Commentary

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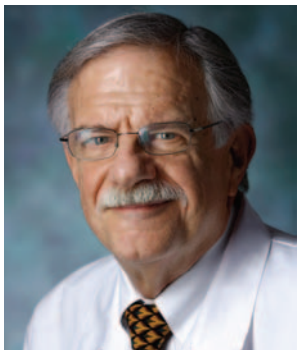
Ten Years of Progress in Non–Small Cell Lung Cancer



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The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.

Lung cancer is the leading cause of cancer death in the United States in both men and women. An estimated 226,160 new cases will be diagnosed in 2012, and 160,340 deaths are estimated to occur from the disease. Only 15.6% of all patients with lung cancer are alive 5 years or more after the diagnosis.

These statistics, however, do not mean that no progress has occurred in treating lung cancer in the past 10 years. In fact, the question of "what has changed since the 2002 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC)" brings to mind several significant advances in screening, staging, surgery, radiation therapy, and chemotherapy/targeted therapy for NSCLC. This commentary details some of those advances.

Screening

In 2011, a randomized study reported that lung cancer screening with low-dose CT may decrease lung cancer mortality (by approximately 20%) in certain high-risk individuals (those aged > 55 years and who smoke > 30 packs/year).[1] This led to the development of the recently published NCCN Guidelines for Lung Cancer Screening.

Staging

Version 1.2002 of the NCCN Guidelines for Lung Cancer stated that use of PET scan was optional in stage I disease and recommended for stage IIB and IIIA "if available." The guidelines noted at the time that use of PET scan was being evaluated in lung cancer staging at many NCCN Member Institutions.[2] Now the PET/CT scan has been shown to improve cancer staging and prevent unnecessary thoracotomies.

In addition, the use of endobronchial ultrasound (EBUS)–guided fine-needle aspiration and endoscopic ultrasound (EUS) in histologically staging the mediastinum has increased significantly, with a high sensitivity rate (> 90%), low false-negative rate (< 10%), and a specificity rate of almost 100%.[3] As the availability of EBUS and EUS increases, the need for mediastinoscopy will decrease.

In 2010, the AJCC changed the staging for lung cancer. The T classification was redefined; no changes were made to the N classification; and the M classification was redefined with M_1, which is divided into M_{1a}, referring to pleural nodules or pleural and pericardical effusion, and separate tumor nodules in the contralateral lung, and M_{1b}, referring to distant metastases.[4] In addition, adenocarcinoma was recently reclassified. For example, adenocarcinoma in situ replaced bronchoalveolar carcinoma.[5] Other changes include minimally invasive adenocarcinoma, invasive adenocarcinoma, and invasive adenocarcinoma variants.

Surgery

Although only 20% of pulmonary resections in the United States use video-assisted thoracoscopic surgery (VATS), this technique seems to be gaining greater acceptance in early-stage lung cancer.[6] Data show that VATS lobectomy decreases morbidity (e.g., decreased postoperative pain, shorter chest tube duration, shorter length of stay in the hospital, preservation of pulmonary function, shorter recovery time) compared with routine thoracotomy. In one study,[6] 945 patients (73.8%) had no complications after VATS lobectomy, compared with

847 patients (65.3%) with no complications after lobectomy via thoracotomy ($P < .0001$). Compared with open thoracotomy, VATS lobectomy was associated with a lower incidence of reintubation (1.4% for VATS vs. 3.1% for thoracotomy; $P = .0046$), blood transfusion (2.4% vs. 4.7%; $P = .0028$), and arrhythmias (7.3% vs. 11.5%; $P = .0004$), and a shorter length of stay (4.0 vs. 6.0 days; $P < .0001$) and chest tube duration (3.0 vs. 4.0 days; $P < .0001$). No difference was seen in operative mortality.

Radiation Therapy

Since stereotactic body radiation therapy was developed in the mid-1990s at the Karolinska Institute in Sweden, its use has increased significantly for treating medically inoperable early-stage NSCLC and oligometastases in the lung, liver, spine, and adrenal gland. In the past 10 years, its efficacy and safety has been demonstrated, and its use continues to increase.[7] Several published studies of stereotactic body radiation therapy in NSCLC—primarily in stage I medically inoperable disease and usually retrospective—show a local control rate from 80% to 100%. The reported overall survival (OS) has been variable partly because of the heterogeneity in the criteria used to select patients.

Systemic Therapy: Chemotherapy, Targeted Therapy, and Personalized Medicine

More than 40% of NSCLC is stage IV disease at diagnosis. Before 2006, the treatment of stage IV NSCLC was empiric, usually a platinum-based doublet. However in 2006, the FDA approved use of the anti-vascular endothelial growth factor monoclonal antibody, bevacizumab, with paclitaxel and carboplatin (PCB). This approval was based on the results of the ECOG randomized phase III study comparing the PCB regimen with paclitaxel and carboplatin, which showed response rates of 35% versus 15%; progression-free survival (PFS) of 6.2 versus 4.5 months; and OS of 12.3 versus 10.3 months.[8] Notably, the 2-year OS rate was 23% versus 15%, in favor of PCB. In this study, histology mattered: bevacizumab was only given to patients with nonsquamous histology (mainly adenocarcinoma), because bleeding was noted in those with squamous cell carcinoma, and therefore they were not eligible for this study.

Approximately a decade ago, studies of the epidermal growth factor receptor (EGFR) inhibitors gefitinib and erlotinib reported response rates of 10% to 20%. Initially, increased response and disease control rates were noted in nonsmokers, women, patients of Asian origin, and those with adenocarcinoma. In a National Cancer Institute of Canada study, BR21 erlotinib significantly improved OS compared with placebo (6.9 vs. 4.7 months), with an overall response rate of 8.9% in previously treated patients.[9] In a similar study with gefitinib, no significant improvement in OS was seen. Therefore, although erlotinib was approved for use by the FDA in previously treated patients, gefitinib was taken off the market by the FDA after the drug was given accelerated approval by the agency.

As first-line therapy, gefitinib resulted in a high response rate (71.2% vs. 47.3%) and a prolonged PFS (hazard ratio, 0.48; $P < .001$) compared with chemotherapy in patients with activating EGFR mutations.[10] Erlotinib as first-line therapy showed similar results in the European Tarceva (Erlotinib) Versus Chemotherapy (EURTAC) study involving Caucasians rather than Asians.[11] Based on the studies with the activating EGFR mutations predicting better response and survival rates in patients with adenocarcinoma, the NCCN Guidelines and ASCO recommend obtaining the EGFR mutation analysis from the tumor tissue at the time of diagnosis,[12] if possible. The EGFR mutation is found in 10% of patients with adenocarcinoma, compared with only 3% of patients with squamous cell carcinoma.

In 2011, crizotinib, a tyrosine kinase inhibitor of analplastic lymphoma kinase (ALK), received accelerated approval by the FDA for use in patients with the *ALK* gene rearrangement.[13,14] This rearrangement is present in approximately 4% of all lung cancers and is a fusion of part of EML-4 (echinoderm microtubule-associated protein-like protein 4) with the intracellular signalling of ALK, resulting in the fusion gene *EML-4 ALK*. This mutation seems to be mutually exclusive with the *EGFR* and *KRAS* mutation in the phase I study.

Adjuvant Therapy

In 2004, the International Adjuvant Lung Cancer Trial showed an approximately 5% survival advantage for adjuvant therapy compared with no therapy in patients with resected stage I–III NSCLC after 4.7 years of follow-up.[15] However, a second study after 7.5 years of follow-up showed an increased risk of noncancer deaths in the adjuvant group despite data that showed that the therapy prevented recurrences.[16] Despite this, adjuvant therapy is the "standard" in patients with resected stage II and III NSCLC.

Maintenance Therapy

During the past decade, maintenance therapy became increasingly prominent either as continuous maintenance (bevacizumab, cetuximab, pemetrexed, or gemcitabine) or switch maintenance (pemetrexed or erlotinib). In July 2009, the FDA approved use of pemetrexed as maintenance therapy in patients with NSCLC with nonsquamous histology based on a study comparing the drug with a placebo and showing a significant improvement in time to disease progression (4.04 vs. 1.97 months).[17] In addition, although first-line pemetrexed/cisplatin was not inferior to gemcitabine/cisplatin as treatment for patients with stage IV NSCLC, a significant survival advantage was noted in patients with nonsquamous histology receiving the pemetrexed doublet.

Conclusions

Over the past 10 years, significant advances have been made in the screening, diagnosis, surgery, radiation therapy, and systemic therapy (chemotherapy, targeted therapy) of lung cancer. The next 10 years will surely bring further advances to provide patients with lung cancer an opportunity for a better quality of life and longer survival, including more possible cures in what remains the number one cancer killer of both men and women.

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