Management of Lung Cancer in Older Adults

Arti Hurria, MD; Mark G. Kris, MD

ABSTRACT  Lung cancer is the leading cause of cancer death in the United States. At the time of diagnosis, most patients are older than 65 years and have Stage III or IV disease. More than 80% of patients have non-small cell lung cancer and the rest have small cell lung cancer. Age is not a significant prognostic factor for overall survival and response to treatment for patients with either type of lung cancer. Treatment options should be tailored to older patients based on the same selection process and benefits seen in the population as a whole. This article reviews the available data regarding surgery, radiation, and systemic treatment for older patients with lung cancer and considers the role of geriatric assessment in the evaluation of older patients.

(CA Cancer J Clin 2003;53:325–341.) © American Cancer Society, 2003.

INTRODUCTION

Lung cancer is the most common cause of cancer death and the second most common cause of new cancer cases among men and women in the United States. In 2003, there are an estimated 171,900 new cases and 157,200 deaths from lung cancer.1 Two thirds of the U.S. population with lung cancer is 65 years or older. Cancer, in general, is a disease of aging. Persons older than 65 years have a 9.8-fold increased incidence of cancer and a 16.5-fold increased cancer-related mortality rate compared with those younger than 65 years2 (Table 1). The absolute number of older patients with cancer is increasing because our population is aging. In the United States, in the year 2000, 35 million persons were 65 years or older. This number is expected to double in the next 30 years, so that in 2030, 70.2 million persons will be 65 and older, accounting for 20% of the population.3

Among newly diagnosed cases of lung cancer, more than 80% are non–small cell lung cancer (NSCLC) and the rest are small cell lung cancer (SCLC). Smoking is the greatest risk factor for lung cancer (Table 2). This risk depends on the duration and quantity of tobacco use.4,5 Patients of any age should be encouraged to discontinue smoking, because those who quit smoking will have a lower risk than those who continue to smoke.4

Stage III or IV disease (according to AJCC staging criteria) is diagnosed in nearly three quarters of patients (Table 3). As such, the overall 10-year survival rate for patients with lung cancer is only 7%. The survival rates decrease with increasing age at diagnosis, as demonstrated by the five- and 10-year survival rates for patients younger than 50 years (16% and 10%, respectively) compared with patients older than 70 (12% and 5%, respectively).6

Our knowledge about the optimal treatment for lung cancer in older patients is limited secondary to an under-representation of older patients in clinical trials.7 In addition, most randomized clinical trials did not plan to evaluate older versus younger patients ahead of time. Therefore, much of our knowledge is based on post hoc subgroup analysis based on chronological age. Finally, physician bias may influence which “older” patients are even included in trials, making it difficult to extrapolate results to the general population.

DEFINITION OF THE “OLDER” PATIENT: THE ROLE OF GERIATRIC ASSESSMENT

The focus of this article is on lung cancer in the older population; however, there is no standard chronological age for what is considered an “older” or “elderly” person. Historically, this was defined by the chronological age of 65 or older because people were eligible for entitlement programs in the United States (Social Security and Medicare,
for example) and this was the traditional age for retirement. Given the heterogeneity of patients older than 65 years, it is clear that older is not adequately defined by a chronological age, but instead requires a more comprehensive assessment of a person’s physiologic age. A tool used by geriatricians, a comprehensive geriatric assessment, can contribute to our understanding of physiologic age through an evaluation of prognostic factors that are independent predictors of morbidity, mortality, and resource requirement. This includes an evaluation of a person’s functional status (ability to be independent in daily tasks at home and in the community), comorbid (coexisting) medical

| Age, yrs | Incidence Rates | Mortality Rates |
|----------|-----------------|-----------------|
| < 65     | 228.1           | 68.5            |
| ≥ 65     | 2,224.5         | 1,128.0         |

Data from Ries, et al.²

| Age, yrs | Incidence Rates | Mortality Rates |
|----------|-----------------|-----------------|
| 65       | 24.0            | 19.2            |
| 70       | 352.3           | 316.6           |

TABLE 2

Risk of Death in Next 10 Years From Lung Cancer Versus Any Cause Based on Smoking History

| Age, yrs | Smokers | Nonsmokers |
|----------|---------|------------|
|          | Lung Cancer (#/1,000) | Any Cause (#/1,000) | Lung Cancer (#/1,000) | Any Cause (#/1,000) |
| 65       | Women 85 | 301 | Women 85 | 301 |
|          | Men 152 | 516 | Men 152 | 516 |
| 70       | Women 124 | 470 | Women 124 | 470 |
|          | Men 249 | 786 | Men 249 | 786 |
| 75       | Women 137 | 725 | Women 137 | 725 |
|          | Men 330 | >950 | Men 330 | >950 |
| 80       | Women 136 | >950 | Women 136 | >950 |
|          | Men 275 | >950 | Men 275 | >950 |
| 85       | Women 103 | >950 | Women 103 | >950 |
|          | Men 211 | >950 | Men 211 | >950 |
| 90       | Women 64 | >950 | Women 64 | >950 |
|          | Men 133 | >950 | Men 133 | >950 |

Adapted with permission of Oxford University Press from Woloshin, Schwartz, and Welch.⁵

TABLE 3

American Joint Committee on Cancer Staging

| Stage | Tumor (T) | Lymph Node (N) | Metastasis (M) |
|-------|-----------|---------------|---------------|
| IA    | T1        | N0            | M0            |
| IB    | T2        | N0            | M0            |
| IIA   | T1        | N1            | M0            |
| IIB   | T2        | N1            | M0            |
| IIIA  | T1        | N2            | M0            |
|      | T2        | N2            | M0            |
|      | T3        | N1            | M0            |
|      | T3        | N2            | M0            |
| IIIIB | Any T     | N3            | M0            |
|      | T4        | Any N         | M0            |
| IV    | Any T     | Any N         | M1            |

Primary Tumor (T)

T1: Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura.

T2: Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension.

Involved main bronchus, 2 cm or more distal to the carina.

Invades the visceral pleura.

Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3: Tumor of any size that directly invades any of the following: chest wall, diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant effusion.

Regional Lymph Nodes (N)

N0: No regional lymph node metastasis.

N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor.

N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).

N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

Distant Metastasis (M)

M0: No distant metastasis.

M1: Distant metastasis present.
conditions, nutritional status, cognition, psychological functioning, social support, and medication review. Each of these domains is discussed here.

**Functional Status**

A diagnosis of cancer is often associated with increased dependence in functional status. The traditional measures to assess functional status are activities of daily living and instrumental activities of daily living. The activities of daily living are basic self-care skills, which are essential to maintain independence in the home. These include the ability to bathe, dress, maintain continence, toilet, transfer, and feed independently. Dependence in these activities has been predictive of survival, prolonged hospital stay, nursing home placement, and greater home care use. Instrumental activities of daily living include more advanced self-care skills that are required to maintain independence in the community. These include the ability to prepare meals, do housework, shop, use the telephone, travel, take medications, and manage finances. Dependence in these activities is predictive of shorter survival rate and risk for cognitive impairment.

**Comorbid Medical Conditions**

Comorbid medical conditions are concurrent medical problems that are a competing source of morbidity or mortality. The number of comorbid medical conditions increases as one ages and adversely affects projected life expectancy. A thorough understanding of comorbid medical conditions is important to determine whether another competing cause of death will limit a person’s life expectancy more than the cancer and consider the effect of these coexisting medical problems on the patient’s ability to tolerate treatment.

**Nutritional Status**

Poor nutritional status, defined as a body mass index less than 22 kg/m², is associated with increased dependence in activities of daily living (odds ratio, 1.21; 95% confidence interval [CI], 1.01 to 1.45) and decreased one-year survival rate (relative risk, 0.85; 95% CI, 0.74–0.97). In addition, unintentional weight loss is associated with lower chemotherapy response rates and decreased performance status. Weight loss of 5% or more is associated with an increased risk for death (hazard ratio, 1.67; 95% CI, 1.29–2.15).

**Cognition**

The presence of dementia is an independent prognostic indicator of survival. A baseline assessment of cognition is important to rule out subtle findings of metastatic disease and to determine whether a patient needs additional assistance to participate in a complex treatment plan. A caregiver can be essential in maintaining safety by ensuring adherence to the treatment plan and recognizing signs of toxicity that require immediate medical attention.

**Psychological State and Social Support**

Older patients often demonstrate an enhanced psychological adjustment to a diagnosis of cancer. The presence of social support plays an important role in psychological adjustment, and the presence of social isolation is an independent predictor of mortality among older patients. Adequate social support is especially important for a patient with cognitive impairment.

**Medication Review**

Older patients use three times more medications than do younger patients and are more vulnerable to adverse drug events. A review of the patient’s medication list is an important part of the geriatric assessment to determine whether newly prescribed medications may cause a drug interaction.

The information provided by a geriatric assessment can be valuable to the oncologist in the following ways. First, it helps the clinician make individualized treatment decisions using important prognostic factors other than chronological age. Second, it helps identify patients at high risk for functional decline or toxicity to
treatment, for whom targeted interventions may be beneficial. Third, it allows for standardization of patient characteristics across clinical trials and the ability to control for confounding factors contributing to mortality.

**Non-Small Cell Lung Cancer**

**Prognostic Factors and Treatment Patterns**

Several studies have evaluated the role of prognostic factors for survival and response to chemotherapy for patients with NSCLC. The Southwest Oncology Group reviewed the clinical course of 2,531 patients with extensive-stage NSCLC and determined that aged 70 years and older was a favorable prognostic factor. Other favorable prognostic factors were good performance status, female sex, and receipt of cisplatin-based therapy. The Eastern Cooperative Oncology Group (ECOG) analyzed data from 893 patients with metastatic NSCLC with good performance status enrolled in Phase III combination chemotherapy trials. The pretreatment characteristics that distinguished patients who survived more than one year were initial performance status of 0, no bone metastases, female sex, no subcutaneous metastases, non–large cell histology, less than 5% previous weight loss, no symptoms of shoulder or arm pain, and no liver metastases. Age was not a significant prognostic factor. The relative importance of 77 prognostic factors, including age, were reviewed in a study of 5,000 patients with inoperable lung cancer entered in Veteran Administration Lung Group protocols. The most important prognostic factors for survival were performance status, extent of disease, and weight loss in the past six months. The European Lung Cancer Working Party analyzed the role of age as a prognostic factor for response to chemotherapy. Data from 1,052 patients with unresectable NSCLC treated with cisplatin– or carboplatin-based chemotherapy showed that increased age was associated with a significantly greater response to chemotherapy in both univariate and multivariate analyses.

These studies indicate that age is not a poor prognostic factor for overall survival or response to treatment for patients with NSCLC and that treatment decisions should be based on performance status rather than age. Despite these findings, there is a pattern of undertreatment of older patients. Older patients are less likely to receive surgery for localized disease (80.2% younger than 65 years versus 54.8% aged 65 years and older). There is a 65% decrease in the likelihood of receiving surgery for locoregional disease with each decade of life after 65. Older patients are less likely to receive chemotherapy for metastatic disease (19% younger than 65 versus 5% aged 65 and older). Patients who are 65 years and older are more likely to receive no treatment compared with younger patients (29% younger than 65 versus 12% aged 65 and older). Below we describe the data supporting the efficacy and risk for toxicity of each of these treatment options for older patients.

**Surgery**

Surgery remains the mainstay of treatment for patients with Stages I to III NSCLC. The five-year survival rate for patients with Stage I NSCLC is better than 60%. In the older patient, decisions regarding surgical treatment involve an assessment of the patient’s life expectancy (Table 4). Because the life expectancy from untreated NSCLC is so poor, every effort should be made to allow for curative surgery if possible. Curative resection is feasible in older patients. In a study of octogenarians undergoing curative treatment for lung cancer, in which most were treated with standard lobectomy, the complication rates were 3.7% perioperative death, 11% major complications, and 42% nonfatal complications. The survival rates for patients with Stage I disease were 86% at one year, 62% at three years, and 43% at five years. Yamamoto, et al. analyzed the surgical results of 797 patients with Stage I NSCLC. Patients aged 70 and older (n = 132) had similar five- and 10-year survival rates compared with patients younger than 70 years (P = .35).
In a study of prognostic factors predicting outcome for patients who underwent surgical resection for Stages I and II NSCLC, older age (defined as 65 years or more), anemia, and higher stage were independent prognostic factors for survival. Patients older than 65 had a shorter event-free survival time (34 versus 55 months, \( P = 0.002 \)) and overall survival (39 versus 58 months, \( P = 0.002 \)) compared with younger patients.\(^{31}\)

The difference in five-year survival rate in older and younger patients may be secondary to comorbid (coexisting) illnesses other than lung cancer. For example, van Rens, et al.\(^{32}\) analyzed the records of 2,361 patients who underwent pulmonary resection for Stages I, II, and IIA NSCLC. The overall five-year survival rate for patients younger than 65 was 44% compared with 38% for older patients (\( P < 0.001 \)); however, the authors note that survival rates were similar for as long as four years after surgery, and thus the five-year survival rate difference may be secondary to comorbid disease.

The challenge of surgical treatment for older patients is the age-related physiologic changes in the cardiovascular and respiratory systems that may effect tolerance to surgery. Age-related cardiovascular changes include a decrease in cardiac output, decrease in maximal heart rate, prolonged recovery after exertion, and a decreased response to catecholamines during times of stress. Age-related pulmonary changes include a decreased response to hypoxemia or hypercapnia, decreased elasticity of the lung tissue, increased ventilation-perfusion mismatch, and decreased forced expiratory volume.\(^{33}\) In addition, other comorbid medical conditions can contribute to this risk. In a study of 3,864 patients with lung cancer, the most frequent concomitant diseases included cardiovascular disease and chronic obstructive pulmonary disease.\(^{34}\) Therefore a careful preoperative evaluation, guided by the patient’s internist or geriatrician, can be valuable to the surgeon. In addition, close postoperative monitoring and aggressive pulmonary toilet is essential. Specific consultation by a pulmonary physician and care in a specialized treatment unit should also be considered for older patients and those at higher risk.

The risks from surgical treatment can also be minimized with the selection of the surgical procedure performed. For example, patients undergoing a lobectomy or wedge resection will be at lower risk for postoperative complications compared with patients undergoing pneumonectomy. In a study of patients 70 years and older, 78.5% of patients receiving pneumonectomy experienced a postoperative complication compared with 58% of patients undergoing lobectomy or wedge resection. All cases of postoperative death occurred in patients undergoing pneumonectomy. Prognostic factors predictive of the risk for postoperative complications in the patients receiving pneumonectomy were poor performance status (WHO 2 or more), chronic obstructive pulmonary disease, and elevated levels of blood urea nitrogen.\(^{35}\)

The volume of procedures performed at a hospital can also influence survival rate and the risk for postoperative complications. Bach, et al.\(^{36}\) performed a population-based study of 2,118 patients 65 years and older who underwent surgical resection for lung cancer, to estimate the extent that the volume of procedures performed at the hospital influenced mortality and postoperative complication rates. Patients who underwent the procedure at hospitals with the highest volume had better five-year survival rates (44% versus 33%), lower postoperative complication rates (20% versus 44%), and lower 30-day mortality rates (3% versus 6%) compared with patients who underwent operations at hospitals with the lowest volume.

### TABLE 4

| Life Expectancy by Age | Age (yrs) | Now | Age at Death |
|------------------------|----------|-----|-------------|
|                        | 65       | 17.9| 82.9        |
|                        | 70       | 14.4| 84.4        |
|                        | 75       | 11.3| 86.3        |
|                        | 80       | 8.6 | 88.6        |
|                        | 85       | 6.3 | 91.3        |
|                        | 90       | 4.7 | 94.7        |
|                        | 95       | 3.5 | 98.5        |
|                        | 100      | 2.6 | 102.6       |

*Data derived from the United States Life Tables, 2000.\(^{27}\)*
In summary, surgery remains the mainstay of treatment for early-stage disease for both older and younger patients. Cure is uncommon in persons with lung cancer who do not undergo surgical resection. The risk of postoperative complications in the older patient can be minimized through the selection of the surgical procedure performed, as well as consideration of the volume of procedures performed at the hospital. In addition, careful preoperative evaluation and aggressive and specialized postoperative care are needed, taking into account the physiologic changes that occur with aging. This argues for close collaboration among the patient’s surgeon, internist or geriatrician, cardiologist, and pulmonologist. Additional studies reporting prognostic factors that influence the outcome of surgical procedures in the older patient are needed to develop interventions to optimize surgical outcomes and minimize risks. The increasing use of minimally invasive surgery has the potential to further diminish the morbidity and mortality from thoracic surgery in all age groups.

**Radiation**

**Radiation Alone**

Radiation therapy is used for cure and palliation. The proportion of patients who receive radiation decreases with increasing age. Among patients who receive treatment, the likelihood of receiving radiation is higher than any other therapy \( (P < .0008) \). In a study of treatment patterns for 1,706 patients with NSCLC, patients 65 years and older were more than twice as likely than younger patients to receive radiation for local disease (14% of patients younger than 65 versus 31% of patients 65 and older).\(^{24}\)

Radiation can be given for curative intent for patients with early-stage lung cancer who are not surgical candidates; however, the survival rates are lower than those reported after surgery. Gauden and Tripcony\(^{37}\) performed a retrospective review of patients with Stage I NSCLC (median age, 70 years; age range, 34–90 years) who received radiation therapy with curative intent for the treatment of T1 and T2N0M0 tumors. Surgery was withheld because of older age, poor performance status, or patient refusal. This study revealed similar overall survival and recurrence-free survival rates in older and younger patients, with a trend for older patients to fare better. For patients who were 70 years and older, the overall survival rate at five years was 34% and the median survival time was 26 months. In addition, age did not adversely influence the tolerability or delivery of the radiation.\(^{37}\)

Additional studies have shown that treatment tolerance and efficacy of thoracic radiation is similar in younger and older patients.\(^{38}\) In a study of 1,208 patients who received thoracic irradiation, there was no significant difference in survival rate between patients younger than 65, aged 65 to 70, and older than 70 years \( (P = .82) \). Age had no effect on acute or late radiation toxicity, including nausea, dyspnea, esophagitis, or weakness. Older patients, however, were more likely to experience weight loss than were younger patients \( (P = .002) \). Weight loss has been found to be an independent predictor of death in older community-dwelling adults, and thus close attention should be paid to nutritional status in older patients who receive radiation.\(^{15}\)

Radiation is frequently used for palliation of lung cancer-related symptoms. In particular, radiation can palliate thoracic pain and hemoptysis in 60% to 80% of cases and control other local symptoms in approximately 50% to 70% of cases. The median duration of benefit is 7 to 14 weeks. The main toxicity is esophagitis, which is self-limiting.\(^{39}\)

**Concurrent Versus Sequential Chemotherapy and Thoracic Irradiation**

The role of concurrent versus sequential chemotherapy and thoracic radiation for older patients with locally advanced NSCLC was analyzed in Radiation Therapy Oncology Group 94–10, a Phase III trial comparing concurrent cisplatin-based chemotherapy and thoracic radiotherapy (given once or twice daily [hyperfractionated]) versus sequential chemotherapy and radiotherapy (Table 5). Data were analyzed by age (younger than 70, \( n = 488 \); 70 years and older, \( n = 104 \)), revealing that older
patients had a survival benefit for concurrent chemotherapy and radiation compared with sequential treatment. The risks for Grade ≥3 neutropenia and Grade ≥4 toxicities were increased in the older patient, but there was no difference in long-term toxicity. Grade ≥4 toxicities occurred in most older patients regardless of the treatment, but they were most common with the concurrent daily chemotherapy and radiation schedule.\textsuperscript{40}

The Intergroup performed a Phase III trial of sequential chemotherapy (cisplatin, vinblastine) and radiation versus standard radiation or hyperfractionated radiation for the treatment of surgically unresectable Stages II, IIIA, and IIIB lung cancer. When the results were examined by age, patients younger than 60 years had superior survival rates with sequential chemotherapy and radiation (15 months sequential treatment, 12 months radiation therapy alone, and 12 months for hyperfractionated radiation). In contrast, patients older than 70 had superior survival rates with radiation therapy alone (13 months for radiation therapy alone; 11 months for sequential treatment). All deaths from toxicity of chemotherapy occurred in patients older than 70. Of note, only patients with good performance status (Karnofsky performance status [KPS] ≥70) were included in the study.\textsuperscript{41}

Pooled data from six prospective Phase II or III Radiation Therapy Oncology Group studies of patients with locally advanced lung cancer were analyzed with respect to age. Data were included for 979 patients with Stages II to IIB inoperable NSCLC who received one of six treatment regimens of either concurrent chemoradiation or radiation therapy alone. This study examined the effect of age and quality-adjusted survival scores in patients receiving combined therapy compared with radiation therapy alone. Quality-adjusted survival scores were calculated, taking into account tumor progression and weighing the length of time spent with toxicity from treatment. Patients younger than 60 had improvement in survival rate and quality-adjusted survival scores with chemotherapy and radiotherapy compared with radiation therapy alone. Patients 60 to 70 years old had a trend toward improved outcome with combined therapy. Patients older than 70 achieved the best quality-adjusted survival rate with radiation alone. For patients receiving concurrent chemoradiation, lung and upper gastrointestinal toxicities had the greatest effect on quality-adjusted survival.\textsuperscript{42}

In summary, radiation therapy can be given with curative or palliative intent to older patients with lung cancer. For patients with early-stage lung cancer who are not surgical candidates in whom radiation is given with curative intent, survival rate statistics are inferior to those seen with surgery. In locally advanced lung cancer, the data suggest that although a survival rate benefit was shown with concurrent chemotherapy and thoracic radiation in the population at large, there is a significant risk for short-term toxicities in older patients who receive this treatment, which may outweigh the benefits in this subgroup. Radiation alone may represent the best choice for

| TABLE 5 |
| RTOG 94-10: Concurrent Versus Sequential Chemotherapy and Radiation for Locally Advanced Non–Small Cell Lung Cancer |

| Age (yrs) | <70 | ≥70 |
|-----------|-----|-----|
| Study Arms | Sequential (n = 161) | Concurrent Daily (n = 177) | Concurrent 2x Daily (n = 153) | Sequential (n = 40) | Concurrent Daily (n = 24) | Concurrent 2x Daily (n = 40) |
| Survival (months) | 15.7 | 15.5 | 16 | 10.8 | 22.4 | 16.4 |
| Grade ≥ 4 Toxicity (%) | 57 | 63 | 38 | 68 | 75 | 55 |
| Grade ≥ 3 Neutropenia (%) | 73 | 77 | 48 | 83 | 92 | 68 |

Data derived from Langer, et al.\textsuperscript{40}
many older persons when both toxicity and survival rate are weighed. Therefore, these older patients would best benefit from enrollment in a clinical trial that focuses on the means for maximizing efficacy and ameliorating toxicities in older patients. For both younger and older patients with incurable disease, radiation is an effective palliative treatment for lung cancer symptoms.

**Chemotherapy**

There is no curative treatment for patients with Stage IV NSCLC. The goals of chemotherapy are to treat symptoms of the disease and lengthen survival time. In a meta-analysis of trials of chemotherapy, treatment with a cisplatin-based regimen lead to a reduced risk for death by 27% and improvement in one-year survival rate by 10% (95% CI, 5%-15%) compared with outcomes in similarly fit patients randomized to receive best supportive care.43 Subgroup analysis revealed no difference in benefit by age or performance status (KPS ≥60%); however, most (78%) patients included in clinical trials were younger than 65 years and patients with KPS ≤50% were not included. The hazard ratio for death for the subgroup of patients 65 and older was 0.87, although this number was based on only 120 patients.44 A similar magnitude of benefit was seen in a retrospective review of 6,232 patients older than 65 from the Survival, Epidemiology, and End Results tumor registry. In this cohort of older patients with Stage IV NSCLC, treatment with chemotherapy increased one-year survival rate by 9%.44

**Single-Agent Chemotherapy Versus Best Supportive Care**

Given the survival rate benefit from cisplatin-based combination chemotherapy and the risk for increased toxicity in older patients, the question of whether single-agent chemotherapy would lead to improved quality of life or a survival rate benefit in older persons was explored. The Phase III Elderly Lung Cancer Vinorelbine Italian Group Study (ELVIS) trial evaluated the efficacy of single-agent chemotherapy compared with best supportive care in older persons with Stage IIIB or IV NSCLC (Table 6). In this study, patients 70 years and older with ECOG performance status of 0 to 2 were randomized to receive best supportive care or 30 mg/m² vinorelbine, given on days 1 and 8 of a 21-day cycle for a maximum of six cycles. The study was suspended after 154 assessable patients were enrolled because of poor accrual. Patients treated with vinorelbine had improved quality of life (the primary endpoint of the study) and lengthened one-year survival rate from 14% with best supportive care to 32%. The relative risk for death in patients treated with vinorelbine was 0.65 (95% CI, 0.45–0.93).45 The ELVIS trial was the first Phase III study that established the benefit of single-agent vinorelbine compared with best supportive care in older persons with NSCLC. Several Phase II studies have focused on the efficacy and toxicity profiles of other single agents in the treatment of older persons with NSCLC, including gemcitabine, docetaxel, or paclitaxel. Table 7 summarizes the results of selected trials.46–48

**Single-Agent Versus Combination Chemotherapy**

Building on the results of the ELVIS Trial, the next set of Phase III trials sought to determine whether there was a benefit of combination chemotherapy compared with single-agent chemotherapy in older patients with NSCLC (Table 6). The Multicenter Italian Lung Cancer in the Elderly (MILES) trial included patients 70 years and older with Stage IIIB or IV NSCLC randomized to receive treatment with vinorelbine (30 mg/m²), gemcitabine (1,200 mg/m²), or vinorelbine (25 mg/m²) plus gemcitabine (1,000 mg/m²) given on days one and eight of a 21-day cycle for a maximum of six cycles. Six hundred ninety-eight patients were included. The investigators found no difference in response rates or survival rate for older patients with NSCLC who received combination chemotherapy with gemcitabine–vinorelbine compared with vinorelbine alone or gemcitabine alone. Quality of life was similar for the combination versus single-agent therapy; however, toxicity was
greater for patients who receive combination chemotherapy.49

The Southern Italian Cooperative Oncology Group (SICOG) trial was a Phase III trial of 120 patients 70 years and older with Stage IIIB or IV NSCLC randomized to receive treatment with gemcitabine (1,200 mg/m²) plus vinorelbine (30 mg/m²) versus vinorelbine (30 mg/m²) alone, with treatment given on days one and eight every three weeks for a maximum of six cycles (Table 6). At a median follow-up of 14 months (range, 3–22 months), patients treated with combination chemotherapy had an improved one-year survival rate (30% for gemcitabine plus vinorelbine versus 13% for vinorelbine alone). In addition, patients who received combination chemotherapy had improved symptom control, with a higher probability of being alive without symptomatic deterioration at six months (43% for gemcitabine plus vinorelbine versus 22% for vinorelbine). Patients with a higher comorbidity score or poor performance status were more likely to have an early withdrawal from treatment.50

The results of the MILES and SICOG trials yielded different conclusions regarding the benefits of combination chemotherapy. A possible reason for the discrepancy is that patients in the vinorelbine-alone arm of the SICOG trial had poorer than expected median and one-year survival rates. In fact, the results for the vinorelbine group in the SICOG trial were similar to those reported for the best supportive care group in the ELVIS trial. Differences between the two trials include that the sample size

ELVIS, Elderly Lung Cancer Vinorelbine Italian Group Study.
MILES, Multicenter Italian Lung Cancer in the Elderly.
SICOG, Southern Italian Cooperative Oncology Group.
Data derived from The Elderly Lung Cancer Vinorelbine Italian Study Group,45 Gridelli, et al.,49 and Frasci, et al.50

| TABLE 6 | Phase III Randomized Controlled Trials in Patients With Stage IIIIB or IV Non–Small Cell Lung Cancer |
| --- | --- |
| Trial | Patient Characteristics | Study Arms | Response Rate (%) | Median Survival (weeks) |
| ELVIS | Stage IIIIB or IV Age ≥ 70 years n = 154 patients | Vinorelbine | 20 | 28 |
| | | Best supportive care | NA | 21 |
| MILES | Stage IIIIB or IV Age ≥ 70 years n = 698 patients | Vinorelbine | 18 | 36 |
| | | Gemcitabine | 16 | 28 |
| | | Vinorelbine and gemcitabine | 21 | 30 |
| SICOG | Stage IIIIB or IV Age ≥ 70 years n = 120 patients | Vinorelbine | 15 | 18 |
| | | Vinorelbine and gemcitabine | 22 | 29 |

ELVIS, Elderly Lung, Cancer Vinorelbine Italian Group Study.
MILES, Multicenter Italian Lung Cancer in the Elderly.
SICOG, Southern Italian Cooperative Oncology Group.

| TABLE 7 | Selected Phase II Studies of Single-Agent Chemotherapy for Older Patients With Stage IIIIB/IV Non–Small Cell Lung Cancer |
| --- | --- |
| Author | Chemotherapy | Patients (n) | ECOG PS | Median Age, yrs (range) | Response (%) | Median Survival (months) |
| Ricci, et al.46 | Gemcitabine, 1,000 mg/m² (3 weeks on, 1 week off) | 44 | 0–2 | 75 (70–81) | 22 | 6.8 |
| McKay, et al.47 | Docetaxel, 36 mg/m² (6 weeks on, 2 weeks off) | 36 | 0–2 | 71 (55–82) | 19 | 5 |
| Fidias, et al.48 | Paclitaxel, 90 mg/m² (6 weeks on, 2 weeks off) | 35 | 0–3 | 76 (70–85) | 23 | 10.3 |

ECOG PS, Eastern Cooperative Oncology Group Performance Status.
in the MILES trial was larger than that in the SICOG trial (698 versus 120 patients), making the results of the MILES trial more robust. In addition, the dosing between the two trials varied in that higher doses of gemcitabine and vinorelbine were given in the combination arm of the SICOG trial. Based on the conflicting results of these Phase III trials, the benefit of single-agent versus combination chemotherapy in the older patient is an area that needs additional study.

**Platinum Therapy**

The role of cisplatin-based combination therapy in the treatment of older patients with NSCLC is another area of controversy. Patients participating in ECOG 5592 received one of three cisplatin-based combination regimens, consisting of cisplatin in combination with etoposide, high-dose infusional paclitaxel, or low-dose infusional paclitaxel (Table 8). Of the 574 patients enrolled on the trial, 86 (15%) were 70 years or older. Only two patients were older than 80. All patients had an ECOG performance status of 0 to 1. When the results were stratified by age (younger than 70 versus 70 years and older), there was no significant difference in response rates \( P = .67 \) or survival rate \( P = .29 \). Toxicity between the two groups were similar except that older men were more likely to experience Grade 4 leukopenia than were their younger counterparts (42% versus 17%; \( P < .001 \)) and had a higher incidence of neuropsychiatric effects. Older women were more likely to experience weight loss of 10% of their body weight than were younger women (33% older women versus 17% younger women; \( P = .006 \)). When analyzing the small subgroup of patients who were older than 75 \( (n = 24) \) compared with those aged 70 to 75 years \( (n = 62) \), there were no significant differences other than a borderline increase in the risk for neutropenia \( P = .06 \)\(^{51} \).

Other studies have suggested that a cisplatin-based combination may be too toxic for an older patient. In an analysis of the Southwest Oncology Trials 9509 (which compared paclitaxel plus carboplatin to vinorelbine plus cisplatin) and 9308 (which compared vinorelbine plus cisplatin to cisplatin alone), 46% of patients aged 70 and older who received vinorelbine plus cisplatin discontinued treatment secondary to toxicity compared with 16% of patients who received paclitaxel plus carboplatin.\(^{52} \) Of note, only 19% of patients in these clinical trials were 70 years or older.

The substitution of carboplatin for cisplatin may help to ameliorate toxicity. A retrospective review of a Phase III trial of carboplatin and paclitaxel revealed similar response and survival rates and toxicity patterns for patients younger than 70 years compared with those 70 years and older.\(^{53} \) A study from the Cancer and Leukemia Group B, presented in 2002 by Lilenbaum and colleagues\(^{54} \) demonstrated a survival rate benefit to combination chemotherapy with carboplatin and paclitaxel compared with paclitaxel alone for patients with Stage IIIIB or IV NSCLC. A subgroup analysis of patients older than 70 also revealed a benefit to combination chemotherapy, although this was not statistically significant. A randomized study powered to answer this question specifically in older patients would be appropriate.

These studies demonstrate several important points. First, patients aged 70 to 79 years who have good performance status may benefit from a cisplatin-based regimen to the same extent as younger patients. Second, older patients will be at increased risk for certain toxicities, including an increased risk for neutropenia. This is consistent with the observation that hematopoietic reserve decreases with age and the empiric use of growth factors should be considered to ameliorate this toxicity. Third, older patients are at increased risk for significant weight loss. Therefore, a close evaluation of the nutritional

| TABLE 8 |
| ECOG 5592: Cisplatin-Based Therapy: Response and Survival by Age |

| Age < 70 years \((n = 488)\) | Age ≥ 70 years \((n = 86)\) |
|-----------------------------|-----------------------------|
| Response Rate (%)           | 22                          | 23                          |
| Median Survival (months)    | 9.1                         | 8.5                         |
| One-Year Survival Rate (%)  | 37.7                        | 29.1                        |

Data derived from Langer, et al.\(^{51} \)
status of older patients is important. Finally, too few patients older than 80 years were included in these studies to make any conclusions regarding this age group. Additional studies specifically focusing on patients aged 80 and older or those with poorer performance status are needed. A randomized study of a cisplatin versus noncisplatin combination for older patients would provide valuable information about the optimal treatment in persons in this age group.

**Novel Agents**

In May 2003, the Food and Drug Administration approved the epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib (Iressa; ZD1839), for patients with advanced NSCLC with disease progression or intolerance to cisplatin or carboplatin and docetaxel based on two Phase II trials that showed symptom improvement and radiographic regressions. This once-daily oral tablet was developed to block the tyrosine kinase component of the epidermal growth factor receptor and thereby block signaling modulated by the pathway. Most NSCLCs tested have shown that the epidermal growth factor receptor protein is either expressed or overexpressed.

For the recommended 250-mg dosage, radiographic response rates were 18% and 12%, symptomatic benefits were seen in 40% and 43% of patients, and one-year survival rate was 35% and 27%. In both trials, there was no difference in the rates of symptomatic or radiographic response or toxicity when younger and older patients were compared.55,56

Unlike chemotherapy, there also appears to be no difference in the incidence of adverse effects when any age groups were compared. The availability of this agent offers a new approach to patients with NSCLC. This agent appears to be most effective in women, never smokers, and those with bronchoalveolar histology.

**Small Cell Lung Cancer**

Small cell lung cancer comprises slightly fewer than 20% of all cases of lung cancer. The disease is characterized by early metastatic spread. Treatment typically consists of combination chemotherapy with or without thoracic radiation. A response to chemotherapy can be expected in approximately 70% to 80% of patients with limited-stage disease (defined as disease confined to one hemithorax that can be encompassed in a tolerable radiation field) and in 60% to 70% of patients with extensive-stage disease (defined as disease beyond that included in limited disease).57 Despite the high chemotherapy response, most patients relapse and the overall survival rates are low. Only 5% of people with SCLC live for 5 years, and only 2% live for 10 years.6 The median survival time of patients with limited-stage disease is 12 to 16 months, whereas the median survival time of those with extensive-stage disease is 9 to 11 months.57,58 Therefore, the approach to treatment in NSCLC versus SCLC is clearly different. For NSCLC, chemotherapy leads to improvements in response and survival, whereas for SCLC the same is true but in addition a small percentage will be cured. Therefore, this favors a more aggressive approach to initial treatment.

**Prognostic Factors and Treatment Patterns**

Older patients with SCLC are more likely to receive lower chemotherapy doses or dose reductions compared with younger patients; however, in retrospective studies this did not influence response or survival rates. Shepherd, et al.59 reported that 65% of patients 70 years and older had an initial dose reduction, more than half required two or more dose reductions, and only 42% completed the full chemotherapy course of six cycles. Survival was strongly correlated with stage of disease ($P < .0001$) and number of chemotherapy cycles received ($P < .0001$). There was no significant difference in survival based on age ($P = .40$) and only a marginal difference based on performance status ($P = .077$). A retrospective review of data from two randomized National Cancer Institute of Canada trials for patients with limited-stage SCLC revealed that patients younger than 70 and patients aged 70 and older had no significant difference in response
rates (78% versus 82%; \( P = .50 \)) or five-year survival rates (11% versus 8%; \( P = .14 \)). Patients older than 70 received lower total doses of drugs compared with the intended dose of the protocol.60

**Chemotherapy**

Chemotherapy is the mainstay of treatment for patients with SCLC. For patients with limited-stage disease, standard treatment consists of four to six cycles of etoposide and cisplatin in conjunction with thoracic irradiation. Prophylactic cranial irradiation is recommended for those who achieve a complete response. Often older patients are not offered such treatment because of concerns for possible treatment-related morbidity and mortality. Of the older patients who receive treatment, a high proportion will receive dose reductions or be unable to complete the full chemotherapy course.59

**Carboplatin and Etoposide Combinations**

A number of Phase II studies of combination chemotherapy with the commonly used regimen of carboplatin and etoposide have been performed in older patients. Carboplatin offers advantages over cisplatin in terms of ease of administration and a decreased incidence of renal, auditory, and neurologic toxicities. Taken together, these studies reveal a response rate of 60% to 80%, with median survival time ranging from 37 to 46 weeks. This comes at the expense of hematologic toxicity, with Grade 3 or 4 neutropenia ranging from 13% to 84% and the toxicity-related death rate ranging from 2% to 9%.61–65

To minimize toxicity, the role of individualized carboplatin dosing based on the glomerular filtration rate was explored. Carboplatin was dosed via the Calvert formula, in which the desired area under the curve (AUC) of the drug is individualized based on a patient’s renal function (dose [mg/body] = AUC \times [glomerular filtration rate + 25]). A Phase II study of carboplatin (dosed by the Calvert formula) and etoposide was performed in 36 patients (median age, 73 years; age range, 70–80 years) with WHO performance status of 0 to 2. Sixteen patients had limited-stage disease and 20 had extensive-stage disease. Chemotherapy consisted of carboplatin (dosed at an AUC 5 given intravenously on Day 1) and etoposide (100 mg/m² given on days 1, 2, and 3), with treatment cycles repeated every four weeks for up to four courses. This treatment yielded a median response rate of 75% with a one-year survival rate of 47%. There was a significant rate of hematologic toxicity including 57% and 3% of patients with Grade 3 or 4 leukopenia, respectively, 47% and 44% with Grade 3 or 4 neutropenia, and 40% and 11% with Grade 3 or 4 thrombocytopenia. Despite the fact that 91% of patients experienced Grade 3 or 4 neutropenia, a Grade 3 or 4 infection developed in only one patient. One treatment-related death occurred secondary to hemoptysis. There was no difference in toxicity for those younger than 75 years and those 75 and older.63

Another Phase II study of carboplatin (dosed according to the Calvert formula) and etoposide was performed in 34 patients (median age, 73.9 years; age range, 70–79 years) with WHO performance status of 0 to 2.61 Eighteen percent of patients had limited-stage disease, and 82% had extensive disease. Chemotherapy consisted of carboplatin (AUC 5) and etoposide 100 mg/m² given orally on days one to five, with treatment cycles repeated every four weeks for a total of six courses. Patients with limited-stage disease received thoracic irradiation after chemotherapy. The overall response rate was 59% and the median survival time was nine months. The primary toxicity was hematologic, with 59% with Grade 3 or 4 neutropenia and febrile neutropenia occurring in 15% of courses. Nine percent of patients died of a toxicity-related cause, secondary to septic shock during neutropenia. Therefore, this regimen had a 59% response rate; however, there was a 9% risk of treatment-related mortality, which was possibly explained by the inclusion of patients with poor performance status (47% WHO 2) or the use of oral etoposide, which may have varying bioavailability among different patients.61

These studies raise several important points. First, the combination of carboplatin and etoposide is active in older patients; however, it
carries a significant risk for hematologic toxicity and associated treatment-related mortality, especially when the etoposide is given orally. Therefore, future studies should focus on the use of empiric growth factors to decrease this risk. Second, given that there is a significant decrease in glomerular filtration rate with aging, it makes sense to continue to individualize carboplatin dosing based on an individual’s renal function and desired area under the curve. Third, the study that included oral etoposide had an increased risk for toxicity that may be secondary to varying bioavailability of the oral medication. Finally, few studies include persons older than 80 years and further trials including patients in this age group are needed.

Single-Agent Etoposide: A Lesson Learned at the Expense of Older Persons With SCLC

Phase II studies of single-agent etoposide in older patients demonstrated a “favorable response” with acceptable toxicity profiles. Based on these early reports, single-agent oral etoposide was widely promoted for use in older persons. Subsequently, two randomized Phase III studies were developed to compare treatment with single-agent etoposide to standard treatment with intravenous combination chemotherapy (Table 9). In the first study, patients with a poor performance status (WHO 2–4) were randomized to receive treatment with oral etoposide (50 mg twice daily for 10 days every three weeks for four cycles) compared with an intravenous treatment with etoposide and vincristine or cyclophosphamide, doxorubicin, and vincristine. The study was stopped early because patients treated with oral etoposide had a lower overall response rate and shorter survival time (risk ratio for death, 1.35; 95% CI, 1.03–1.79). The palliative effects of chemotherapy were similar between the two groups.

The second Phase III trial compared oral etoposide (100 mg twice daily for five days) to intravenous chemotherapy consisting of alternating cycles of cisplatin plus etoposide and cyclophosphamide, doxorubicin, and vincristine. The chemotherapy was administered at 21-day intervals for six cycles. Interim study results showed inferiority of the oral etoposide arm, with poorer response rates (33% versus 46%; \( P < .01 \)) and one-year survival rate (10% for oral versus 19% for intravenous; difference, 9%; 95% CI for difference, 0.3%–19%). Patients who received oral etoposide had shorter palliation of lung cancer symptoms (\( P < .01 \)) and a smaller improvement in quality of life (\( P < .01 \)) than did patients who received intravenous chemotherapy. Based on these results, early study closure was recommended.

These two randomized studies show that treatment with single-agent etoposide is inferior to combination chemotherapy and is not an adequate substitute in the treatment of older patients with SCLC. Although the reasons to use single-agent etoposide were laudable and credible to maintain (efficacy with less toxicity), the results were disastrous. The primary goal of care in SCLC is to combat the cancer. When the cancer is arrested, patients live longer and better. The lesson here is clear. Whenever regimens are developed in attempt to decrease side effects, investigators (and practitioners) must be certain that the primary goal of treatment is not compromised.

Newer Approaches to the Treatment of SCLC

Most older patients do not complete a six-cycle polychemotherapy course secondary to toxicity. Therefore, Murray, et al. sought to evaluate the efficacy of an abbreviated chemotherapy course for older patients with limited-stage SCLC. Treatment consisted of one cycle of cyclophosphamide, doxorubicin, and vincristine followed three weeks later by one cycle of etoposide and cisplatin. Thoracic irradiation was administered concurrently with the etoposide and cisplatin combination. All patients received the cyclophosphamide, doxorubicin, and vincristine combination and 89% received the etoposide and cisplatin combination. Fifty-one percent of patients had a complete response and 38% had a partial response. The two-year survival rate was 28%, with a median survival time of 13 months. Despite the shorter duration of chemotherapy, 3 of the 55 patients died of a treatment-related death, suggesting that the risk of toxicity is high early in
the treatment course and trials are needed to focus on ways to ameliorate this toxicity.\textsuperscript{70}

Other investigators have tried new combinations of available drugs in older patients. Westeel, et al.\textsuperscript{71} performed a Phase II study of the PAVE regimen (cisplatin, doxorubicin, vincristine, and etoposide) repeated at intervals of three weeks for four cycles. Patients who received concurrent thoracic irradiation had the etoposide–cisplatin regimen substituted for the PAVE regimen at the time of the second chemotherapy course. Only 58\% of patients who received chemotherapy and thoracic irradiation could complete all four chemotherapy cycles and 64\% of patients who received PAVE alone could complete the regimen. The median survival time for patients with limited-stage disease was 17 months, and for patients with extensive-stage disease it was 11 months. One patient (3\%) on the combined modality arm experienced a toxic death. Forty-two percent of patients on the combined-modality arm and 15\% receiving chemotherapy alone were hospitalized, mainly for neutropenic fever.\textsuperscript{71}

Noda, et al.\textsuperscript{58} performed a multicenter Phase III study of irinotecan and cisplatin compared with etoposide plus cisplatin for the treatment of extensive-stage SCLC. The study was terminated after enrollment of 154 patients because an interim analysis showed an improvement in survival rate for the patients receiving irinotecan plus cisplatin. The median survival rate was 13 months for irinotecan plus cisplatin versus 9 months for the etoposide plus cisplatin group \( (P = .002) \), and the 2-year survival rate was 20\% irinotecan plus cisplatin versus 5\% etoposide plus cisplatin. The median age of patients in the study was 63 years; however, there were no patients older than 70 included in the study and therefore, the applicability of these results to the older patient population is not known.\textsuperscript{58}

### Chemotherapy and Thoracic Irradiation

Combined-modality therapy with chemotherapy and thoracic irradiation has proven to be beneficial in the treatment of limited-stage SCLC with a survival benefit to combined-modality treatment of approximately 5\% at three years. A meta-analysis of trials of thoracic radiotherapy for SCLC showed a trend toward a larger reduction in the mortality rate for younger patients compared with older patients who received combined-modality treatment versus chemotherapy alone. The relative risk for death was 0.72 (95\% CI, 0.56–0.93) for patients less than 55 years old versus 1.07 (95\% CI, 0.70–1.64) among patients older than 70 years.\textsuperscript{72} The cause of the decreased treatment benefit in older patients is not known.

A retrospective review of 608 patients who received thoracic irradiation in a sequential or concurrent approach in combination with chemotherapy in two trials (BR.3 and BR.6) was analyzed with respect to age. Chemotherapy consisted of cyclophosphamide, doxorubicin, and vincristine-based and etoposide plus cisplatin-based regimens given in either a sequential or alternating approach. In BR.3, thoracic irradiation was given after chemotherapy, whereas in BR.6 it was given concurrently with chemotherapy, with randomization to radiation either early or late in the course. In this study, there were no differences between younger (<70 years; \( n =

| Trial                      | Patients (n) | Age, yrs (range) | Study Arms                  | Response Rate (%) | Median Survival |
|----------------------------|--------------|------------------|-----------------------------|-------------------|-----------------|
| Medical Research Council\textsuperscript{68} | 339          | 67 (35–82)       | Oral etoposide              | 45                | 130 days       |
|                            |              |                  | IV Chemotherapy (EV or CAV) |                   |                 |
| Souhami, et al.\textsuperscript{69} | 155          | 68 (45–83)       | Oral etoposide              | 51                | 183 days       |
|                            |              |                  | IV Chemotherapy (PE or CAV) | 33                | 4.8 months     |

EV, Etoposide and vincristine; CAV, Cyclophosphamide, doxorubicin, and vincristine; PE, Cisplatin and etoposide.
520) and older patients (≥70 years; n = 88) in terms of time to completion of thoracic irradiation, mean dose delivered, or acute or late toxicities. In addition, there was no difference in response or survival rates between the two groups. No patients older than 80 years were included in this trial.73

A Phase II study of carboplatin, etoposide, and accelerated hyperfractionated radiation therapy was performed in patients with limited-stage SCLC who were older than 70 years (age range, 70–77 years). It showed an overall response rate of 75%, with 57% of patients attaining a complete response. The median survival time was 15 months. A Grade 4 acute toxic effect (thrombocytopenia) developed in only one patient. Grade 3 toxicity consisted of leukopenia (8.3%), thrombocytopenia (11%), anemia (2.8%), infection (4.2%), alopecia (57%), esophagitis (2.8%), and nausea and vomiting (4.2%).74

A retrospective review of patients who received combined-modality treatment on Intergroup Trial 0096 was analyzed with respect to age (Table 10). This trial included 381 patients with limited-stage SCLC who received treatment with cisplatin (60 mg/m² on Day 1) and etoposide (120 mg/m² on Days 1–3) for four cycles, with concurrent thoracic radiotherapy (administered once or twice daily to 45 gray). Patients 70 years and older had a response rate similar to that of younger patients; however, the overall five-year survival rate favored patients younger than 70 years. Much of the difference in survival rate occurred in the first six months, secondary to the increased incidence of toxic death in older patients. Older patients had an increased risk for Grades 4 and 5 hematologic toxicity; however, there was no difference in the frequency of nonhematologic toxicity. Older patients who received attenuated doses had a lower response rate (36% versus 92%; P = .0003) and median survival rate (6.2 months versus 17.1 month; log rank, P = .0021) compared with those who received full treatment. The authors concluded that selected older patients with good performance status should be considered for combined-modality therapy.75

| Age < 70 years (n = 331) | Age ≥ 70 years (n = 50) | P Value |
|--------------------------|------------------------|---------|
| Response (%)              | 88                     | 80      | 0.11    |
| Five-Year Survival Rate (%)| 22                     | 16      | 0.05    |
| Grade 4 or 5 Hematologic Toxicity (%) | 61 | 84 | <0.01 |
| Fatal Toxicity (%)        | 1                      | 10      | 0.01    |

Data derived from Yuen, et al.76

**Prophylactic Cranial Irradiation**

The role of prophylactic cranial irradiation for patients with limited-stage SCLC in complete remission was summarized in a meta-analysis of seven trials comparing prophylactic cranial irradiation to none. This showed that prophylactic cranial irradiation leads to an improvement in survival rate of 5.4% (from 15.3% in the control group to 20.7% in the treatment group) at three years. There was no difference in the magnitude of benefit in the subgroup of patients younger than 55 from the subgroup that was older than 65 years.76 Older patients with subtle cognitive deficits at baseline may be more vulnerable to any additional insults in cognitive functioning secondary to cranial irradiation, and this should be considered when discussing prophylactic cranial irradiation with these patients.77

**CONCLUSIONS**

Because the population is aging and lung cancer affects a significant number of older persons, we need to focus additional resources on efforts to maximize treatment efficacy, minimize toxicity, and understand treatment preferences of this patient population. The mainstay of treatment for early-stage NSCLC is surgery. Older patients with early-stage NSCLC who are not surgical candidates can be treated with radiation with curative intent; however, the survival rate statistics are inferior to those achieved with surgery. Patients with...
locally advanced NSCLC benefit from multimodality treatment either with induction therapy and surgery or concurrent treatment with chemotherapy and radiation; however, there is a significant risk of short-term toxicity in older patients that may outweigh any potential benefit. Randomized studies show that fit older patients with advanced NSCLC benefit from treatment with single-agent chemotherapy, which improves survival and quality of life compared with best supportive care. Cisplatin- or carboplatin-based combination chemotherapy should be offered to fit older patients based on the same selection process and benefits seen in the population as a whole.

Standard treatment for SCLC consists of combination chemotherapy with or without thoracic irradiation. Older adults have equivalent outcomes but more toxicity compared with younger adults with these approaches. Randomized studies have shown that treatment with single-agent etoposide is inferior to standard combination chemotherapy. Additional studies are needed to develop more tolerable yet equally or more efficacious regimens for all patients. Future studies should incorporate the use of geriatric assessment to help clinicians make individualized treatment decisions based on each patient’s physiologic age.

REFERENCES

1. Jemal A, Murray T, Samuel A, et al. Cancer statistics, 2003. CA Cancer J Clin 2003;53:208–226.
2. Ries LAG, Eisner MP, Kosary CL, et al. (eds). SEER. Cancer Statistics Review, 1975–2000. Bethesda, MD: National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2000. Accessed August 29, 2003.
3. Yancik R, Ries LA. Aging and cancer in the population as a whole. Lung Cancer 2003;47:1072–6.
4. Bach PB, Kattan MW, Thornquist MD, et al. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 1995;13:235–52.
5. Smith TJ, Penberthy L, Desch CE, et al. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 1995;13:235–52.
6. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.
7. National Center for Health Statistics. United States Life Tables, 2000. Available at http://www.cdc.gov/nchs/products/pubs/pubd/nvsr/51_03.htm. Accessed August 29, 2003.
8. Hanagiri T, Muranaka H, Hashimoto M, et al. Results of surgical treatment of lung cancer in octogenarians. Lung Cancer 1999;23:129–33.
9. Pagni S, Federico JA, Ponz RB. Pulmonary resection for lung cancer in octogenarians. Ann Thorac Surg 1997;63:785–9.
10. Yamamoto K, Padvila Alaron J, Calvo Medina V, et al. Surgical results of stage I non-small cell lung cancer: comparison between elderly and younger patients. Eur J Cardiothorac Surg 2003;23:21–5.
11. Jazieh AR, Hussain M, Howington JA, et al. Prognostic factors in patients with surgically resected stages I and II non-small cell lung cancer. Ann Thorac Surg 2000;70:1168–71.
12. van Rens MT, de la Riviere AB, Elbers HR, van Den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. Chest 2000;117:374–9.
13. Cohen H. Cancer care in the older population: physiology of aging. Presented at the American Society of Clinical Oncology Educational Symposium; November 5–6, 2000; Orlando, Fla.
14. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. CA Cancer J Clin 2003;53:208–226.
15. Stafford RS, Cyr PL. The impact of cancer on the physical function of the elderly and their utilization of health care. Cancer 1997;80:1973–80.
16. Narain P, Rubenstein LZ, Wieland GD, et al. Predictors of immediate and 6-month outcomes in hospitalized elderly patients. The importance of functional status. J Am Geriatr Soc 1998;36:775–83.
17. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist 2000;5:224–37.
18. Reuben DB, Rubenstein LV, Hirsch SH, Hays RD. Value of functional status as a predictor of mortality: results of a prospective study. Am J Med 1992;93:663–9.
19. Barberger-Gateau P, Fabrigoule C, Helmer C, et al. Functional impairment in instrumental activities of daily living: an early clinical sign of dementia? J Am Geriatr Soc 1999;47:456–62.
20. Landi F, Zuccala G, Gambassi G, et al. Body mass index and mortality among older people living in the community. J Am Geriatr Soc 1999;47:1072–6.
21. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980;69:491–7.
22. Newman AB, Yanez D, Harris T, et al. Weight change in old age and its association with mortality. J Am Geriatr Soc 2001;49:1309–18.
23. Eagles JM, Beattie JA, Restall DB, et al. Relation between cognitive impairment and early death in the elderly. BMJ 1990;300:239–40.
24. Wolfson C, Wolfson DB, Asgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001;344:1111–6.
25. Seeman TE, Berkman LF, Kohout F, et al. Intercommunity variations in the association between social ties and mortality in the elderly. A comparative analysis of three communities. Ann Epidemiol 1993;3:325–35.
26. Vestal RE. Aging and pharmacology. Cancer 1997;80:1302–10.
27. Albaum KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991;9:1618–26.
28. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small cell lung cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1986;4:702–9.
29. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. J Nat Cancer Inst 1980;65:25–32.
30. Borges M, Schuler JP, Paesmans M, et al. Prognostic factors for response to chemotherapy containing platinum derivatives in patients with unresectable non-small cell lung cancer (NSCLC). Lung Cancer 1996;16:21–33.
31. Hillner BE, McDonald MK, Desch CE, et al. A comparison of patterns of care of nonsmall cell lung carcinoma patients in a younger and Medicare commercially insured cohort. Cancer 1998;83:1930–7.
32. Smith TJ, Penberthy L, Desch CE, et al. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 1995;13:235–52.
33. Smith TJ, Penberthy L, Desch CE, et al. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 1995;13:235–52.
34. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. CA Cancer J Clin 2003;53:208–226.
Early post-pneumonectomy complications in the elderly. Eur J Cardiothorac Surg 2000;17:246–50.
36. Bach PB, Cramer LD, Schrag D, et al. The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 2001; 345:181–8.
37. Gauden SJ, Tripcony L. The curative treatment by radiation therapy alone of Stage I non-small cell lung cancer in a geriatric population. Lung Cancer 2001;32:71–9.
38. Pignon T, Gregor A, Schake Koning C, et al. Age has no impact on acute and late toxicity of curative thoracic radiotherapy. Radiother Oncol 1998;46:239–48.
39. Numico G, Russi E, Merlano M. Best supportive care in non-small cell lung cancer: Is there a role for radiotherapy and chemotherapy? Lung Cancer 2001;32:213–20.
40. Langer CJ, Hsu C, Curran W, et al. Do elderly patients (pts) with locally advanced non-small cell lung cancer (NSCLC) benefit from combined modality therapy? A secondary analysis of RTOG 94–10. L. J. Radiat Oncol Biol Physics 2002;51(Suppl 1):1–2.
41. Sause W, Kolesar P, Taylor SL, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 2000;117:358–64.
42. Movas B, Scott C, Sause W, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. Int J Radiat Oncol Biol Phys 1999;45:1143–9.
43. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-Small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899–909.
44. Earle CC, Tsai JS, Gelber RD, et al. Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. J Clin Oncol 2001;19:1064.
45. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999;91:66–72.
46. Ricci S, Antonuzzo A, Galì L, et al. Gemcitabine monotherapy in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. Lung Cancer 2000;27:75–80.
47. McKay CE, Hansworth JD, Burris HA 3rd, Yardley DA, et al. Weekly docetaxel in the treatment of elderly patients with advanced non-small cell lung cancer (NSCLC): a Minnie Pearl Cancer Network Phase II Trial. Proc Am Soc Clin Oncol 2000;19:502a. Abstract 1964.
48. Fidias P, Supko JG, Martins R, et al. A phase II study of weekly paclitaxel in elderly patients with advanced non-small cell lung cancer. Clin Cancer Res 2001;7:3942–9.
49. Grindelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003;95:362–72.
50. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000;18:2529–36.
51. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small cell lung cancer: implications of Eastern Cooperative Oncology Group 5S92, a randomized trial. J Natl Cancer Inst 2002;94:173–81.
52. Kelly K, Giarratta S, Akerley W, et al. Should older patients (pts) receive combination chemotherapy for advanced stage non-small cell lung cancer (NSCLC)? An analysis of Southwest Oncology Trials 9509 and 9308. Proc Am Soc Clin Oncol 2001;20:329a. Abstract 1313.
53. Hensing TA, Socinski MA, Schell MJ, et al. Age does not alter toxicity or survival for patients (pts) with stage IIB/IV non-small cell lung cancer (NSCLC) treated with carboplatin (C) and paclitaxel (P). Proc Am Soc Clin Oncol 2001;20:346a. Abstract 1382.
54. Lilenbaum RC, Herndon J, List M, et al. Single-agent (SA) versus combination chemotherapy (CC) in advanced non-small cell lung cancer (NSCLC): a CALGB randomized trial of efficacy, quality of life (QOL), and cost-effectiveness. Proc Am Soc Clin Oncol 2002;21:1a. Abstract 2.
55. Kris MG, Natale RB, Herbst RS, et al. A phase II trial of ZD1839 (Iressa) in advanced non-small cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2). Proc Am Soc Clin Oncol 2002;21:292a. Abstract 1166.
56. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small cell lung cancer. J Clin Oncol 2003;21:2237–46.
57. Gridelli C, De Vivo R, Monfardini S, Management of small cell lung cancer in the elderly. Crit Rev Oncol Hematol 2002;41:79–88.
58. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small cell lung cancer. N Engl J Med 2002;346:85–91.
59. Shepherd FA, Amidmichael E, Evans WK, et al. Treatment of small cell lung cancer in the elderly. J Am Geriatr Soc 1994;42:64–70.
60. Stu LL, Shepherd FA, Murray N, Feld R, et al. Influence of age on the treatment of limited-stage small cell lung cancer. J Clin Oncol 1996;14:821–8.
61. Larive S, Bombaron P, Riou R, et al. Multimodal combination chemotherapy for elderly patients with limited-stage small cell lung cancer. J Radiat Oncol Biol Phys 1999;45:39–45.
62. Jeremic B, Shibamoto Y, Acinovic L, Milsav-Jevic S, Carboplatin, etoposide, and accelerated hyperfractionated radiotherapy for elderly patients with limited small cell lung carcinoma: a phase II study. Cancer 1998;82:1618–24.
63. Quon H, Shepherd FA, Payne DG, et al. The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. Int J Radiat Oncol Biol Phys 1999;43:9–45.
64. Carney DN. Carboplatin/etoposide combination chemotherapy in the treatment of poor prognostic patients with small cell lung cancer. Lung Cancer 1995;12(Suppl 3):S77–S83.
65. Evans WK, Radwi A, Tomiak E, et al. Oral etoposide and carboplatin. Effective therapy for elderly patients with small cell lung cancer. Am J Clin Oncol 1995;18:149–155.
66. Smut EF, Carney DN, Harford P, et al. A phase II study of oral etoposide in elderly patients with small cell lung cancer. Thorax 1989;44:631–633.
67. Carney DN, Grogan L, Smut EF, et al. Single-agent oral etoposide for elderly small cell lung cancer patients. Semin Oncol 1990;17:49–53.
68. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. Lancet 1996;348:563–6.
69. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small cell lung cancer: randomized comparison with intravenous chemotherapy. J Natl Cancer Inst 1997;89:577–80.
70. Murray N, Grafton C, Shah A, et al. Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small cell lung cancer. J Clin Oncol 1998;16:3323–8.
71. Westeel V, Murray N, Gelmon K, et al. New combination of the old drugs for elderly patients with small cell lung cancer: a phase II study of the PAVE regimen. J Clin Oncol 1998;16:1940–7.
72. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small cell lung cancer. N Engl J Med 1992;327:1618–24.
73. Quon H, Shepherd FA, Payne DG, et al. The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. Int J Radiat Oncol Biol Phys 1999;43:9–45.
74. Jeremic B, Shibamoto Y, Acinovic L, Milsav-Jevic S, Carboplatin, etoposide, and accelerated hyperfractionated radiotherapy for elderly patients with limited small cell lung carcinoma: a phase II study. Cancer 1998;82:836–41.
75. Yuen AK, Zou G, Turner AT, et al. Similar outcome of elderly patients in intergroup trial 0096: carboplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer 2000;89:1953–60.
76. Aupeain A, Arrigada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476–84.
77. Crossen JR, Garwood D, Glattstein E, Newwell EA. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol 1994;12:627–42.