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

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Abstract

In recent years huge change regarding the treatment of early-stage lung cancer I–IIIA NSCLC. Traditionally Surgery use to be the best treatment for early-stage NSCLC. Postoperative adjuvant chemotherapy has been associated with better overall survival (OS) in patients with early-stage disease. However, even for the patients with stage I NSCLC, the 5-year lung cancer-specific mortality rate after radical resection has remained unsatisfactory such stage. With the introduction of target therapy as well immunotherapy new hope came at the end of the tunnel to treat early-stage NSCLC. (1). Such regimens have gradually been adopted in early-stage NSCLC, with encouraging short- and long-term outcomes. (2). In this review consensus of management well be discuses based upon the most recent international conferences like Translational Lung Cancer Research and American Association of Thoracic Surgery will help physicians as well as surgeons all around nation to deliver the best the treatment strategy for the patients. The consensus well includes appropriate diagnostic, surgical modality, definition of the concept complete lung resection, features of resected N2 disease, role of target, immunotherapy in management of early-stage lung cancer I–IIIA NSCLC and role of radiotherapy in resected N2 disease.

Keywords: *Consensus surgical modality for early-stage lung cancer I–IIIA; Definition of the concept complete lung resection; Features of resected N2 disease; Role of target; Immunotherapy in management of NSCLC; Role of radiotherapy in resected N2 disease*

Description

In recent years the mainstay of treatment for stages I–IIIA NSCLC is radical surgery coupled with neoadjuvant or adjuvant therapy in the appropriate setting [1]. Such regimens have gradually been adopted in early-stage NSCLC, with encouraging short- and long-term outcomes [2] In this review consensus of management well be discuses based upon the most recent international conferences to ensure the treatment strategy was state of the art. Guideline development panel consisting of thoracic surgeons and oncologists from around the world was established to decide best treatment strategy [3,4].

Treatment decision of NSCLC depend upon conformation of the diagnosis using the 8th TNM staging system. The appropriate staging for those patients should include Oncological CT scan of the chest and PET imaging. Brain imaging as well as invasive mediastinal staging should be performed in patient with central tumors, tumors more than 3 cm. Invasive Mediastinal lymph node sampling to be done using EBUS/EUS.

Video assisted mediastinoscopy should be delayed after multimodality treatment in case of positive node to confirm negative lymph node before major surgery [5].

Application of Surgical principles for treatment of those patient have not been changes. These priceable include

1. The tumor and all accessible Mediastinal lymph node stations should be removed completely.
2. En bloc resection of closely adjacent or invaded structures.
3. Avoid tumor spillage during surgery.
4. Assesses the resection margins by frozen-section analysis.
5. Positive resection margins should be Re-resected whenever is possible [6].

The International Association for the study of lung cancer define the concept of complete lung resection [7].

• Free resection margins (microscopically) including bronchial, vascular, other

• Lobe-specific systematic nodal dissection (these should include total of six lymph nodes, three mediastinal nodal stations, always including the subcarinal, two others depending on the lobar location of the primary tumor, and three hilar-intrapulmonary stations)

• No extracapsular involvement in those lymph nodes, removed separately

• The highest mediastinal lymph node must be negative.

Type of surgical resection

Surgical stander of treatment has been changes over last years. Early in 1940s the stander of treatment used to be Pneumonectomy. Lobectomy become stander of treatment in 1960. Randomized trial of lobectomy versus limited resection for T1 NO non-small cell lung cancer in published in 1995 by lung cancer group become standard of treatment [8]. This paper prove that limited resection has higher death as well as higher locoregional recurrence rate in compare to lobectomy for patients with peripheral T1 NO NSCLC. Since that time lobectomy become the stander operation for resection of NSCLC. In 2005 video assisted thoracoscopic surgery for resection of lung cancer has gain popular for the procedure. Robotic surgery started in 2010 with excellent outcome [9].

Recently phase three randomized control trail of Segmentectomy versus lobectomy for small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L) shows new concept [10]. It clearly demonstrates the superiority of Segmentectomy in compare to lobectomy, however the progression free survival shows no difference between both groups. Segmentectomy was associated with higher incidence of local relapse 10.5% compare to 5.4% lobectomy group. 10 patients in segmentectomy group had recurrence in surgical margin in compare to 0 patent in another group.

The American Association for Thoracic Surgery clinical practice standard committee Panel Committee Consensus that up-to-date lobectomy still the stander of care for resection of operable patient. segmentectomy is an acceptable approach for patient with high risk for lobectomy or who have multiple nodules [4,10].

Early initiation of a molecular sequence epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and other rare gene alterations as well as the anti–programmed death ligand 1 (PD-L1) and other biomarker analysis are necessary to guide new strategic treatment. These play an essential role in the planning of multidisciplinary therapy. Early patient referral to oncology team should be done once the diagnosis of NSCLC is confirmed to aid the decision-making process regarding neoadjuvant or adjuvant therapy for the best patient outcome [4].

Stage III non-small cell lung cancer (NSCLC) with N2 disease

This describes group of patients with heterogeneous disease. The presentation of the disease can range from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky nodal disease [11]. British Thoracic Society establish guideline for resectable N2 disease. N2 disease with non-fixed, non-bulky, single station N2 with reasonable chance clear margins should be treated with surgery after neoadjuvant therapy [12].

Surgical criteria for N2 resection should include: conformation of the diagnosis of NSCLC, prober radiological staging, prober using of mediastinal staging using EPUS or surgical mediastinoscopy, the original tumor is distinct from the nodal disease, with N2 discreet easily measurable not encasing mediastinal structure. This should aim to achieve R0 resection using lobectomy. Pneumonectomy or other resection should be avoided as it carries morbidity with adjuvant therapy. Patient should have good Physiologic reserve to tolerate surgery as well as adjuvant therapy post operative to achieve cure.

Neoadjuvant therapy

For oncological resect able stage II & III NSCLC lacking a EGFR and ALK mutation regardless of the PD-LA status platinum base neoadjuvant chemotherapy in combination with immunotherapy is the preferred neoadjuvant regimen [13].

This is based on checkmate 816 study. The addition of nivolumab resulted in a statistically significant improvement in EFS, with a 37% reduction in the risk of progression, recurrence, or death [hazard ratio (HR) 0.63; 95% CI: 0.45–0.87; P=0.0052] compared to chemotherapy alone. Nivolumab plus chemotherapy yielded a median EFS of 31.6 months [95% CI: 30.2 to not reached (NR)] compared to 20.8 months for patients treated with chemotherapy alone (95% CI: 14.0–26.7). Additionally, 24% of patients treated with nivolumab plus chemotherapy achieved pathologic complete response rate (pCR) (95% CI: 18.0–31.0), compared to 2.2% in those treated with chemotherapy only (95% CI: 0.6–5.6; estimated treatment difference 21.6; 95% CI: 15.1–28.2; P<0.0001). This combination in fact did not impact in surgical procedure or 90 days complications.

This combination is preferred as neoadjuvant over adjuvant therapy except for patient with EGFR/ALK and other mutation.

Neoadjuvant platinum base chemotherapy alone is recommended for patients who have contraindication to immunotherapy. New adjuvant immunotherapy alone or in combination with other agents and/or radiation therapy should not be considered outside the setting of a clinical trials [4].

Adjuvant therapy

Medical oncology referral as well as discussion in tumor board should be done for all new cases of NSCLC. Post-surgical resection all NSCLC patient with pathological stage IB–III should be referred to medical oncology for discussion of adjuvant

systemic therapy. Especially patients without pathological nodal Disease, high risk features (lymph vascular invasion, visceral plural invasion, large tumor size, positive margin, in adequate nodal sampling) as adjuvant therapy well improve outcome of those patients [4].

All resected stage IB-III NSCLC should undergo comprehensive testing for molecular alteration as well PD-L1 stanning. Patients with resected stage II-IIIA lung squamous cell carcinoma should undergoPD-L1 stanning [4].

All resected stage IB-III lung adenocarcinoma and with EGFR mutation should be discus for adjuvant Osimertinib with or without adjuvant chemotherapy [14]. The ADURA study shows that Osimertinib as adjuvant therapy is an effective new treatment strategy for these patients after complete tumor resection. Osimertinib result in 80% reduction in the risk of disease recurrence or death, indicated that disease-free survival was significantly longer among patients in the group than among those in the placebo group (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001). The ADURA trail shows an 82% reduction in the risk of CNS disease recurrence or death with Osimertinib (Hazard ratio, 0.18; 95% CI, 0.10 to 0.33). The disease-free survival benefit with Osimertinib was observed irrespective of whether patients received adjuvant chemotherapy or not [14].

All restricted stage II-IIIA NSCLC with (PD-L1) stanning > /=1% should be referred for medical oncology for consideration of adjuvant Atezolizumab after adjuvant chemotherapy (based on IMpower110) [4,15]. Among patients with EGFR and ALK wild-type tumors who had high PD-L1 expression, the median overall survival was significantly longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months *vs.* 13.1 months; stratified hazard ratio for death,0.59; 95% confidence interval [CI], 0.40 to 0.89; P=0.01).it have been found that most benefit was in patients with high expression of PD-L1> 50% [15].

Role of radiotherapy in Management early of Early-Stage Resected NSCLC

In patients with non-small-cell lung cancer (NSCLC), the use of postoperative radiotherapy has been controversial since 1998, because of one meta-analysis showing a deleterious effect on survival in patients with pN0 and pN1, but with an unclear effect in patients with pN2 NSCLC [16].

For a patient with Ontologically Resectable and medically Operable NSCLC with N2 for whom surgery is planned, preoperative systemic therapy without radiotherapy is recommended. Only those patients with superior sulcus tumor with no evidence of N2 disease, neoadjuvant chemoradiotherapy is preferred [4].

Recent randomized, phase 3 trial (Lung ART) demonstrate no benefit of routine postoperative radiotherapy in patients with completely resected N2 NSCLC S. In fact, this well not affect the overall survival rather than it well result in increased the cardiopulmonary toxicity [17].

Conclusion

Conclusion Treatment for stages I–IIIA NSCLC with radical surgery coupled with neoadjuvant or adjuvant therapy using target therapy as well as immunotherapy change the outcome of the disease. Traditional way of treating such dieses have been changes with better short- and long-term outcomes. New knowledge is coming so fast and physicians have to keep up to date to deliver the best treatment strategy for the patients.

Conflict of Interest Statement:

We have no conflicts of interest. This consensus delivers the last update of resent knowledge in treatment of earl stage NSCLC treatments.

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