

# The evolving locally-advanced non-small cell lung cancer landscape: Building on past evidence and experience

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## Summary

Lung cancer is a major public health concern worldwide. Progress in improving 5-year survival is lagging behind comparable survival rates in other common cancers. The majority of patients with locally advanced non-small cell lung cancer (NSCLC) are not suitable for surgical resection, hence the major role of radical radiotherapy. Advances in radiotherapy techniques allow targeted treatment of the disease, whilst minimizing the dose to organs at risk. Recent research into fractionation schedules, with hyperfractionated and accelerated radiotherapy regimens has been promising. Platinum-based chemotherapy has long been the standard of care for the initial treatment of advanced NSCLC. However, if radical radiotherapy remains the cornerstone of treatment for patients with unresectable advanced NSCLC either as single modality treatment or with concomitant chemotherapy, advances in understanding of tumor molecular biology and targeted drug development should bring targeted agents into the NSCLC management. The development of numerous therapeutic approaches has made the locally advanced NSCLC world change. An up-to-date overview of the current literature on updated chemotherapeutic agents, targeted therapy, immunotherapy, radiotherapy in stage III NSCLC is provided.

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## 1. Introduction

Non-small-cell lung cancer is the most frequent cause of death due to cancer in men in the Western world, and its incidence among women is increasing [1]. NSCLC is a heterogeneous disease but consists of two main histological varieties: squamous and non squamous cell carcinomas. Surgical resection is the well recognized treatment for localized NSCLC, but more than one-third of patients present with locally advanced and unresectable tumors (stage IIIA or IIIB) at initial diagnosis [2]. The standard of care for locally advanced inoperable NSCLC is a concurrent chemoradiation in order to offer these patients the highest potential for prolonged disease-free and overall survival [3,4]. The outcome of these patients with stage III disease at presentation remains poor with median survival from 15.3 to 21.7 months [5]. Chemotherapy regimen generally contains a platinum doublet with modest efficacy [6], necessitating the search for renewal treatment approaches to improve clinical outcomes. Furthermore, an estimated 60% of patients with locally advanced disease are not fit enough for concomitant chemo-radiotherapy due to poor performance status and co-morbidities [7]. Subsequently, novel therapeutic strategies are urgently needed and the best treatment strategy has yet to be framed. Recent advances in systemic cytotoxic and molecularly therapies coupled with technologic strides in radiotherapy could have the potential to improve outcomes for patients with NSCLC. Investigations are ongoing to identify optimal chemo-radiotherapy regimens. The influence of specific histologic and molecular mutation status on the combination of targeted therapies and radiotherapy is also being actively studied [8,9]. The aim of the present article is to provide an overview on the current and optimum radiochemotherapy strategy in 2015 for treating locally advanced NSCLC.

## 2. Management of locally-advanced NSCLC: Context and caveats

The most important recent advance in NSCLC has been the revisions to the lung cancer staging classification. Historically, stage III lung cancer was defined as locoregionally advanced disease attributed to primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0). With the 2009 revisions to the TNM staging system, stage III lung cancer now includes T3 tumors when associated with hilar (N1) nodal involvement [10,11]. Nearly 50,000 Americans are diagnosed each year with NSCLC that is confined to the thorax and not amenable to potentially curative resection because of invasion of adjacent structures and/or lymph node metastases. These patients have stage III disease according to the 2010 American Joint Commission on Cancer (AJCC) staging system and the optimal management of this large and heterogeneous population remains controversial [12]. The poor prognosis of patients with locally

advanced NSCLC has remained essentially unchanged in recent decades. At diagnosis, only 15% of all patients are considered candidates for surgery [13]. Furthermore, an exact definition of the term “unresectable” may not be possible according to Detterbeck and al; data show that a substantial proportion of patients with stage IIIA (N2) tumors judged to be resectable end up undergoing an R1,2 resection, further calling into question the accuracy of this term [14]. The importance of appropriate stage evaluation must be emphasized, particularly for patients with stage III. The introduction of PET imaging has created a significant stage shift through finding asymptomatic occult distant metastases, resulting in better survival of patients with stage III. Accurate preoperative staging of mediastinal lymph nodes in patients with potentially resectable NSCLC is of paramount importance. Currently, invasive mediastinal staging either by fine needle aspiration using EBUS-EUS or by tissue sampling by video mediastinoscopy classifies correctly almost 90% of cases but still some patients are found to have macro or microscopically evidence of mediastinal spread at thoracotomy if mediastinal staging is performed according to internationally admitted criteria [15–17]. Of course, other factors such as performance status and comorbidities are important to consider in planning the best treatment approach for patients with stage III NSCLC. In these patients, complete tumor resection can be achieved in selected cases. Each case should be discussed at the tumor board to plan the best treatment strategy. If T4N0–N1 (IIIA) patients should be treated with aggressive multidisciplinary therapy in a manner that maximizes the chance for long-term cure, it is not the case for T4N2 disease (IIIB). This subgroup should be considered as a potential contraindication to resection of T4 tumors. The 5-year survival rates are 43% vs. 17% for T4N0-1 and for T4N2-3 respectively [18]. Multiple nodal station and especially with a N2 disease is a worsen prognosis factor for T4 tumor [19]. Advances, in the perioperative management and postoperative care, along with a careful patient selection, will likely make the operative mortality and morbidity less prohibitive and yield a more favorable prognosis. Sleeve lobectomy has to be considered whenever possible because pneumonectomy is still a contraindication in this setting, particularly when it is a right resection [20]. Thorough and individualized discussion of each stage IIIB case is encouraged in the context of a multidisciplinary team. We have to keep in mind that surgery still has a paramount role in the therapy of advanced NSCLC, for a small percentage of cases. In parallel, for patients with unresectable tumors, approximately 20% of patients achieve durable disease control, arguing for treatment with curative intent in those able to tolerate aggressive therapy [21–23].

## 3. Combined chemotherapy with radiotherapy in locally-advanced NSCLC

Treatment strategies for stage III NSCLC have evolved substantially in recent years but a cornerstone remains:

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