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Non–Small Cell Lung Cancer: Epidemiology, Risk Factors, Treatment, and Survivorship

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Abstract

Lung cancer is the leading cause of cancer-related mortality not only in the United States but also around the world. In North America, lung cancer has become more predominant among former than current smokers. Yet in some countries, such as China, which has experienced a dramatic increase in the cigarette smoking rate during the past 2 decades, a peak in lung cancer incidence is still expected. Approximately two-thirds of adult Chinese men are smokers, representing one-third of all smokers worldwide. Non–small cell lung cancer accounts for 85% of all lung cancer cases in the United States. After the initial diagnosis, accurate staging of non–small cell lung cancer using computed tomography or positron emission tomography is crucial for determining appropriate therapy. When feasible, surgical resection remains the single most consistent and successful option for cure. However, close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. Chemotherapy is beneficial for patients with metastatic disease, and the administration of concurrent chemotherapy and radiation is indicated for stage III lung cancer. The introduction of angiogenesis, epidermal growth factor receptor inhibitors, and other new anticancer agents is changing the present and future of this disease and will certainly increase the number of lung cancer survivors. We identified studies for this review by searching the MEDLINE and PubMed databases for English-language articles published from January 1, 1980, through January 31, 2008. Key terms used for this search included *non–small cell lung cancer, adenocarcinoma, squamous cell carcinoma, bronchioalveolar cell carcinoma, large cell carcinoma, lung cancer epidemiology, genetics, survivorship, surgery, radiation therapy, chemotherapy, targeted therapy, bevacizumab, erlotinib,* and *epidermal growth factor receptor*.

Lung cancer has become the number one killer among cancers worldwide. Although lung cancer remains the leading cause of cancer-related mortality in the United States, its incidence is decreasing. In 2008, 215,020 new cases are expected and 161,840 persons are projected to die from the disease in the United States.[1]

The 2 main types of lung cancer are small cell lung cancer (SCLC) and non-SCLC (NSCLC); NSCLC accounts for approximately 85% of all cases of lung cancer.[2,3] Regional incidence variations directly reflect smoking prevalence; specifically, the lowest and the highest

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incidences of lung cancer are found in Utah and Kentucky, where the lowest and the highest smoking prevalence are also found, respectively. With the decrease in the prevalence of smoking, lung cancer has become more frequent among former than current smokers. In a cohort study of more than 5000 patients whose lung cancer was diagnosed between 1997 and 2002, only 25% were current smokers and more than 60% were former smokers.[4] Although cigarette smoking has peaked and declined in the United States and several other areas, it has dramatically increased in the past 2 decades but has yet to peak in China and other developing countries. Approximately two-thirds of adult Chinese men are smokers, representing one-third of all smokers worldwide.[5] The average daily consumption of tobacco per person in China was 10 cigarettes in 1990, a rate similar to that of the United States 40 years earlier. Therefore, the peak of smoking-related deaths is still to come in China.

RISK AND PROTECTIVE FACTORS

CIGARETTE SMOKING

The emergence of the lung cancer epidemic in the 20th century has no doubt been caused by cigarette smoking. The effect of pipe and cigar use on the risk of lung cancer is similar to that of light cigarette smoking.[6,7] In the United States and the United Kingdom, the decline in lung cancer rates is projected to level off in 2 decades because of the slow progress in smoking cessation at present. Lung cancer will remain among the top killers for decades unless radical reductions in smoking prevalence are achieved.[8]

SECONDHAND OR PASSIVE SMOKING

The causal association that has been established between secondhand tobacco smoking and lung cancer can explain 1.6% of lung cancers.[9] Results from a meta-analysis[10] and a comprehensive review[11] showed a relative risk between 1.14 to 5.20 in people who had never smoked but who lived with a smoker. A more recent study reported that passive smoking during childhood increased lung cancer risk in adulthood by 3.6 fold.[12]

DIET AND FOOD SUPPLEMENTS

Fruits and vegetables that are a rich source of antioxidant vitamins and other micronutrients, particularly carotenoids, are thought to benefit health by decreasing the risk of lung and other cancers.[13–16] Although some studies indicate carotenoids decrease lung cancer risk, results have been ambiguous, and some have even indicated that high-dose supplements can be harmful. Lutein, zeaxanthin, lycopene, and α-carotene displayed a certain protective trend, yet β-cryptoxanthin showed a more consistent protective effect. There is some evidence of a protective role for vitamins C and E, but not vitamin A; no associations were observed between intakes of total or specific types of fat and lung cancer risk regardless of smoking status. In contrast, cured meat (eg, sausage, pressed duck, and cured pork), deep-fried cooking, and chili have been associated with an increased lung cancer risk.[13–16]

ALCOHOL

From a pooled analysis of 7 prospective studies with 399,767 participants and 3137 lung cancer cases, a slightly greater risk of lung cancer was indicated among people who consumed at least 30 g/d of alcohol than among those who abstained from alcohol.[17]

EXERCISE AND PHYSICAL ACTIVITY

Available data suggest that physically active individuals have a lower risk of lung cancer: moderate to high levels of leisure-time physical activity were associated with a 13% to 30% reduction in lung cancer risk.[18–21] Overall, physical activity could help to reduce lung cancer risk and mortality among heavy smokers.[18–21]

AIR POLLUTION

Lung cancer could be one of the long-term adverse effects of cumulated exposure to ambient air pollution, such as emissions rich in various polycyclic aromatic hydrocarbon compounds, likely through oxidative stress, inflammation, induction of a procoagulatory state, and dysfunction of the autonomic nervous system.[22,23] The proportion of lung cancers attributable to urban air pollution in Europe is estimated to be 11%.[9]

OCCUPATIONAL EXPOSURE

Many work settings could have exposed workers to carcinogens, leading to an increased risk of lung and other cancers. Crystalline silica and chrysotile asbestos are well-known human carcinogens; as expected, workers exposed to silica dust and asbestos fiber are at a higher risk of developing lung cancer. Uranium miners and nuclear plant workers are also known to have an increased cancer risk because of exposure to radioactive particulate mass.[24]

LUNG CANCER SUSCEPTIBILITY GENES

Familial clustering or aggregation of lung cancer has been reported repeatedly in the past 60 years, suggesting a hereditary base to disease development.[25–30] An increased risk of lung cancer was found in the carriers of *TP53* (for expansion of gene symbols, use search tool at www.genenames.org) germline sequence variations, and carriers who smoked cigarettes are more than 3 times more likely to develop lung cancer than carriers who did not smoke.[26] The germline epidermal growth factor receptor (EGFR) T790M sequence variation was reported in a family with multiple cases of NSCLC.[27] Finally, a genome-wide linkage study of 52 extended families identified a new major susceptibility locus influencing lung cancer risk at 6q23–25p.[28] Laryngeal and throat cancers were also included in this study.

Recently, 3 independent genetic studies have found a marker on chromosome 15 associated with lung cancer. In all 3 studies, the risk was approximately 30% higher for people with 1 copy of the marker and 70% to 80% higher for people with 2 copies. The region where the marker resides contains 3 genes coding for subunits of the nicotinic acetylcholine receptor, a protein on the cell surface onto which nicotine molecules latch, triggering cell change. Although the 3 studies agree about the risk of developing lung cancer for carriers of a mutated copy of the gene, one of the investigators thinks that the genes promote cancer by making people more vulnerable to nicotine addiction.[29–31]

STAGING OF LUNG CANCER

After the initial diagnosis of NSCLC, accurate TNM staging of lung cancer is crucial for determining appropriate therapy. Most patients with stages I to II NSCLC benefit from surgical resection, whereas patients with more advanced disease are candidates for nonsurgical treatment. Conventional clinical staging is most often performed with computed tomography (CT) of the thorax and upper abdomen. Nevertheless, CT imaging has limited sensitivity for microscopic metastatic disease and is frequently unable to discriminate between mediastinal lymph nodes that are enlarged owing to malignancy and those that are enlarged owing to benign reactive hyperplasia.[32–36] In contrast, positron emission tomography (PET) with fluorine 18–labeled fluorodeoxyglucose has been shown to have greater sensitivity for the detection of metabolically active malignant disease and can lead to changes in initial staging and treatment plans for NSCLC when used in combination with conventional work-up.[35]

Although PET or PET-CT imaging is more useful than other imaging modalities for determining the nodal stage of a lung cancer, PET findings of pathology are often confirmed by mediastinoscopy. Mediastinoscopy or thoracotomy has been considered the criterion standard for mediastinal staging of lung cancer, which is necessary to define optimal treatment.

Preoperative staging is being transformed by the integration of newer technologies, such as endoscopic bronchial ultrasonography and esophageal ultrasonography to guide biopsies.[37] These technologies, in conjunction with PET scanning to aid in localization and increase the biopsy yield, might offer less invasive adjuncts to cervical mediastinoscopy.[37,38] However, currently and for the foreseeable future, cervical mediastinoscopy remains the criterion standard in preoperative nodal staging because it provides near-perfect specificity and extremely high sensitivity (>93%).[39]

A novel variation on cervical mediastinoscopy, transcervical extended mediastinal lymphadenectomy (TEMLA), is being developed in a few centers in Europe.[40] In preliminary reports, TEMLA appears to be fairly sensitive (90%) but is more invasive; it is not yet clear how this invasive procedure adds to what is obtainable by conventional cervical mediastinoscopy coupled with endoscopic bronchial endoscopy or esophageal ultrasonography. Unfortunately, a recent randomized trial comparing conventional cervical mediastinoscopy to TEMLA was halted prematurely because it was thought that the question of sensitivity had been addressed,[41] leaving trial data underpowered to comment in any plausible fashion on the equally important issue of the comparative safety of these 2 procedures. Because TEMLA is also time-consuming (median operative time, 191 minutes; range, 120–350 minutes), it does not lend itself well to completion of the pulmonary resection within the same anesthetic session when no positive lymph nodes are found.

LUNG CANCER SCREENING

Lung cancer has a dismal 5-year survival rate of 15%. Timely detection in individuals at risk could prevent, interrupt, or delay lung cancer progression. The first hurdle to overcome in achieving the goal of timely detection is precise identification of individuals at risk. After initial inconclusive studies during the 1970s, a seminal article by Henschke et al[42] in 1999 ignited a controversy about lung cancer screening by means of radiographic techniques. In a recent article, Henschke, writing for the International Early Lung Cancer Action Program, reported that, among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92%.[43] However, no current guidelines recommend mass screening for early detection of lung cancer. Further, the US Preventive Services Task Force reported that existing evidence was inadequate to either recommend or warn against the use of tools to detect lung cancer in asymptomatic patients.[44] The American Cancer Society also does not advocate screening for at-risk individuals.[45] This controversy will likely be resolved by the National Lung Screening Trial, which compares 2 ways of detecting lung cancer: spiral CT and standard chest radiography. By February 2004, this trial had registered nearly 50,000 current or former smokers; the final results of this trial are eagerly awaited.

TREATMENT

SURGERY

Surgical resection remains the single most consistent and successful option for cure for patients diagnosed as having lung cancer. For this option to be feasible, the cancer must be completely resectable, and the patient must be able to tolerate the proposed surgical intervention. Issues of resect-ability refer to preoperative staging including imaging studies and biopsy, whereas issues of operability pertain to the evaluation of patient factors and operative approaches that minimize surgical risk and morbidity. Indeed, surgery for lung cancer is prominent in diagnosis, staging, curative treatment, and palliative care. Staging remains integral to and essential for management of patients with lung cancer. Mediastinal staging, in particular, is paramount because the prognostic information it provides is invaluable in determining appropriate treatment.[46]

Surgical treatment of lung cancer for potential cure remains predicated on achieving a complete resection (R0 resection). The current criterion standard for extent of pulmonary resection is lobectomy for resectable tumors in patients deemed able to tolerate such a resection. This standard is based on the findings of a prospective randomized controlled trial showing increased long-term survival and decreased local recurrence in patients undergoing lobectomy compared with those undergoing limited resections (ie, wedge resection or segmentectomy).[47]

Recently, however, several surgical initiatives have focused on expanding eligibility for surgical resection of lung cancer to patients on the margins of operability. First, various reports are revisiting whether lobectomy is necessary for small (<2 cm) tumors with no evidence of lymph node spread.[48–50] With mixed results from mostly small retrospective series, lobectomy remains the standard for surgical management of NSCLC, with an operative mortality of 1.3%.[51] Whether segmentectomy or wedge resection can adequately treat small, peripheral bronchoalveolar or other low-grade lung cancers so as to prevent local recurrence and improve long-term survival will not be definitively answered until a prospective randomized trial revisits this issue.

On a separate front, minimal-access surgical procedures are expanding the applicability of surgical resection to patients of marginal operability. Video-assisted lobectomy, which is offered by a growing number of surgical centers, can provide a less invasive method of accomplishing the same oncologic resection with a similar long-term survival rate,[52,53] thereby allowing some patients to undergo resection who were not candidates for standard thoracotomy because of its morbidity. As the age of the general population increases, so too does the mean age of patients referred for surgical resection of lung cancer.[54,55] As techniques for limited or less invasive resections become available, patients in their ninth decade are increasingly undergoing successful surgical resection of their lung cancers with meaningful long-term survival.

CHEMOTHERAPY

Close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. Chemotherapy is beneficial for palliation in patients with locally advanced and metastatic disease.[56] Adjuvant chemotherapy is generally indicated for patients with resected stages IIA through IIIA NSCLC.

Although chemotherapy is appropriate for many patients with lung cancer, there is a sense that the use of traditional chemotherapeutic agents has reached a therapeutic plateau. Increased understanding of cancer biology has revealed numerous potential therapeutic strategies, including targeting EGFR and other signal transduction and angiogenesis pathways.

Adjuvant Chemotherapy for Resected Early-Stage NSCLC—Patients with resected lung cancer have a high risk of relapse. A meta-analysis conducted in 1995 using updated data on patients from 52 randomized clinical trials compared outcomes after surgery alone with outcomes of surgery followed by chemotherapy.[57] It showed a 5-year survival benefit of borderline significance for patients receiving platinum-based chemotherapy and prompted the initiation of several lung cancer adjuvant trials (Table).[58–66]

The International Adjuvant Lung Cancer Trial enrolled 1867 patients with resected stages IA through IIIA cancer. Patients were randomized to receive platinum-based chemotherapy or observation.[58] At 5 years, the absolute survival benefit was 4.1%, and the relative reduction in risk of death was 14% (hazard ratio, 0.86; 95% confidence interval, 0.76 to 0.98; $P<.03$).[58] The National Cancer Institute of Canada and Intergroup Study JBR.10 included 482 patients with completely resected stage IB and II (excluding T3N0) cancers. Patients in this trial were

randomized to receive 4 cycles of adjuvant vinorelbine and cisplatin or observation alone.[59] Overall survival strongly favored patients in the adjuvant chemotherapy arm, with an absolute survival benefit of 15% at 5 years and a 30% relative reduction in the risk of death (*P*=.03). The Adjuvant Navelbine International Trialist Association trial randomized 840 patients with completely resected stage IB, II, or IIIA NSCLC to receive adjuvant therapy with vinorelbine and cisplatin or observation alone.[60] After a median follow-up time of more than 70 months, a statistically significant survival advantage was detected for patients receiving adjuvant chemotherapy, with an absolute overall survival benefit of 8.6% at 5 years. The Cancer and Leukemia Group B 9633 trial failed to demonstrate a statistically significant survival advantage at 5 years.[61] This trial enrolled 344 patients with resected stage IB NSCLC who were randomized to receive 4 cycles of adjuvant paclitaxel (PTX) and carboplatin (CBDCA) or observation alone.[61] For the most part, however, phase 3 randomized clinical trials strongly support the use of chemotherapy after complete resection of stages IIA to IIIA lung cancer (Table).[58–60]

Several trials performed in Japan have addressed the issue of adjuvant chemotherapy for early-stage lung cancer.[62–69] These studies used an oral agent that combines tegafur (a 5-fluorouracil prodrug) and uracil in a 1:4 mol/L ratio (uracil-tegafur [UFT], which is given as a single agent or in combination with other chemotherapeutic agents). Currently, UFT is unavailable in the United States. In one of these studies, UFT was given to 979 patients with resected stage I lung cancer.[69] This study showed a survival benefit in favor of the UFT arm. However, a subset analysis showed that the benefit was limited to patients with stage IB lung cancer. Thus, future studies are needed to better determine the role, if any, of adjuvant chemotherapy in the treatment of patients with stage IA resected lung cancer.[66]

Treatment of Metastatic Lung Cancer—Many phase 3 studies have shown the superiority of systemic chemotherapy over best supportive care in patients with locally advanced and metastatic lung cancer. Platinum-based chemotherapy has been widely accepted as the standard of care. Several randomized clinical trials as well as meta-analyses have suggested the superiority of platinum-based over non–platinum-based therapy.[70,71] Agents such as PTX, docetaxel, gemcitabine, and vinorelbine have been incorporated into platinum-based therapy doublets and have proven to be equally effective.

Chemotherapeutic Regimens—Because of the toxicities associated with platinum-based chemotherapy, non–platinum-based regimens, in particular taxane-based regimens, have been the focus of intense research. A recent meta-analysis compared platinum-based with non–platinum-based chemotherapy in patients with advanced NSCLC.[70] This study analyzed 37 randomized phase 2 and 3 clinical trials comparing first-line palliative platinum-based chemotherapy in 7633 patients.[70] A 62% increase in the odds ratio for response was attributable to platinum-based therapy (odds ratio, 1.62; 95% confidence interval, 1.46–1.80; *P*<.001). The 1-year survival rate was increased by 5% with platinum-based regimens (34% vs 29%, respectively). No statistically significant increase in the 1-year survival rate was found when platinum-based therapies were compared with third-generation–based combination regimens.[70] Platinum-based regimens were associated with significant increases in hematologic toxicity, nephrotoxicity, and nausea and vomiting, but no such increases were noted in neurotoxicity, febrile neutropenia rate, or toxic death rate. The study concluded that, when compared with third-generation–based combination regimens, platinum–based regimens do not result in a 1-year survival rate advantage but are associated with higher toxicity.[70]

The most recent treatment guidelines from the American Society of Clinical Oncology reflect the growing acceptance by oncologists that non-platinum doublets provide advantages for certain patients.[56] The American Society of Clinical Oncology currently allows primary oncologists to decide between a platinum-based and a non–platinum-based chemotherapeutic

regimen for the initial treatment of patients with stage IV disease and good performance status.[56] Currently, 3-drug cytotoxic combination regimens have no role in management of advanced NSCLC; clinical trials have shown that combination regimens consisting of 3 cytotoxic drugs produce greater toxicity without improving outcomes in this setting.

TARGETED THERAPY

Alteration of the major cell-signaling and regulatory pathways either by overexpression or gene sequence variation is a frequent event in lung cancer. These changes include alterations in receptor tyrosine kinases (TKs), such as EGFR, and alterations in angiogenesis pathways, apoptosis, proteosome regulation, and cell cycle control, among others.

Epidermal Growth Factor Receptor Inhibitors—In 40% to 80% of patients with NSCLC, EGFR is overexpressed, and its overexpression is associated with a poor prognosis.[72] During the past few years, several EGFR inhibitors have been developed that are in either the receptor TK domain or are monoclonal antibodies. Gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) is the first targeted therapy to be registered and later approved by the Food and Drug Administration (FDA) for use in lung cancer.[73] Unfortunately, the results from two phase 3 randomized trials of gefitinib failed to show a survival benefit for gefitinib vs placebo. The Iressa Survival Evaluation in Lung Cancer trial was a randomized phase 3 study comparing daily therapy with 250 mg of gefitinib vs placebo.[74] This study of 1692 patients whose lung cancer was refractory to chemotherapy failed to show improved survival time with gefitinib therapy, either in the overall population (median improvement, 5.6 vs 5.1 months, respectively; P=.11) or in patients with adenocarcinoma (median improvement, 6.3 vs 5.4 months; P=.07). However, a benefit was shown in Asians and those who had never smoked. The Southwest Oncology Group 0023 trial, a phase 3 randomized study in patients with stage IIIB NSCLC, was intended to show the potential benefit of maintenance gefitinib therapy over placebo after chemoradiation and consolidation chemotherapy.[75] This study was closed after an unplanned interim analysis showed no survival benefit and a potential detrimental effect for gefitinib therapy at a daily dose of 250 mg.

Erlotinib (OSI 774, Tarceva; OSI Pharmaceuticals, Melville, NY) is another EFGR TK inhibitor with a slightly different pharmacologic profile. Erlotinib has been approved by the FDA for second- or third-line treatment of NSCLC. In a phase 2 trial of 57 patients with refractory NSCLC, erlotinib was administered as monotherapy with an objective response rate of 12.3% and a median survival time of 8.4 months. The response rate did not correlate with prior exposure to chemotherapy, but a survival advantage was observed for patients with skin toxicity.[76] These results were later confirmed by the National Cancer Institute of Canada Clinical Trials Group in the BR.21 trial, which was a phase 3 study that randomized 731 patients who had not responded to first- or second-line chemotherapy with erlotinib or to placebo. The overall response rate to erlotinib compared with placebo was statistically significant at 8.9% and produced a median survival time of 6.7 months compared with 4.7 months in the placebo group (P=.001).[77] On the basis of these results, the FDA approved the use of erlotinib for patients with locally advanced or metastatic NSCLC who had not responded to 1 previous round of therapy.

Sequence Variations in EGFR and Response to EGFR-TK Inhibitors—The observation that certain subgroups of patients, particularly female patients, those who have never smoked, those who have adenocarcinoma histology, and those who are of Asian descent, have a higher response rate and clinical benefit with gefitinib and erlotinib therapy prompted research to elucidate the molecular mechanism responsible for this increased response. Three research groups have presented studies showing a positive relationship between the presence of activating mutations in the EGFR TK domain and a clinical response to gefitinib.[78–80]

The most common sequence variations were in-frame deletions that resulted in the insertion of a serine residue in 3 sequence variations (delE746-A750, delL747-T751insS, and delL747-P753insS) on exon 19. Other sequence variations consisted of an amino acid substitution within exon 21 (leucine to arginine [L858R] and leucine to glutamine [L861Q]). Epidermal growth factor receptor sequence variations (L858R and delL747-P753insS) had increased TK activity compared with wild-type receptors and were more sensitive to inhibition by gefitinib. These data suggest that adenocarcinomas among those who have never smoked constitute a distinct subset of lung cancers, frequently containing sequence variations within the TK domain of EGFR that are associated with gefitinib and erlotinib sensitivity. Sordella et al[81] demonstrated that EGFR sequence variations, such as L858R and delL747-P753insS, selectively activate antiapoptotic pathways by way of the increased phosphorylation of the EGFR downstream effectors, AKT1 and STAT, but do not affect the extracellular signaling pathways of EFGR. They postulated that the effectiveness of gefitinib in lung cancers harboring mutant EGFRs reflects both its inhibition of critical antiapoptotic pathways, on which these cells have become strictly dependent, and altered biochemical properties of the mutant receptors.[81]

Vascular Endothelial Growth Factor Inhibitors—Vascular endothelial growth factor (VEGF) binds to the VEGF receptors (VEGFRs) VEGFR1 (FLT1) and VEGFR2 (kinase insert domain–containing receptor) on vascular endothelial cells. Activation of VEGFR2 alone is necessary and sufficient to affect the VEGF-induced processes of mitogenesis, angiogenesis, and vascular permeability.

Previous attempts to combine chemotherapy and targeted therapy in lung cancer have been unsuccessful. In fact, several negative studies have compared standard chemotherapy doublet and targeted therapy (including agents such as EGFR inhibitors, antisense molecules, and immune modulators) to first-line regimens. Eastern Cooperative Oncology Group trial E4599[82] was the first to show a survival advantage with the addition of a targeted agent to standard chemotherapy in lung cancer. Trial E4599 combined the monoclonal antibody bevacizumab (Avastin; Genentech, South San Francisco, CA), which targets VEGF, with chemotherapy, showing significantly longer survival times for patients with advanced nonsquamous NSCLC. This trial compared therapy using CBDCA and PTX, the most common chemotherapeutic regimen prescribed in North America for lung cancer, with therapy using CBDCA, PTX, and bevacizumab in 855 patients with advanced or recurrent NSCLC. Patients with squamous cell histology, hemoptysis at baseline, and brain metastases or those receiving anticoagulation therapy were excluded from the trial because these characteristics were associated with a higher risk of bleeding in the phase 2 trial.[82] Both response and survival parameters were significantly better after the addition of bevacizumab to chemotherapy. A slightly but significantly higher rate of serious bleeds was observed in the chemotherapy-plus-bevacizumab arm of the study. On the basis of these trial results, bevacizumab in combination with chemotherapy received FDA approval for use in lung cancer.

RADIATION THERAPY

The first major trial to address the role of radiation therapy (RT) in the treatment of unresectable lung cancer was performed by the Veterans Administration Lung Cancer Study Group.[83,84] Patients with both small cell and non–small cell histologies were randomly assigned to receive thoracic RT or a placebo. Treatment included 40 to 50 Gy administered in daily fractions of 1.75 to 2.0 Gy using orthovoltage or cobalt-60 RT. Survival was significantly higher with RT than with placebo (1-year and median survival rates were 18.2% and 142 days with RT compared with 13.9% and 111 days with placebo).

After the Veterans Administration RT trial, the standard treatment for locally advanced inoperable lung cancer was RT alone.[83,85] The Radiation Therapy Oncology Group (RTOG)

performed a phase 3 trial to evaluate the influence of dose on outcome, comparing 40 Gy in 20 daily fractions, 50 Gy in 25 fractions, and 60 Gy in 30 fractions. The local failure rates were 48% with 40 Gy, 38% with 50 Gy, and 27% with 60 Gy. Although the differences in survival rates were not significant, 60 Gy in 30 daily fractions became the RT dose-fractionation standard used for stage III NSCLC.[86] Conventional RT alone resulted in a median survival of 10 months and a 5-year survival rate of 5%. Many phase 3 trials have confirmed that cisplatin-based chemotherapy plus RT produces better survival rates than RT alone.[86–88] In addition, both RTOG 9410 and a trial reported by Furuse et al[89] revealed significantly improved survival for concurrent RT plus chemotherapy compared with sequential therapy.

Stereotactic RT—Stereotactic RT techniques include fixation, ultraprecise treatment planning, RT directed to gross disease alone, and high doses per fraction. They are used to treat small lung tumors (T1-2, N0, M0). In a study of 257 patients, the local control rate was 92% and the 5-year survival rate was 81% for a biologically effective dose of 100 Gy or more. Pulmonary complications (grade, >2) occurred in 5.4% of patients.[90]

Hadron Therapy—A *hadron* is a subatomic particle (proton, neutron, or heavy ion) composed of quarks that is influenced by a strong nuclear force. Potential advantages of hadron RT compared with conventional RT (x-rays and electrons) include higher relative biologic effectiveness, higher linear energy transfer, lower oxygen-enhancement ratio, and excellent dose distribution. The major disadvantages of hadron therapy are its complexity and extremely high cost.

Bush et al[91] reported the Loma Linda experience treating 68 patients with medically unresectable stage I NSCLC with proton RT. They delivered 51 Gy equivalents (GyE) in 10 daily fractions to the first 22 patients. The next 46 patients received 60 GyE in 10 daily fractions. The 3-year local control and disease-specific survival rates were 74% and 72%, respectively.

Miyamoto et al[92] performed 2 trials that included 81 patients with stage I NSCLC who received carbon-ion RT. In the first study (9303), the primary tumors received between 59.4 and 95.4 GyE in 18 fractions during a 6-week period. In the second study (9701), the tumors received between 68.4 and 79.2 GyE in 9 fractions during a 3-week period. Grade 3 lung toxicity occurred in only 3.7% of patients; local recurrence, in only 23%. The 5-year survival rate was 60%. Miyamoto et al concluded that the local control (77%) achieved with carbon-ion RT was equivalent to that obtained with surgical resection.

DETERMINANTS OF SURVIVAL

Factors that have emerged as prognostic indicators of survivorship in lung cancer include tumor cell grade of differentiation, smoking cessation, dietary supplements, tumor molecular markers, and pharmacogenomics and treatment outcomes.

TUMOR CELL GRADE OF DIFFERENTIATION

In a study of 5018 hospital-based patients and 712 population-based patients, tumor grade was found to be significantly associated with survival after adjusting for the effects of age, sex, smoking history, tumor stage, histological cell type, and treatment modality. Patients with poorly differentiated or undifferentiated carcinoma had a 70% elevated risk of death compared with those with well-differentiated carcinoma. A 40% elevated risk was observed for patients with moderately differentiated carcinoma.[93]

SMOKING CESSATION

In a study of 5229 patients with NSCLC and SCLC, the median survival among those who had never smoked, former smokers, and current smokers with NSCLC was 1.4 years, 1.3 years, and 1.1 years, respectively ($P<.01$). Female patients with NSCLC had a significantly lower risk of mortality with a longer duration of smoking abstinence. Specifically, the relative risk per 10 years of smoking abstinence was 0.85, supporting a direct biologic effect of smoking on survival.[94]

DIETARY SUPPLEMENTS

The use of vitamin and mineral supplements was associated with improved survival in multivariate analyses among patients with both SCLC and NSCLC.[95] The rate of death was reduced by 26% for patients with NSCLC and by 37% for patients with SCLC.

TUMOR MOLECULAR MARKERS

One of the important findings in cancer therapeutics is the identification of somatic mutations in the TK domain of the EGFR in NSCLC and a correlation with response to EGFR inhibitors.[96–98] Epidermal growth factor receptor gene amplification is more prevalent in Western populations, whereas the amplification of the closely related *HER2* gene, which could also have implications for the treatment of NSCLC, is more common in East Asian patients. These findings imply that common tumors have different genetic backgrounds, which influence clinical outcome and response to therapy.[99]

PHARMACOGENOMICS AND TREATMENT OUTCOMES

Because drug resistance, whether inherent or acquired, is a cause of chemotherapy failure, pharmacogenomic studies have begun defining multiple gene variations responsible for varied drug metabolisms. The glutathione metabolic pathway is directly involved in the detoxification or inactivation of platinum-based compounds, the most commonly used drugs in lung cancer treatment. Available evidence supports the role of the glutathione pathway in acquired and inherited drug resistance through rapid drug detoxification or through drug-activation bypassing, which adversely affects the treatment outcome of patients with lung cancer.[4]

Another critical mechanism of resistance to platinum-based chemotherapy is DNA repair. It is hypothesized that tumor cells with reduced DNA repair have a higher sensitivity to treatment, leading to a better outcome after radiotherapy or chemotherapy, whereas increased repair capability causes tumor resistance and a poorer response.[100] Clinical studies show that overexpression of *ERCC1* correlates with poor survival for gemcitabine-cisplatin–treated patients with NSCLC, and the allelic variants of *ERCC1* or *ERCC2* are significantly associated with survival times for patients treated with platinum-based chemotherapy.[101–104]

Ionizing radiation, another commonly used treatment for late-stage lung cancer, also acts on DNA, causing double-strand and single-strand breaks and base lesions, particularly double-strand DNA breaks. The damage is repaired by at least 2 distinct pathways: homologous recombination and nonhomologous end-joining (NHEJ). Homologous recombination requires an undamaged template molecule that contains a homologous DNA sequence, generally from its sister chromatid.[105] The RAD51 and RAD52 proteins are involved in this pathway. For NHEJ, no undamaged partner DNA homologues are needed for rejoining of DNA breaks. However, RAD50 and DNA-dependent protein kinase can participate in the NHEJ repair process.[106,107] Genetic defects in homologous recombination or NHEJ can impair DNA replication and enhance radiation sensitivity.[106]

LONG-TERM SURVIVORS

Outcome varies among patients with NSCLC, even within groups that have the same stage at the time of diagnosis and that are treated in similar ways. People who are alive 5 years after a diagnosis of primary lung cancer are referred to as long-term lung cancer (LTLC) survivors.[108] Although the chance is only 15%, more than 25,000 persons become LTLC survivors every year in the United States.[109,110] Most LTLC survivors have undergone invasive treatment such as lung resection, RT, or chemotherapy; comorbidity in these survivors is especially high when compared with that of survivors of cancers at other sites.[111] Disease can recur in a subgroup of LTLC survivors more than 10 years after diagnosis, and survivors are extremely vulnerable (10-fold higher risk than other adult smokers) to developing new aerodigestive tract tumors, especially subsequent primary lung cancer (SPLC) and other smoking-related cancers.[112,113] The Lung Cancer Study Group reported that the incidence of SPLC at more than 5 years after surgery was twice that during the first 5 years after surgery. The cumulative risk of developing SPLC or other smoking-related cancers reaches 13% to 20% at 6 to 8 years.[114] Chest radiotherapy and continued smoking were found to significantly increase the risk of SPLC in these patients.[115]

CONCLUSION

Lung cancer is the leading cause of cancer-related mortality in the United States. Non–small cell lung cancer accounts for most lung cancer and carries a 5-year survival rate of 15%. Lung cancer incidence has peaked and declined in several regions of the world but has yet to peak in many other parts of the world, particularly China. With the decline in smoking in most Western countries, NSCLC is now predominant among former rather than current smokers. The treatment of NSCLC is surgery for early stages, chemotherapy with concurrent radiation for some locally advanced cancers, and palliative chemotherapy for metastatic disease. The introduction of antiangiogenesis agents and TK inhibitors of the EGFR protein has resulted in improved response rates for selected groups of patients with NSCLC.

Glossary

CBDCA, Carboplatin
CT, computed tomography
EGFR, epidermal growth factor receptor
FDA, Food and Drug Administration
GyE, Gy equivalent
LTLC, long-term lung cancer
NHEJ, nonhomologous end-joining
NSCLC, non–small cell lung cancer
PET, positron emission tomography
PTX, paclitaxel
RT, radiation therapy
SCLC, small cell lung cancer
SPLC, subsequent primary lung cancer
TEMLA, transcervical extended mediastinal lymphadenectomy
TK, tyrosine kinase
UFT, uracil-tegafur
VEGF, vascular endothelial growth factor
VEGFR, VEGF receptor

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TABLE

Adjuvant Trials in Patients With Resected NSCLC*

Reference	No. of patients	Pathologic stage	Treatment Adherence (%)	5-y survival (%)		*P* value	Regimen
				Adjuvant Chemotherapy group	Observation group		
IALT[58]	1867	I-III	74	45	40	<.03	CDDP + ETP or + VNR or + VBL
Winton et al[59] (NCIC JBR.10)	482	IB-II	50	69	54	.03	CDDP + VNR
Douillard et al[60] (ANITA)	840	IB-IIIA	56	51	43	.01	CDDP + VNR
Strauss et al[61] (CALGB)	344	IB	85	60	57	.32	CBDCA + PTX
Xu et al[62]	70	I-III	91	49	31	.05	CDDP + CPA + VCR + DOX + UFT
Mineo et al[63]	66	IB	76	63	45	.04	CDDP + ETP
Tada et al[64] (OLCS)	95	II-III	49	38	37	.54	CDDP + VDS + UFT
Imaizumi et al[65] (ACLC)	150	I	61	88	66	.045	CDDP + VDS + UFT
Tada et al[66]	119	IIIA	58	28	36	.89	CDDP + VDS

*ACLC = Adjuvant Chemotherapy for Lung Cancer; ANITA = Adjuvant Navelbine International Trialist Association; CALGB = Cancer and Leukemia Group B; CBDCA = carboplatin; CDDP = cisplatin; CPA = cyclophosphamide; DOX = doxorubicin; ETP = etoposide; IALT = International Adjuvant Lung Cancer Trial; NCIC = National Cancer Institute of Canada; NSCLC = non–small-cell lung cancer; OLCS = Osaka Lung Cancer Study; PTX = paclitaxel; UFT = uracil-tegafur; VBL = vinblastine; VCR = vincristine; VDS = vindesine; VNR = vinorelbine.