plan. Mediastinal lymph node status should be initially assessed via this method[3]. However, false positive lymph nodal involvement on PET-CT scan can be seen in mycobacterium tuberculosis (TB), especially in Taiwan where pulmonary TB is endemic[4], and single PET-CT scan positive distant lesions require pathological confirmation before accepting stage IV diseases. Therefore, minimally invasive techniques, such as endobronchial ultrasound (EBUS), endoscopic ultrasounds (EUS), mediastinoscopy, and thoracoscopy were preferred to assess lymph node status and distant lesions, ideally within 4 weeks before the start of treatment[5]. In contrast, pathological evaluation may not routinely be needed if patients presents with bulky lymph nodes at N2 level, including more than 3 cm in short-axis, evidenced by extracapsular nodal involvement, and involved more than two lymph node stations[6].

### *Minimal invasive mediastinal staging or mediastinoscopy*

A retrospective analysis of lung cancer patients assessed with 18F-FDG PET scan, showed that about 51% of stage III non-small cell lung cancer patients will harbor occult metastases[7]. Mediastinal lymph nodes could also be assessed by up-front 18F-FDG-PET which maintains quality of TNM staging with the use of less invasive surgery[3]. Although the accuracy of PET is higher than contrast-enhanced CT, the positive predictive value is not widely accepted because pulmonary TB is endemic in Taiwan[4]. Therefore, PET-positive mediastinal lymph nodes should receive pathological assessment by minimally invasive procedure, such as EBUS, EUS, mediastinoscopy, video-assisted thoracoscopy (VATS), or video-assisted mediastinoscopy (VAMS)[8-11]. If the mediastinal nodes are PET-negative, they should be assessed when high risk of tumor involvement presents. According to the revised ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC, minimally invasive mediastinal staging should be performed in patients with tumors larger than 3 cm, located at the inner two thirds of the lung field, and the presence of N1[12]. If the EUS was not available, the use of EUS with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) could be performed to evaluate para-esophageal lymph nodes[13].

If the results of endoscopic procedure are negative, despite the high risk of mediastinal lymph node involvement, surgical staging should be considered. VATS is the preferred technique for the para-aortic lymph nodes (station 6) and the subaortic lymph nodes (station 5), whereas VAMS is preferred for upper mediastinal lymph node[12].

## *Contrast-enhanced Brain CT and MRI*

There was a higher incidence (24-51%) of true positive occult metastasis in Patients with stage III NSCLC[7],especially with intracranial involvement. Patients with local advanced T4 tumors and N2 or N3 mediastinal nodal involvement also had high risk of brain metastasis[14].Based on the above, early detection of brain metastasis can enable early treatment prior to the onset of complications. In addition, initial comprehensive staging of adequate brain images was important in the curative treatment plan of stage III diseases[15]. Therefore, contrast-enhanced MRI or CT is mandatory to exclude brain metastasis. Contrast-enhanced MRI is the preferred method for staging of the brain in stage III diseases.

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# What are the most relevant comorbidities assessed in the clinical work-up of stage III NSCLC patients?

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Comorbidities are of paramount importance since the potential risks of toxicity, morbidity, and mortality have to be balanced with the potential benefit of any aggressive curative-intent treatment strategy. Therefore, based on their specific comorbidities, other treatment modalities may be considered in some patients[1].

The majority of lung cancer patients are smokers who have smoking-related comorbidities such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, cardiovascular disease, or cerebral vascular disease. In such patients, stage III disease curative-intent strategies, including surgery, radiotherapy, and chemotherapy, require considerable expertise to ensure that these treatments can be safely delivered.

Regarding surgery, evaluation of preoperative cardiopulmonary function is essential. Cardiac function may be investigated by electrocardiography(ECG), echocardiography, radionucleotide imaging, stress ECG (optional), stress echocardiography (optional), and in some cases, coronary angiography[2]. Patients with a known history of coronary artery disease with increased surgical risk should be evaluated for the indication of coronary revascularization before surgery[3]. Pulmonary function tests include spirometry, diffusion capacity, low-technology exercise pulmonary function tests (optional), cardiopulmonary exercise testing (optional), and split-function studies (especially perfusion scintigraphy) (optional). Postoperative lung function parameters can be calculated to evaluate the patients' fitness for radical surgical treatments, such as pneumonectomy or lobectomy[1]. Smoking cessation is strongly encouraged. Treatments for respiratory, cardiovascular, and renal diseases, diabetes mellitus,

and obstructive sleep apnea should be optimized before surgery, as should strategies for perioperative nutrition support and pulmonary or physical rehabilitation.

As for curative radiotherapy, the risk of radiation pneumonitis is related to treatment factors such as the radiation dose, daily fractionation, irradiated lung volume, concurrent platinum-based chemotherapy, and immune checkpoint inhibitor treatment; additionally, patient factors such as age, gender, performance status, preexisting lung disease, especially COPD, preexisting cardiovascular disease, tumor location, genetic predisposition, and heart disease are important. The Charlson comorbidity index, a score calculated from 19 different disorders, can also be used for risk assessment[4]. Unfortunately, post-radiotherapy lung function cannot be readily predicted due to the heterogeneity of radiation-induced lung toxicity. Dose-volume histogram parameters, particularly the percentage of lung volume receiving a dose in excess of 20 Gy and the mean lung dose, are widely accepted predictors of radiation pneumonitis[5,6].

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# What are the optimal multi-modality combinations for the different stage III disease sub-stages?

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### *Resected NSCLC with incidental IIIA (N2) disease (unforeseen N2)*

Despite thorough preoperative staging procedures, when incidental N2 disease is identified intraoperatively and complete resection can be achieved, pulmonary resection with mediastinal lymph node dissection should be continued with the planned procedure, followed by platinum-based doublet adjuvant chemotherapy with or without radiotherapy (RT)[1]. Limited evidence indicates that postoperative RT (PORT) potentially increased survival among patients with incidental N2 disease[2-4] and could be delivered sequentially after adjuvant chemotherapy by using modern RT techniques to minimize toxicity in selected patients, among whom the benefit of improved locoregional control appear to outweigh the harms of adverse effects[5,6].

Taiwan Lung Cancer Society (TLCS) consensus

Patients with potentially resectable lung cancer should all be discussed in the multidisciplinary meeting. Among patients with incidental N2 disease, after undergoing upfront resection, adjuvant chemotherapy, with or without RT, can be administered to all suitable patients with stage III disease regardless of mutation status. PORT should be considered for incidental N2 disease in patients with resected NSCLC among whom the benefit outweighs the risk.

### *Potentially resectable IIIA (N2) disease*

Surgery in patients with proven N2 disease

Much controversy remains about the role of surgery in preoperatively confirmed stage IIIA (N2) NSCLC owing to the heterogeneity of disease, diversity of clinical management, and the paucity of well-designed randomized trials to elucidate some important issues, such as neoadjuvant or adjuvant therapy[5]. There remains no widely agreed

guideline regarding the definition of resectability. According to the Asian Thoracic Oncology Research Group expert consensus statement on the optimal management of stage III NSCLC, patients with non-bulky (less than 3 cm, discrete or single-level N2 involvement) N2 disease may be appropriate candidates for surgical resection as a part of the multimodality treatments[5] owing to the increasing efficacy of contemporary treatment approaches[7].

Patients with potentially moderate N2 involvement, including central tumor location or tumor diameter more than 3 cm, should undergo comprehensive staging procedures, including radiologic and invasive staging[8,9]. Pathologic confirmation of positive mediastinal findings is mandatory except for patients with multi-level infiltrative lymph node involvement who are not candidates for curative-intent surgery. The integration of surgery into the management of stage III NSCLC should be performed at experienced institutions and discussed in a multidisciplinary team to determine the best treatment strategy[5].

### *Neoadjuvant therapy followed by surgery in stage IIIA (N2) disease*

The role of preoperative neoadjuvant chemotherapy or chemoradiotherapy is still debated[5].

A subgroup meta-analysis of 13 randomized controlled trials revealed significant overall survival (OS) benefit in stage III NSCLC patients who received neoadjuvant chemotherapy followed by surgery, compared with those who underwent surgery alone[10]. The optimal timing of RT in the trimodality therapy (preoperative RT with chemotherapy or PORT) remains controversial[11,12]. There is no evidence to suggest that preoperative chemoradiotherapy

can improve the survival among patients with stage IIIA (N2) disease when compared with preoperative chemotherapy alone[12]. In a phase III randomized controlled trial, neoadjuvant chemoradiotherapy followed by surgery demonstrated better progression free survival (PFS), but no significantly different OS compared to concurrent chemoradiotherapy (CCRT) without surgery in patients with stage IIIA (N2) NSCLC. However, exploratory analysis revealed improved OS among patients who underwent lobectomy, but not pneumonectomy in comparison with CCRT alone[13]. In brief, neoadjuvant (preoperative) therapy, including chemotherapy and chemoradiotherapy, is suggested for select patients after multidisciplinary evaluation[14].

### *Neoadjuvant TKI followed by surgery and adjuvant TKI*

The potential effect and feasibility of neoadjuvant EGFR-TKI has been reported in a phase II trial of neoadjuvant/adjuvant erlotinib versus neoadjuvant gemcitabine plus cisplatin in patients with treatment-naïve stage IIIA (N2) NSCLC harboring EGFR mutation[15] .Neoadjuvant erlotinib showed significantly longer PFS compared with chemotherapy, providing a rationale for considering neoadjuvant TKI in EGFR-mutant stage III NSCLC.

TLCS consensus

Patients with potentially resectable stage III lung cancer should be discussed in the multidisciplinary meeting. A comprehensive preoperative staging procedure, including positron emission tomography/computed tomography scans, brain magnetic resonance imaging, and pathological confirmation of suspected mediastinal lymph nodes is mandatory. Adjuvant chemotherapy with or without RT can be provided to appropriate patients with stage III disease who have incidental N2 disease after undergoing upfront surgery. Lobectomy with mediastinal lymph node dissection

for select patients with resectable N2 disease is the preferred surgical procedure and should ideally be pre-planned with neoadjuvant chemotherapy or chemoradiotherapy through a multidisciplinary discussion at experienced institutions. PORT should be considered for pathologic N2 disease among patients with resected NSCLC in whom the benefit outweighs the risk. Neoadjuvant EGFR-TKI is not the standard of care for potentially resectable stage III NSCLC. However, neoadjuvant erlotinib may be considered as an alternative treatment option for potentially resectable stage III (N2) NSCLC harboring sensitizing EGFR mutations after careful evaluation in the multidisciplinary meeting.

### *Patients with unresectable IIIA (N2) and IIIB/IIIC disease*

CCRT is the treatment of choice in patients with unresectable stage IIIA and IIIB/IIIC diseases[14,16]. The addition of induction or consolidation chemotherapy has not shown a survival benefit and might increase treatment toxicity[17-19]. Nonetheless, additional cycles of chemotherapy before or after CCRT might be appropriate in select patients after multidisciplinary evaluation. For example, consolidation chemotherapy may be an alternative after CCRT for patients without consolidation durvalumab owning to contraindications or other reasons.14 If CCRT is not feasible, sequential chemoradiotherapy is appropriate for patients unable to tolerate concurrent therapy[16].

TLCS consensus

CCRT is the treatment of choice for unresectable stage IIIA and IIIB/IIIC diseases. The addition of induction or consolidation chemotherapy has not shown a survival benefit. However, additional cycles of chemotherapy before or after CCRT might be appropriate after multidisciplinary evaluation. If CCRT is not feasible, sequential chemoradiotherapy is appropriate.

### *Prophylactic cranial irradiation*

## TLCS consensus

Currently, prophylactic cranial irradiation (PCI) in stage III NSCLC after CCRT is not routinely suggested owning to the lack of survival benefit, though PCI may decrease the occurrence of symptomatic brain metastases at the cost of increased low-grade toxicities[5,16,20].

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# III.Treatment

# What is the optimal chemotherapy to be administered to patients with stage III disease?

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### *Neoadjuvant chemotherapy followed by surgery in stage III disease*

The preoperative role of neoadjuvant chemotherapy remains controversial. Several trials demonstrated a trend toward improved survival, but the patient numbers were small. A meta-analysis revealed that patients with resectable non-small-cell lung carcinoma (NSCLC) showed a trend favoring neoadjuvant chemotherapy (hazard ratio=0.65; 95% confidence interval, 0.41–1.04) in the subset with stage III disease; however, this was not statistically significant[1]. An updated meta-analysis of 13 randomized trials demonstrated significant overall survival (OS) benefit in patients who received neoadjuvant chemotherapy in addition to surgery, including those with stage III NSCLC[2]. A randomized trial revealed no difference in survival between preoperative versus postoperative chemotherapy[3]. Patients with stage IIIA (T3, N1) disease may be treated with neoadjuvant chemotherapy preoperatively if they are candidates for therapy postoperatively[4].

### *Neoadjuvant chemoradiotherapy followed by surgery in stage III disease*

The INT-0139, which compared CCRT with neoadjuvant CCRT followed by surgery in stage III N2 NSCLC, demonstrated a longer progression free survival, but no survival benefit with surgery[5]. However, a survival advantage was observed in patients who did not undergo pneumonectomy. Several trials assessed whether preoperative CCRT was better than neoadjuvant chemotherapy in stage III NSCLC[6-9] and showed that adding RT did not improve survival despite an increase in mediastinal down-staging. For patients with resectable or possibly resectable(T3 invasion, N0-1)superior sulcus tumor, neoadjuvant chemoradiotherapy is recommended[10-16] .Neoadjuvant

chemoradiotherapy is also a treatment option for tumors of the chest wall, proximal airway, or mediastinum (T3-4, N0-1).

### *Concurrent chemoradiotherapy versus sequential chemoradiotherapy for unresectable stage III NSCLC*

CCRT is the standard treatment for unresectable stage III NSCLC[17]. A meta-analysis of 6 clinical trials demonstrated an absolute OS benefit of 4.5% at 5 years when CCRT was compared to sequential chemoradiation[18]. Recommended chemotherapeutic regimens in concurrent chemoradiation that may be used for the initial treatment of all histologic types include 2–4 cycles of cisplatin/etoposide and carboplatin/paclitaxel[19-26]. For nonsquamous NSCLC, additional concurrent chemoradiation regimens may be used including carboplatin/pemetrexed and cisplatin/pemetrexed [27-29].

For sequential chemoradiation, regimens included are also used for preoperative and postoperative chemotherapy (i.e., cisplatin combined with pemetrexed [nonsquamous only], docetaxel, etoposide, gemcitabine, and vinorelbine)[22-25]. For those who are not able to tolerate cisplatin, recommended regimens include carboplatin/gemcitabine, carboplatin/paclitaxel, and carboplatin/pemetrexed (nonsquamous only)[35-38]. In the absence of contraindications, the optimal chemotherapy to be combined with radiation in stage III NSCLC should be based on cisplatin. A phase III trial showed non-inferiority but better tolerability with pemetrexed compared to etoposide, in combination with cisplatin, making it an ideal option for patients with nonsquamous histologic types[38].

There is some evidence that CCRT with carboplatin and paclitaxel in the Asian context may result in higher rates of radiation pneumonitis and should be used with caution, particularly in large volume disease[39]. The eligibility for CCRT should be assessed primarily based

on the patient' s fitness and appropriateness for high dose thoracic RT with concurrent platinum-based chemotherapy. The minimum requirement is that the patient' s ECOG performance status is at least 1. Advanced age alone should not be an absolute contraindication since there is no evidence to suggest that carefully selected older patients fare worse after CCRT[26]. Sequential chemoradiotherapy may be considered for less-fit patients who are not candidates for standard concurrent chemoradiotherapy.

### *Adjuvant chemotherapy or chemoradiotherapy after surgery*

Patients with stage III NSCLC initially treated with surgery may receive chemotherapy alone if the surgical margins are negative. The postoperative chemotherapeutic regimen for all histologic types is platinum combined with vinorelbine, taxane, etoposide, or gemcitabine[40-41]. Cisplatin/vinorelbine is the most frequently studied regimen. Platinum is combined with pemetrexed for nonsquamous NSCLC[40-41].

In patients who have undergone upfront resection for incidental N2 disease, adjuvant chemotherapy, with or without RT, can be offered to all patients with stage III disease who are deemed suitable irrespective of mutational status. For those with N2 nodes after surgery, concurrent chemoradiation is recommended for those with positive margins and an R2 resection; either concurrent or sequential chemoradiation is recommended after an R1 resection[38].

### *Induction and consolidation chemotherapy*

Induction or consolidation chemotherapy in addition to definite chemoradiotherapy are not routine approaches for stage III disease

but may be acceptable in select cases[39-41] .If full-dose radiotherapy was not administered concurrently with RT, two additional cycles of full-dose chemotherapy can be given.

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# What is the optimal radiation regimen given to stage III NSCLC patients?

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### *Systemic therapy-RT sequence for unresectable stage III NSCLC*

For unresectable stage III non-small cell lung cancer (NSCLC), concurrent chemoradiotherapy (CCRT) is the standard of care[1] with an absolute overall survival (OS) benefit of 4.5% at 5 years when CCRT is compared to sequential chemoradiation[2]. However, Asian and epidermal growth factor receptor mutation positive (EGFRm+) NSCLC patients are under-represented in these studies. There is some concern regarding CCRT with carboplatin and paclitaxel possibly related to higher rates of radiation pneumonitis[3,4] and they should be used with caution. The eligibility for CCRT should be assessed thoroughly[1,5]. Patients not eligible for standard CCRT may be considered for sequential chemoradiation instead[1,6]. Reduced dose CCRT may be another alternative[7]. For those who are not able to tolerate chemotherapy, definitive radiotherapy alone is an alternative, although it is associated worse outcomes[1,6,8].

### *Dosimetric considerations for radiotherapy*

In the standard CCRT setting, many guidelines recommend a radical RT dose around 60 Gy delivered in daily fractions of 1.8–2 Gy[1,6,9]. RT doses as low as 50 Gy or as high as 70 Gy have been reported in the literature[1,9-11].Dosimetric constraints in terms of the adjacent normal tissue must be considered and this has been reported in many studies[1,12,13]. However, the limitations of dosimetry alone in predicting pulmonary complications should be recognized and risk assessment tools may be helpful in patient selection[14,15].

Taurolithocholic acid-3 sulfate (TLCS) consensus: Patient selection for combined modality treatment should consider patient characteristics (including but not limited to performance status and comorbidities) and appropriateness for high dose thoracic radiotherapy (RT) concurrent with platinum-based chemotherapy. Radical dose RT delivering around 60 Gy in 1.8–2 Gy daily fractions is usually considered. Dose constraints to normal tissue should be considered.

### *Current and emerging radiotherapy modalities*

Delivery of high dose thoracic RT requires appropriate planning and delivery (including organ motion management such as via 4D simulation) as recommended by many studies[1,12,13,16].Motion management is usually encouraged in these studies, although the clinical benefit was not obvious in one randomized controlled trial [RCT][17]. The RT target is usually the tumor only without elective nodal irradiation[18,19]. Delineation of internal target volumes, as defined in the International Commission on Radiation Units and Measurements (ICRU) Report 62, should be incorporated to account for tumor motion. When 4D computed tomography (CT) is not available, increased margins may be applied for planning target volume (PTV) expansion[1]. Emphasis should be placed on quality assurance and dose reproducibility. Intensity-modulated radiation therapy (IMRT) is often advocated in the literature[1,12] whereas CT-planned 3D conformal radiotherapy [3DCRT] is the minimal standard[12]. A retrospective study from Taiwan had reported no statistical difference in OS when IMRT was compared to 3DCRT20. The addition of daily image-guided radiotherapy (IGRT) to improve RT delivery has also been advocated[1,12].

However, an RCT for prostate cancer patients treated with RT reported inferior OS [2nd endpoint] for those treated with IGRT[21], whereas slightly better OS was reported for lung cancer patients treated with IGRT in a retrospective study from Taiwan[21,22]. Conventional passive scattering proton therapy (PSPT) has not demonstrated superiority over IMRT[23], and the role of more advanced proton therapy is currently being evaluated in ongoing RCTs [such as NCT01993810].

TLCS consensus: High dose thoracic RT requires appropriate organ motion management and robust quality assurance for planning and the delivery process. When available, modern RT techniques are usually favored, and standard 3DCRT should be the minimal standard.

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# What is the optimal surgical management for patients with resectable stage III NSCLC in the era of target and immuno-therapy?

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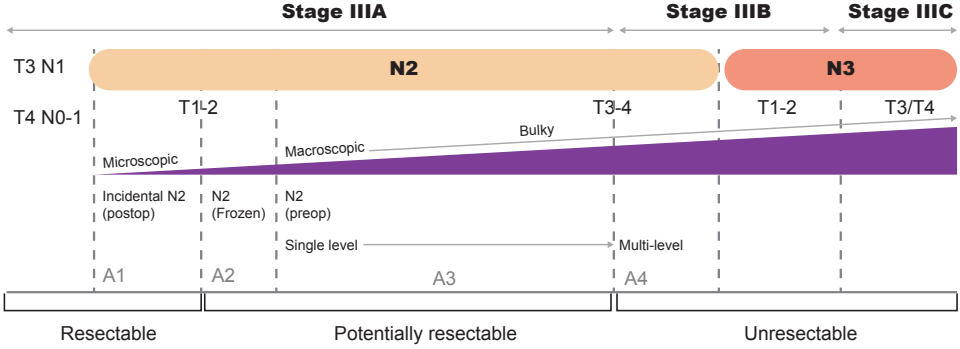
## *Introduction: resectable and unresectabledisease*

Patients with locally advanced clinical stage III NSCLC are a heterogeneous group. Thus, this group of patients could be sub-categorized into cIIIA ($T_4N_{0-1}/T_3N_1/T_{1-2}N_2$), cIIIB* ($T_{3-4}N_2/T_{1-2}N_3$), and cIIIC ($T_{3-4}N_3$)[1]. In general, stages cIIIB* and cIIIC are considered unresectable (Figure 1)[2]. The issue regarding when surgery should be performed in a patient with resectable stage cIIIA NSCLC is currently controversial[3-5].

Figure 1[2]: Spectrum of stage III disease with focus on N2. A schematic diagram showing heterogeneity of stage III NSCLC with different presentations and subgroups (stage IIIA/B/C) depending on the tumor and nodal status, which can be categorized into resectable, potentially resectable, and unresectable disease. A1–4 depicts the Robinson classification for stage IIIA disease. The red triangle represents the spectrum of nodal involvement ranging from incidental/microscopic to macroscopic, then increasing levels of disease bulk, from single to multiple levels of nodal involvement.

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There remains no widely agreed-upon definition of resectability[6]. However, resectable cIIIA could be defined by a tumor of size <3 cm[7]; patients with discrete or single-level N2 involvement may be the best candidates to undergo resection as part of a multimodality approach. When tumors with a central location or of a size >3 cm[8] are treated as potentially resectable, a thorough preoperative staging workup is mandatory.* One type of (cIIIB

(T3N2)) is considered unresectable if the tumor diameter >5–7 cm. Other conditions of T3, such as separate tumor nodules in the same lobe, chest wall (+), pericardium (+), or phrenic N (+), along with N2 disease, are not included. However, when surgical intervention is supposed to be one of the treatments for the T3-4N2 (cIIIB) patients with tumor diameter >5-7 cm or >7 cm, a thorough discussion in the multidisciplinary team is necessary (see the section on unresectable disease below).

### *Types and sequence of staging tools for clinical stage III (cIII) NSCLC*

The assessment of mediastinal lymph nodes (LNs) is the most important part of the evaluation of suspected cIII NSCLC patients. The logical sequence of examination tools is supposed to be computed tomography (CT) scan, positron emission tomography (PET)-CT scan, and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA). There is controversy regarding the sequence of PET-CT scan and EBUS-TBNA[9,10]. However, we prefer that the PET-CT scan be performed ahead of EBUS-TBNA to prevent false positive results[9]. EBUS is preferred for initial mediastinal staging for pathologic confirmation of N2 disease compared to mediastinoscopy[11].

### *Sub-categories of stage cIIIA NSCLC*

Stage cIIIA disease could be classified further according to the lymph node status as IIIA-N0 ($T_4N_0$), IIIA-N1 ($T_4N_1/T_3N_1$), and IIIA-N2 ($T_{1-2}N_2$)[5].

### *Resectable stage cIIIA NSCLC: IIIA-N0 ($T_4N_0$) and IIIA-N1 ($T_4N_1$/$T_3N_1$) (Figure 1)[2]*

Stage T4 (separate tumor nodules in a different ipsilateral lobe) N0/1 and T3 (separate tumor nodules in the same lobe) N1 diseases may be down-staged if multiple tumors are confirmed to be second primary tumors by comprehensive histological assessment (carcinoma in situ is presented in each tumor) and/or molecular testing (at least for EGFRm)[2].

T3N2 (IIIB) tumors with diameter >5–7cm are excluded. Other conditions of T3 such as separate tumor nodules in the same lobe, chest wall (+), pericardium (+), or phrenic N (+) N2 will be discussed in the section titled "Potentially resectable: Single level of N2 LN (+) diagnosed preoperatively."

### *Resectable stage cIIIA NSCLC: Incidental IIIA-N2 ($T_1N_2$) (Figure 1)[2] Incidental IIIA-N2: CT (-), PET-CT (-), or EBUS-TBNA (-)/pathologic (+) N2*

Approximately 14–24%[4] of patients with incidental, microscopic N2 disease postoperatively, who undergo treatment via surgery followed by cisplatin-based doublet adjuvant chemotherapy with or without RT sequentially, have a good 5-year survival rate as high as 44.6%[2,4,12]. The surgical result of this subgroup is as good as that of patients with stage II NSCLC[12].However, we will not be discussing incidental IIIA-N2; our focus will be on clinical stage IIIA-N2 ($T_{1-3}N_2$).

### *Historical surgical results of stage cIIIA-N2 ($T_{1-3}N_2$) disease*

The collective 5-year survival rates for surgery alone in the IIIA-N2 ($T_{1-3}N_2$) disease are reported to be in a wide range of 14–30%[4]. The reasons for such a wide range of survival rates include

high heterogeneity among studies with respect to diagnostic, staging, and treatment procedures, as well as different systems used to detect tumor response in surgical specimens[13]. Therefore, in the current era, pathological confirmation of suspicious mediastinal LN is mandatory. The status of mediastinal LNs must at least be assessed via a combination of PET-CT and EBUS-TBNA[2,14,15].

Stage T3N2 (IIIB) is defined here as follows: Stage T3 disease with tumor diameter >5–7 cm is excluded. Other conditions of T3 stage, such as separate tumor nodules in the same lobe, chest wall (+), pericardium (+), or phrenic N (+) N2 will be discussed in this section.

### *Number of positive levels of N2 LN: single or multiple (Figure 1)[2]*

### *Potentially resectable disease: Single level of N2 LN (+) diagnosed preoperatively*

It is generally accepted that patients diagnosed preoperatively with non-bulky (<3 cm), single-level N2 involvement may be the best candidates to undergo resection as part of a multimodality approach. The treatment options for such patients include 1) induction chemotherapy followed by non-pneumonectomy surgery ± postoperative RT,[16] 2) induction chemo-radiation followed by non-pneumonectomy surgery ± adjuvant chemotherapy,[17] and 3) neoadjuvant TKI followed by non-pneumonectomy surgery and with 2-year adjuvant TKI[2,18].

Tips of caution[2]

- Postoperative RT should be considered for pathologic N2 disease in patients in whom the benefit of improved loco-regional control outweighs the risk of excess toxicity[2].

- Induction or consolidation chemotherapy in addition to definitive chemoradiotherapy is not a routine approach for stage III disease, but may be acceptable in select cases[2].
- Adjuvant TKI for 2 years may be considered for patients with stage III, node positive disease with sensitizing *EGFR* mutations having undergone curative resection, if they are unsuitable candidates for adjuvant chemotherapy after multidisciplinary evaluation. If adjuvant EGFR TKIs are to be considered outside of a clinical trial, first-generation EGFR TKIs should be used[2].

***Unresectable disease: Multiple levels of N2 LN (+) disease diagnosed preoperatively and cIIIB (T3–4N2/T1–2N3), and cIIIC (T3–4N3).***
***T3 conditions such as separate tumor nodules in the same lobe, chest wall (+), pericardium (+), or phrenic N (+) are not included.***

In general, this group of patients should be treated as having unresectable disease[2], at least until after a discussion by a multidisciplinary team. Some cases (T3: 5-7cm,T4:>7cm) might be attributed to a potentially resectable one if single level of N2 LN (+) could be secured preoperatively.

The suggested treatment for unresectable stage III NSCLC (PD-L1 >1%) is CCRT + immunotherapy (durvalumab x12 months)[19] with a median PFS of 17.2 months (vs. 5.6) and a 2-year overall survival rate of 66.3% (vs. 55.6%).

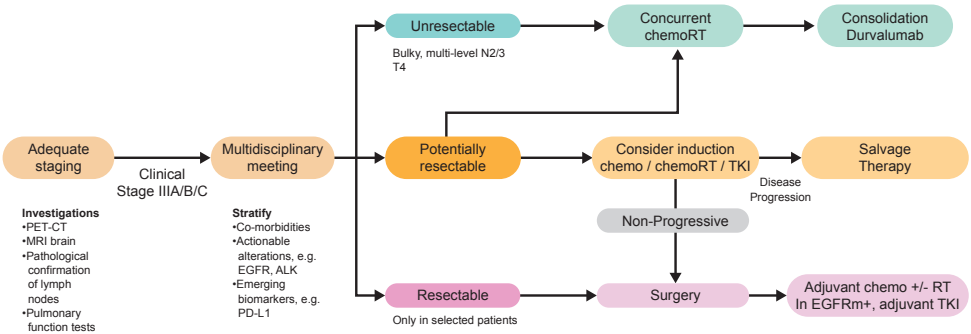


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Figure 2[2]: Proposed clinical algorithm for stage III NSCLC. Defining resectability is crucial to determine subsequent multi-modality management of stage III NSCLC. All patients considered to have potentially resectable disease should be discussed in a multidisciplinary meeting. Thorough preoperative staging work-up, including a PET/CT, brain MRI, and pathological confirmation of suspicious mediastinal lymph nodes, is mandatory. If surgery is considered in carefully selected patients, this should be pre-planned with either neoadjuvant chemotherapy, chemoradiotherapy, or TKI and should ideally be performed in high volume centers with experienced tri-modality teams. Actionable alterations are highly prevalent in Asia and some like EGFR (epidermal growth factor receptor) mutations are becoming more relevant in the management of stage III disease. The roles of other alterations and biomarkers such as ALK (anaplastic lymphoma kinase) rearrangements and PD-L1 (programmed death-ligand 1) remains to be elucidated.

Tips of caution[2]

- Patients with unknown or negative PD-L1 status should not be excluded from treatment with consolidation durvalumab.
- Patients with *EGFR* mutations should not be excluded from consideration for consolidation durvalumab after definitive chemoradiotherapy.

## *Summary*

Treatment for resectable and potentially resectable stage III NSCLC involves a multidisciplinary approach. We have provided a framework for this (Figure 2).

### *Abbreviations*

NSCLC, non-small cell lung cancer; CCRT, concurrent chemo-radiotherapy; PFS, progression free survival; OS, overall survival; LN, lymph node; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; EBUS-TBNA, endobronchial ultrasound guided transbronchial needle aspiration

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# Do patient characteristics contribute to treatment decisions in stage III non-small cell lung cancer (NSCLC)?

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### *Age*

Treatment for stage III NSCLC should not be withheld on the basis of age alone. Previous studies have shown controversial results in elderly NSCLC patients receiving adjuvant chemotherapy[1,2]. Combined-modality therapy can be beneficial in selected older adult patients, although it is associated with an increase in toxicity. A randomized phase III study was conducted to assess whether concurrent chemoradiotherapy (CCRT) with carboplatin resulted in longer survival than radiotherapy alone in patients older than 70 years[3,4]. These studies addressing CCRT in older patients concluded that grade 3–4 hematological toxicity and grade 3 infections were increased with CCRT, but lung toxicity was not increased[3,4]. However, a meta-analysis demonstrated that the highest risk of pneumonitis (>50%) was found in patients >65 years of age receiving carboplatin/paclitaxel[5].

Secondary analyses of older adult patients enrolled in larger trials, as well as database studies, also support the use of CCRT in carefully selected, fit patients[6-8]. These analyses of multicenter trials have focused on older adult patients with particularly good performance status. However, the findings may not be applicable to patients with an impaired performance status[9]. Furthermore, older adult patients treated with chemotherapy and/or RT may be at increased risk of cardiac disorders[10].

One study showed that comprehensive geriatric assessment may help to determine if older adult patients are fit enough to receive combined chemoradiation[11]. In 85 consecutive elderly( $\geq$ 75 years) participants, fit and moderately-fit patients receiving CCRT showed longer overall survival (OS). In those patients, a higher Vulnerable Elders Survey (VES-13) score of $\geq$ 3 was associated with shorter OS

and higher risk of G3-4 toxicity[11]. Another study also suggested that the Glasgow Prognostic Score (GPS) was useful for stratification of older stage IIIB NSCLC patients undergoing CCRT in terms of prognosis and survival[12].

Recently, the Pacific trial showed longer progression-free survival in patients with NSCLC stage III treated with durvalumab after CCRT compared to a placebo. There was no age restriction in this study, and the median age was 64 years (range 23–90 years) but age-related results showed that the experimental arm may not be as efficacious in older adults. Older patients were not analyzed separately[13].

Summary

- While data on the benefit and risk of CCRT in older patients are conflicting, age alone should not preclude CCRT.
- Data are limited for the elderly population and, in particular, in patients above 75 years of age.

### *Performance status (PS)*

No standard approach exists for poor-risk patients who are not candidates for standard combined-modality therapy. While data on age are still controversial, PS is becoming increasingly accepted as a significant negative prognostic factor in stage III disease. This has been demonstrated in the context of patients treated with surgery plus adjuvant chemotherapy and also in definitive chemoradiotherapy protocols[14]. The benefits of RT include palliation of tumor-related symptoms, local control of tumor growth, and possibly a survival advantage. The use of RT alone for patients with stage III NSCLC consistently results in longer survival[15-18].

When treatment decisions are to be made for patients with PS Eastern Cooperative Oncology Group 2 PS, an individual risk/benefit analysis is particularly important. Medical history (e.g. infections) resulting in reduced PS should be analyzed, and every attempt to treat a reversible condition, and thereafter, potentially improve the general condition and the PS, must be considered.

Summary

- Reduced PS is a significant negative prognostic factor with regard to OS results following a treatment strategy of surgery plus adjuvant therapy.
- Treatment planning must therefore be individualized.

### *Comorbidity*

Published trials of CCRT in stage III NSCLC have generally excluded patients with significant comorbidity. Previous studies indicated that patients with significant comorbidities with a PS <2 who are fit to undergo cisplatin-based CCRT achieve median survival similar to that reported in phase III trials and with relatively few late toxic effects[19]. However, another study showed that poorer tolerance and higher incidence of acute esophagitis also noted in the patients with a higher Charlson Comorbidity Index (CCI) of $\geq 5$ in the CCRT group[20]. A prospective multi-institutional study showed that lower $FEV_1$, DLCO, and Fraction of Exhaled Nitric Oxide (FeNO) prior to CCRT predicted the development of radiation pneumonitis in NSCLC[21].

Therefore, concerns about comorbidities should be taken into consideration for patients with underline diseases who are at risk of worsened toxicities associated with CCRT.

Summary

All patients under CCRT should be assessed the major comorbidities to identify high-risk patients for close follow-up and early management of treatment-related toxicities.

### *Histology type, EGFR mutation, and PD-L1 expression*

Few large, prospective, randomized studies have compared the effects of multi-discipline treatments in stage III NSCLC with a diversity of histology type, driven oncogene, or immune status. A nationwide cohort study clarified the role of postoperative radiotherapy in pathological N2 with those of surgical resection alone in lung adenocarcinoma (wild-type EGFR) and squamous cell carcinoma patients[22]. In this study, adjuvant CCRT or sequential CT significantly reduced the mortality rate of female lung adenocarcinoma (wild-type EGFR) and male squamous cell carcinoma N2 patients[22].

In one study, an NSCLC with mutant EGFR group receiving CCRT, the progression-free survival time was significantly shorter compared with the patient group with tumors exhibiting wild-type EGFR[23]. The frequency of distant metastasis was significantly higher in the mutant EGFR group, and the brain was the most common site of distant metastasis[24]. These data suggest that additional studies are required to identify strategies for reinforcing the efficacy of CCRT, with a focus on the potential use of EGFR tyrosine kinase inhibitors for patients exhibiting an EGFR mutation.

Among stage III NSCLC patients who received CCRT, there is a trend toward poor survival in those who expressed PD-L1. A recent study indicated that a combination of lack of PD-L1 expression and CD8+ tumor-infiltrating lymphocytes (TIL) density was significantly associated with favorable survival in these patients[25]. However, the

clinical relevance of PD-L1 expression in stage III NSCLC patients who have received CCRT needs more evidence.

The PACIFIC trial did not select patients based on EGFR mutation or PD-L1 expression, and it reported that durvalumab reduced progression regardless of tumor histology type, PD-L1 expression, or EGFR mutation status[13,26]. There was a trend toward decreasing risk of progression with durvalumab in patients with PD-L1 expression $\geq$ 25%[26]; however, PD-L1 testing was not performed in over one-third of patients[13]. EGFR status was unknown in approximately one-fourth of patients. In the 6% of patients with EGFR mutations, the benefit of durvalumab was unclear[13]. Patients with ALK translocations were not excluded from the PACIFIC trial, but no data specific to their outcomes were reported. Further research into both targeted therapy and immunotherapy in these patients is needed to determine their optimal management.

## Summary

Future research into the development of accurate biomarkers, such as PD-L1 expression and tumor mutation burden, and into the optimal timing between chemoradiation and immunotherapy, will be critical.

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# Operable stage III disease

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) inhibitors provide good treatment efficacy in stage IV non-small-cell lung carcinoma (NSCLC) patients. However, the efficacy and safety of EGFR-TKIs in neoadjuvant/adjuvant therapy for NSCLC remain inconclusive.

Among patients with potentially operable lung cancer, effective neoadjuvant therapy could reduce the risk of incomplete resection and prevent pneumonectomy. A previous study demonstrated that neoadjuvant chemotherapy provided equivalent survival impact with adjuvant chemotherapy[1]. In a randomized phase 2 study (the EMERGING-CTONG 1103 trial) erlotinib was administered neoadjuvantly for 42 days and adjuvantly for 12 months in patients with clinical stage IIIA (N2) EGFR-mutated NSCLC. Neoadjuvant/adjuvant erlotinib was associated with significantly longer progression-free survival (21.5 versus 11.4 months, hazard ratio [HR]=0.39, $p<0.001$) and lower grade 3/4 toxicity (0% versus 29.4%) compared with chemotherapy of gemcitabine/cisplatin. In addition, the use of erlotinib was also associated with a relatively higher objective response rate (ORR) (54.1% versus 34.3%, $p=0.092$), higher R0 resection rate (73.0% versus 62.9%, $p=0.358$), and higher lymph node down-staging (10.8% versus 2.9%, $p=0.185$)[2]. Similarly, a cohort study which enrolled 11 ALK-positive N2 NSCLC patients also revealed that neoadjuvant crizotinib was feasible and well-tolerated[3]. However, there is no other study supporting the use of EGFR-TKIs in the neoadjuvant setting and no randomized trial being conducted on ALK-positive NSCLC. The use of neoadjuvant EGFR-TKIs or ALK-TKIs may be considered only as an alternative for patients unsuitable for neoadjuvant chemotherapy. Some ongoing studies also used TKIs in the neoadjuvant setting, including NEOGATE/ NCT02347839 (gefitinib), NCT03088930 (crizotinib), and NCT03433469 (osimertinib).

Since treatment failure following potential curative surgery is frequently encountered, effective adjuvant systemic therapy is an important treatment strategy to reduce the risk of recurrence and improve overall survival (OS) outcomes. A randomized trial (RADIANT) revealed that 2 years of erlotinib treatment provide relatively longer disease free survival (DFS) benefit than placebo (46.4 versus 28.5 months, HR 0.61, p=0.039) in the subgroup with activating EGFR mutation[4]. This difference, however, was not significant according to the initial statistical design. In a phase 2 single arm study (SELECT), 2 years of erlotinib could improve DFS compared with historic genotype-matched controls. In addition, erlotinib rechallenge could still provide durable response in disease recurrence[5]. However, the result must be interpreted with caution since it was a single-arm study. Furthermore, the open-label phase 2 trial (EVAN) revealed that 2 years of erlotinib treatment could provide longer DFS than vinorelbine/cisplatin in patients with pathologic stage IIIA EGFR-mutated NSCLC (42.4 versus 21.0 months, HR=0.268, p<0.001)[6]. Another open-label phase 3 study (the ADJUVANT trial) which focused on patients with pathologic stage II–IIIA EGFR-mutated NSCLC also demonstrated that 2 years of treatment with gefitinib could provide longer DFS than vinorelbine/cisplatin (28.7 versus 18.0 months, HR=0.60, p=0.005)[7]. A post-hoc analysis of the ADJUVANT trial also revealed that 2 years of gefitinib treatment could delay both intracranial and extracranial recurrences[8]. Based on the aforementioned studies, EGFR-TKIs might have promising treatment efficacy in the adjuvant setting regarding better DFS.

However, both the EVAN and ADJUVANT trials did not provide adjuvant chemotherapy in both arms, which limits the use of adjuvant EGFR-TKIs only to patients who do not tolerate chemotherapy. The advantage has not been translated into

prolonged OS. A recent meta-analysis study also reported that among patients with EGFR-mutant NSCLC, adjuvant EGFR-TKIs improved the DFS but not OS compared with the placebo and adjuvant chemotherapy. This meta-analysis also found that treatment with adjuvant EGFR-TKIs was associated with more adverse events compared with the placebo but fewer adverse events compared with adjuvant chemotherapy[9]. The ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) aims to identify patients with EGFR and ALK mutations with resected high-risk NSCLC and facilitate enrolment to adjuvant targeted therapy trials following completion of standard adjuvant therapy. The study will provide evidence regarding whether targeted therapy can be part of curative care in NSCLC and genomic analysis of tumor samples will advance the understanding of the disease biology[10]. There are other ongoing studies that also use TKIs in an adjuvant setting, including IMPACT/ WJOG6410L (gefitinib), ML 28280/ NCT01683175 (erlotinib), ICTAN/ NCT01996098 (icotinib), ADAURA (osimertinib)[11], and ALINA/ BO40336 (alectinib).

### *Inoperable stage III disease*

Previous cohort studies that focused on stage III non-squamous NSCLC treated with definitive CCRT revealed that the presence of EGFR mutation leads to a short PFS and a higher brain metastasis rate[12,13]. Given the high response rate and better intracranial disease control yielded by EGFR-TKI, an increasing number of studies have incorporated EGFR-TKIs into the definitive treatment of unresectable stage III disease. A phase II open-label randomized trial compared concurrent radiotherapy in combination with erlotinib or etoposide plus cisplatin in unresectable stage III NSCLC. The progression-free survival was significantly longer in the erlotinib arm (27.86 vs 6.41 months, HR=0.053, $p<0.001$)[14].

However, the number of patients was too small to support the combination of erlotinib and radiotherapy in clinical practice. A phase III study (LAURA/NCT03521154 trial) assessed the role of osimertinib as maintenance therapy following CCRT among patients with inoperable stage III disease. Another ongoing phase II trial (WJOG6911L) will assess the efficacy of concurrent gefitinib and thoracic radiotherapy in patients with inoperable stage III NSCLC. Durvalumab provides a better OS compared with placebo in patients with unresectable stage III NSCLC after CCRT. However, only 6% of all patients had EGFR mutation and the number of events was too small to assess the OS[15,16]. Therefore, the role of consolidation immunotherapy in patients with inoperable EGFR-mutant NSCLC after CCRT remains controversial.

## *Summary*

Stage III NSCLC is very heterogeneous, and the role of targeted therapy also varies accordingly. For patients with operable stage III disease deemed unsuitable to undergo adjuvant chemotherapy, 2-year adjuvant EGFR-TKI could be considered as an alternative treatment choice after curative resection. Conversely, there is no role for targeted agents in inoperable EGFR-mutant or ALK-positive stage III NSCLC. Enrolment in clinical trials is recommended for this subgroup of patients. In conclusion, stage III NSCLC patients with driver mutations should be evaluated by a multidisciplinary team specifying the situation as a whole and defining the treatment strategy accordingly.

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# Is there a place for immuno-therapy agents in the treatment of stage III NSCLC?

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Immunotherapy based on immune checkpoint inhibitors (ICIs) has been approved by the Food and Drug Administration as second-line treatment against advanced non-small-cell lung carcinoma (NSCLC) since 2015. Subsequent clinical studies about ICIs confirmed their acceptable safety profile and survival benefits for patients with advanced NSCLC, not only as single agent in selected patients, but also as combined agent with chemotherapy with/without anti-angiogenesis inhibitor in non-selected patients.

A preclinical study indicated that radiotherapy may upregulate PD-L1 expression in vivo and in vitro, through the phosphoinositide 3-kinase (PI3K)/AKT and signal transducer and activator of transcription 3 (STAT3) pathways[1]. The expressed PDL-1 ligands would interact with inhibitory PD-1 receptors on T cells and block the T-cell-dependent immune response. Radiotherapy in combination with anti-PD-L1 antibody was proven to enhance synergistically antitumor immunity by promoting CD8-positive T cell infiltration and reducing the accumulation of myeloid derived suppressor cells and tumor-infiltrating regulatory T cells in a mouse model[1].

The PACIFIC trial, a phase III, placebo-controlled, double-blinded study evaluated the efficacy of the anti-PD-L1 antibody durvalumab as consolidation therapy for patients with unresectable stage III NSCLC that remained controlled after concurrent chemoradiotherapy (CCRT). In this trial, patients who met the inclusion criteria were randomized to receive either durvalumab (10 mg/kg every 2 weeks for 12 months) or placebo as consolidation therapy 1–42 days after CCRT[2,3].

Durvalumab significantly improved the overall survival (OS) (not reported vs 28.7 months, hazard ratio [HR]=0.68, p=0.0025) and progression free survival (PFS) (17.2 vs 5.6 months, HR=0.51; 95% confidence interval, 0.41–0.63) compared to placebo. In addition, durvalumab was proven to have better outcomes regarding secondary endpoints, including the overall response rate (30% vs 17.8%, p<0.001) and median duration of response (73.5% vs 52.2% at 18 months)[3]. Besides, the median time to death or distant metastases was 28.3 months for durvalumab and 16.2 months for placebo. Patients who received durvalumab had lower incidence rates of metastases (22.5% vs 33.8%) and brain metastases (6.3% vs 11.8%)[3]. The most frequent adverse events that led to a discontinuation of durvalumab were pneumonitis (4.8% [durvalumab] vs 2.6% [placebo]), radiation pneumonitis (1.3% [durvalumab] vs 1.3% [placebo]), and pneumonia (1.1% [durvalumab] vs 1.3% [placebo]). Serious adverse events occurred in 29.1% of the patients in the durvalumab group and in 23.1% of those in the placebo group, and death due to adverse events occurred in 4.4% and 6.4% of patients, respectively[3].

The PACIFIC trial established consolidation durvalumab as a new standard of care for patients with unresectable stage III NSCLC. However, several questions remain to be answered. First, regarding patient selection, benefits in PFS and OS with durvalumab was observed irrespective of PD-L1 status, except the OS in the subgroup with PD-L1 expression less than 1%. Thus, is it possible to precisely select patients who would benefit from consolidation durvalumab using other markers? Second, the optimal timing between CCRT and durvalumab should be defined more clearly. It appeared that greater PFS improvement was noted in patients with early durvalumab use (less than 2 weeks after

CCRT). The most appropriate ICI (anti-PD-1 vs anti-PD-L1) to be used and the optimal duration of immunotherapy administration (1 vs >1 year) also need to be determined further. Third, among patients who receive sequential chemoradiotherapy or patients who undergo tumor removal after CCRT, the role of ICIs should be clarified. Fourth, the small number of patients with EGFRm+ trial in the PACIFIC trial did not enable a conclusion to be made. No patients with ALK+ disease were included in the PACIFIC trial. The role of ICIs in stage III NSCLC patients with driver mutation after CCRT needs to be confirmed.

## *Recommendation*

Consolidative durvalumab for 12 months after completion of concurrent chemoradiotherapy should be considered in unresectable stage III NSCLC.

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# IV.Follow-up

# What is the optimum follow-up period after radical therapy for patients with stage III NSCLC?

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After radical therapy, NSCLC patients should be followed for treatment-related complications, detection of treatable relapse, or occurrence of second primary lung cancer. Patients may require more frequent clinical follow-up for the management of radiation toxicities during the first year. In addition, NSCLC patients should be offered smoking cessation, as this leads to superior treatment outcomes[1,2].

There is no available evidence from randomized trials to define optimal follow-up among patients treated for stage III NSCLC after radical therapy. Currently, experts can only recommend follow-up strategies, either based on evidence from follow-up policies in large clinical trials, individual physician decisions, or consent policies.

Following radical therapy, patients should be followed up with a contrast-enhanced chest/upper abdominal computed tomography (CT) scan (including the adrenals), in addition to routine history taking and physical examination. As most cases of relapse/recurrence occur within the first few years of treatment, imaging should be performed every 3–6 months for the first 3 years, every 6 months for the next 2 years, and annually thereafter. Routine positron emission tomography-CT scans are not recommended for surveillance but may be considered when abnormalities are detected on CT scan. In cases of suspected relapse/recurrence, pathologic confirmation is advised, particularly if there has been a long interval after radical treatment[3,4].

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# V.MDT

# What is the role and value of the multidisciplinary team in the management of stage III disease and how should it work?

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The management of patients with stage III lung cancer is quite complex. Treatment planning includes multiple staging modalities, neoadjuvant and adjuvant treatments, special surgical techniques, and palliative therapy. It is challenging for single providers to be familiar with the variety of subspecialty treatment options. Treatment recommendations should be made by a multidisciplinary team (MDT). The members of the MDT include a pulmonary specialist, medical and radiation oncologist, thoracic surgeon, pathologist, radiologist, nursing coordinators, nutritionist, social workers, and allied health staff.

MDT care reduces the number of procedures patients have to undergo for diagnosis[1] and significantly increases the proportion of patients who undergo complete staging and adherence to evidence-based guidelines while decreasing the interval from diagnosis to treatment[2]. MDT care increases access to different treatment modalities, including surgery, chemotherapy, and radiotherapy and improves enrollment in clinical trials[3]. It also results in improved survival[4-7] ,patient satisfaction[8], and quality of life among patients.

Several requirements need to be met for the MDT to function effectively: good leadership, positive team dynamics and communication, adequate administrative support, good-quality complete information, and sufficient staff time[9].

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