Management of Lung Cancer in the Elderly

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KEYWORDS

• Lung cancer • Elderly • Geriatric assessment • Palliative care • Early stage
• Advanced stage • Metastatic • Targeted therapy

KEY POINTS

- Lung cancer is a leading cause of cancer-associated mortality and affects the elderly disproportionately.
- Despite high prevalence, high-level evidence specific to the elderly is sparse in lung cancer.
- Fit elderly patients should be offered treatment plans similar to younger patient with the same disease features and stage.
- Geriatric assessment has a predictive role for chemotherapy-associated toxicity.
- Clear communication of palliative, non-curative intent, if such is the case, should be incorporated by the oncologist early in the treatment course.

INTRODUCTION

Demographics and Scope of the Problem

Lung cancer is the leading cause of cancer-related mortality and accounts for more than one-quarter of all cancer-related deaths in both men and women in the United States. It is estimated that in 2015 there will be 221,200 new diagnoses and 158,040 deaths attributable to lung cancer. The probability of developing lung cancer increases considerably as patients age; two-thirds of all new cases will occur in patients more than 65 years of age.[1] Although there is no uniform age cutoff for classifying patients as elderly across the globe, and the World Health Organization defines elderly as patients more than 65 years old, it is reasonable to assume that at the present time age 70 years is the accepted standard for such classification in the United States.[2] Non–small cell lung cancer (NSCLC) accounts for about 80% to 85% of all lung cancers and is of particular concern in elderly patients, and this is the focus of this article.[3] It is estimated that,

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by the year 2030, the number of adults more than 65 years of age in the United States will have doubled, leading to a dramatic increase in the incidence of this disease. It is therefore imperative to study and streamline the management of this disease in the elderly population, which has so far been understudied.

Staging

The management of lung cancer is largely dependent on staging. The American Joint Commission for Cancer (AJCC) staging principles are used by oncologists to stage lung cancer. They are:

1. Early stage: corresponds with stage I and II on the AJCC classification. These tumors are typically amenable to surgery. For tumors larger than 4 cm or with nodal involvement, postoperative adjuvant chemotherapy with cisplatin-based combinations is recommended. For patients who are medically inoperable, radiotherapy or radiosurgery with curative intent is appropriate therapy.
2. Locally advanced disease: corresponds with stage III on the AJCC classification. This stage includes patients with locally (T3–4) and/or regionally (n2/3) advanced cancer. A few patients with limited nodal involvement, good pulmonary reserve, and excellent performance status (PS) may be candidates for surgery. Most are considered inoperable and ideally are treated with concurrent chemotherapy and radiation with curative intent. For the vulnerable or frail, radiation alone with curative or palliative intent may be used.
3. Distant metastatic disease: corresponds with stage IV on the AJCC classification and includes patients with bilateral lung cancer as well as pleural involvement. However, this group accounts for more than half the patients at diagnosis. These patients are typically treated with palliative intent with chemotherapy, targeted therapy, or biologic therapy. The incidence and survival by disease stage as discerned form Surveillance, Epidemiology, and End Results (SEER) is shown in **Fig. 1**. In addition, **Table 1** provides a practical approach to discussing the management of lung cancer.

PRINCIPLES OF MANAGEMENT

Early Stage Disease

Surgery for non–small cell lung cancer

Early stage lung cancer is, by definition, surgically resectable provided the patient is able to withstand thoracotomy medically and if postresection lung function will be

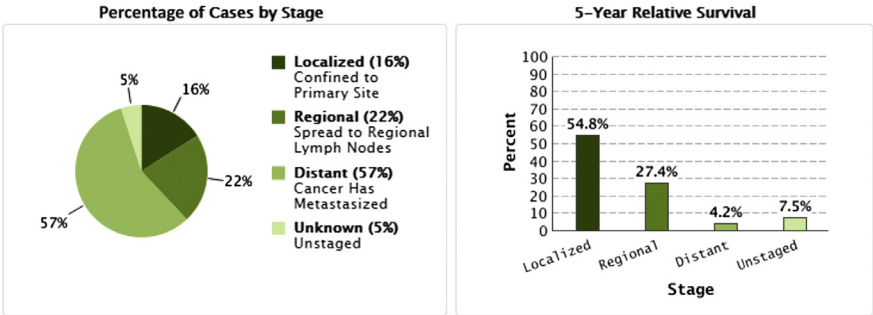

Fig. 1. Percentage of cases and 5-year relative survival by stage at diagnosis: lung and bronchus cancer. (*From* SEER Stat Fact Sheets: lung and bronchus cancer. Surveillance, Epidemiology, and End Results Program. Available at: http://seer.cancer.gov/statfacts/html/lungb.html. Accessed July 11, 2015.)

Table 1
Management principles based on stage in NSCLC

Stage	Ideal Treatment	Alternate Treatment
Early stage (stage IA/IB)	Surgery	• Radiation/SBRT
Early stage but with limited regional spread; N1 disease (stage IIA/IIB)	Surgery followed by cisplatin-based chemotherapy	• Radiation ± chemotherapy if not a surgical candidate • After surgery if not a candidate for cisplatin, consider carboplatin-based chemotherapy
Locally and or regionally advanced disease (stage IIIA/IIIB)	Concurrent chemoradiotherapy for inoperable tumors	• Sequential radiation → chemotherapy • Radiation therapy alone (curative) • Radiation therapy (palliative)
Distant metastatic disease (stage IV)	Cytotoxic chemotherapy and/or targeted therapy	• Best supportive care

Palliative care and hospice should be involved early in the treatment course for elderly patients. Comprehensive geriatric assessment has a predictive role for chemotherapy-associated toxicity.
Abbreviation: SBRT, stereotactic body radiation therapy.

adequate without oxygen and other ventilator support. Age is reported as an independent predictor of postsurgical survival in patients with NSCLC.[4] It is also known that older patients are less likely to be offered surgical resection: only 70% of the population more than 75 years of age, compared with 92% of the younger population, was offered surgical resection ($P<.0001$). By the same token, the median survival of the different age groups was 71 months for those less than 65 years old and 28 months for patients who were more than 75 years old ($P<.0001$).[4] This result was likely based on patients' functional status and their comorbid conditions, which made them poor candidates for surgery. A more recent study, which took into account ongoing improvements in perioperative and intraoperative care in recent times, also showed that older patients are less likely to have curative surgical resection offered to them.[5] This retrospective analysis included 10,923 patients with a median age of 75 years and found that lobectomy was associated with the best long-term outcomes in elderly patients with early NSCLC compared with sublobar resection, conventional radiation, and stereotactic ablative radiotherapy (hazard ratio [HR], 0.71; confidence interval [CI], 0.45–1.12). It also showed that the percentage of patients who received lobectomy decreased with increasing age: 31% of patients 70 to 74 years old received a lobectomy compared with 18% of patients more than 80 years old ($P<.001$).[5]

Adjuvant chemotherapy in the elderly

After surgical resection, patients with large tumors (>4 cm) and/or lymph node involvement should be offered adjuvant cisplatin-based chemotherapy. Adjuvant chemotherapy in elderly patients with resected lung cancer offers many challenges. The potential improvement in survival must be weighed against the potential for immediate and long-term toxicity. The prevailing standard for stages IB to IIIA NSCLC is to treat with cisplatin-based combination chemotherapy for 4 cycles based on the results of large randomized phase III clinical trials reported over the past decade, which showed an improvement in overall survival (OS) ranging from 5% to 15%. The trials that did show a benefit for adjuvant chemotherapy include the International Adjuvant Lung

Trial (IALT), JBR.10, and Adjuvant Navelbine International Trialist Association (ANITA) trials and those that failed to show such benefit include the ALPI, BLT, and CALGB, Cancer and Leukemia Group B (CALGB) 9633 trials[6–11] (**Table 2**). The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis reviewed results from all 5 cisplatin-containing trials and reported an OS benefit of 5.4% at 5 years.[12] Note that only 20% of patients were more than 65 years of age and 9% more than 70 years of age in these trials.[13] The CALGB 9633 trial was novel in that it was restricted to patients with stage IB disease and used a carboplatin-based regimen. However, despite an improvement in progression-free survival, there was no benefit in OS at 5 years. The proportion of subjects greater than 70 years of age was 20% in the LACE meta-analysis compared with cisplatin trials, which remains low for a disease with median age at diagnosis of 70 years. Given that clinical trials have strict eligibility criteria permitting only the fit elderly, it is reasonable to turn to population-based databases to study the impact of adjuvant chemotherapy in older adults. Using the Medicare SEER registry, an observational cohort study has been reported to address this question.[14] In this study, 3324 patients more than 65 years of age were identified as undergoing surgery to treat stage II and IIIA NSCLC with a primary end point of OS. In this group, 21% received platinum-based chemotherapy. There was an OS benefit for patients who received chemotherapy in the population less than 70 years of age (HR, 0.74; 95% CI, 0.62–0.88) and aged 70 to 79 years (HR, 0.82; 95% CI, 0.71–0.94) but not in the population more than 80 years of age (HR, 1.33; 95% CI, 0.86–2.06). The use of adjuvant chemotherapy was associated with an increased odds ratio (OR) of serious adverse events as determined by hospitalization (OR, 2.0; 95% CI, 1.5–2.6). Using the Ontario Cancer Registry, Cuffe and colleagues[15] reported an age-based breakdown in more than 6300 patients with NSCLC treated with surgery from 2001 to 2006. They used change in OS since the advent of adjuvant chemotherapy as a surrogate for benefit from, and hospitalization as a reflection of toxicity from, adjuvant

Table 2
Summary of positive trials of adjuvant chemotherapy in age-unselected patients

Trial	ANITA[1,a]	IALT[6,b]	JBR.10[8,c]	LACE[12,d]	CALGB[11,e]
Total patients (n)	840	1867	482	4584	344
Age>65–69 y; n (%)	170 (20)	328 (18)	84 (17)	901 (20)	NA
Stage	IB–IIIA	I–III	IB–II	I–IIIA	IB
PS	0–2	0–2	0, 1	NA	0–1
Cisplatin dose (mg/m^2)	400	300–400	400	150–400	NA; carboplatin AUC 6
OS increase at 5 y (%)	8.6	4.1	15	5.4	None

Abbreviations: AUC, area under the curve; LACE, Lung Adjuvant Cisplatin Evaluation; NA, not applicable; OS, overall survival.

[a] Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB to IIIA NSCLC: a randomized controlled trial.[7]

[b] Cisplatin-based adjuvant chemotherapy in patients with completely resected NSCLC.[6]

[c] Vinorelbine plus cisplatin versus observation in resected NSCLC. National Cancer Institute of Canada Clinical Trials Group, National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators.[8]

[d] A pooled analysis by the LACE Collaborative Group. A meta-analysis by the NSCLC Meta-analyses Collaborative Group.[12,13]

[e] Adjuvant paclitaxel plus carboplatin compared with observation in stage IB NSCLC: CALGB 9633 with the CALGB, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups.[11]

Data from Refs.[6–8,11–13]

chemotherapy. In all, 2763 (44%) of 6304 surgical patients were 70 years of age or older. Use of adjuvant chemotherapy in this age group increased from 3.3% (2001–2003) to 16.2% (2004–2006). Among older patients, 70% received cisplatin and 28% received carboplatin-based regimens. Requirements for dose adjustments/substitutions as well as hospitalization rates were similar across age groups (28.0% for patients aged <70 years; 27.8% for patients aged ≥70 years; $P = .54$). Four-year OS of older patients increased significantly (47.1% to 49.9% for patients diagnosed 2001–2003 and 2004–2006 respectively; $P = .01$). Survival improved in all subgroups except in patients aged 80 years and older. In a recent report from the Veterans Affairs Cancer Registry of 7593 patients who underwent resection for stage IB to III NSCLC, 2897 (38%) were greater than or equal to 70 years of age.[16] The proportion of older patients who received adjuvant chemotherapy was half that of younger patients who did so (15.3% vs 31.6%; $P<.0001$). Carboplatin-based doublets were used most often in all patients (64.6%). Both younger (HR, 0.79; 95% CI, 0.72–0.86) and older patients (HR, 0.81; 95% CI, 0.71–0.92) had a lower risk of death with adjuvant chemotherapy. Further, cisplatin-based therapy was associated with a similar risk of mortality to carboplatin-based chemotherapy in the younger patients (HR for cisplatin-based therapy, 1.02; 95% CI, 0.83, 1.25). In older patients, there was a nonsignificant 12% decreased risk of deaths with cisplatin-based therapy (HR, 0.88; 95% CI, 0.59–1.30).

Locally Advanced Non–small Cell Lung Cancer

The surgical option is appropriate for a minority of patients with excellent PS and pulmonary reserve as well as limited tumor volume and minimal mediastinal nodal involvement. These patients derive significant benefit from adjuvant chemotherapy after surgery. For most patients with locally advanced NSCLC concurrent chemoradiotherapy is considered the standard treatment. However, because of a lack of prospective data and exclusion and underrepresentation of frail elderly patients from clinical trials, there is no standard of care. The gold standard for chemotherapy used for radiosensitization has long been considered to be cisplatin and etoposide at systemic doses rather than the low doses of paclitaxel and carboplatin commonly used in practice for the ease of administration. The former approach, first explored by the Southwest Oncology Group in S8805 and further studied in stage IIIB in S9019, was deemed the standard in the nonsurgical arm of the intergroup trial 0139.[17–19] In this latter intergroup trial, the median age of participants was 60 years and age was not predictive of outcomes. Its feasibility in the fit elderly has been shown with similar benefit to that obtained by younger patients, albeit at a higher toxicity than experienced by younger patients.[20] In addition, consolidation chemotherapy with docetaxel following cisplatin-based concurrent chemoradiotherapy did not add any survival benefit. The more prevalent practice of using low-dose weekly carboplatin and paclitaxel emerged from CALGB 39801.[21] A post hoc analysis of the CALGB 39801 trial identified factors predictive of decreased survival as weight loss greater than or equal to 5%, age greater than or equal to 70 years, PS of 1, and hemoglobin level less than 13 g/dL ($P<.05$).[22] Patients with greater than or equal to 2 poor prognostic factors (n = 165) had a decreased OS compared with patients with less than or equal to 1 factor (n = 166) (HR for OS was 1.88; 95% CI, 1.49–2.37; $P = .0001$; median survival times were 9 and 18 months, respectively. $P = .0001$). There is benefit to the addition of systemic doses of platinum-based chemotherapy following low-dose radiosensitization; however, this has only been tested in a phase II trial.[23] The recent results from RTOG 0617, which used this low-dose weekly paclitaxel and carboplatin regimen for radiosensitization followed by systemic doses of consolidation

chemotherapy in all patients, found no benefit from escalating the dose of radiotherapy (74 Gy) compared with standard-dose (60 Gy) radiotherapy; survival times with standard radiation were better at 28.7 versus 19.5 months ($P = .0007$).[24] Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume greater than 5 Gy, but not age.

Prospective trials in the elderly

In a randomized study by the Japan Clinical Oncology Group specific to patients more than 70 years old (n = 200) with unresectable stage III NSCLC, patients were randomly assigned to chemoradiotherapy (60 Gy with concurrent low-dose carboplatin at 30 mg/m^2 per day, 5 days a week for 20 days) or radiotherapy alone with a primary end point of OS. Median OS for the chemoradiotherapy and radiotherapy alone groups were 22·4 months and 16·9 months respectively (HR, 0.68; 95.4% CI, 0.47–0.98; $P = .0179$). More patients had grade 3 to 4 hematological toxicity and grade 3 infections in the chemoradiotherapy group than in the radiotherapy-alone group, with no difference in rates of grade 3 to 4 pneumonitis and late lung toxicity between groups.[25] Based on pooled analyses of trials conducted with the NCCTG (North Central Cancer Treatment Group) and CALGB, older patients treated with chemoradiotherapy had improved OS compared with radiation alone but had higher rates of toxicity greater than or equal to grade 3 than patients who received radiation therapy alone.[26,27] A recent meta-analysis of 7 PRCTs (Prospective Randomized Control Trial) (1205 patients) comparing concurrent with sequential chemoradiotherapy in stage III NSCLC reported a significant benefit of concomitant chemoradiotherapy on OS (HR, 0.84; 95% CI, 0.74–0.95; $P = .004$), with an absolute benefit of 5.7% (18.1%–23.8%) at 3 years and 4.5% at 5 years.[28] Concomitant chemoradiotherapy increased acute esophageal toxicity (grade 3–4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1–7.8; $P<.001$). This analysis included 459 (38%) patients greater than or equal to 65 years old and 16% greater than or equal to 70 years old. However, no differences in efficacy outcomes were evident based on age. Thus, older adults fit enough to meet eligibility for prospective randomized studies were as likely to derive survival benefit from concurrent chemoradiotherapy as younger patients.

Results from population databases

Using the SEER registry, a recent study evaluated the prevalence and effectiveness of radiation therapy alone in stage III NSCLC. Of the 10,376 cases identified that were not treated with chemotherapy, 62% received radiation therapy alone. Radiotherapy was associated with improved OS (HR, 0.76; 95% CI, 0.74–0.79), albeit with increased risk of hospitalization for pneumonitis and esophagitis.[29] Another study using the SEER registry reported that in locally advanced NSCLC only 66% of older adults received any treatment (based on cases diagnosed 1997–2009). Of those that were treated, only 45% received combined chemoradiotherapy, which is considered the standard of care for this group of patients.[30] Recent single-institution retrospective reviews suggest that outcomes in the elderly are associated with PS rather than chronologic age alone. In one such study of 189 patients, those greater than or equal to 70 years old (n = 86) were more likely to have Eastern Cooperative Oncology Group (ECOG) PS greater than or equal to 2 ($P<.05$) and receive palliative intent treatment ($P<.05$), and less likely to receive concurrent chemoradiotherapy ($P<.05$) and cisplatin ($P<.05$).[31] Median survival was 10.3 months for the elderly compared with 17.2 months for younger patients ($P<.05$). On multivariate analysis, older age was not associated ($P = .43$) with increased risk of death, whereas poor ECOG PS (≥ 2) was significantly

associated with death ($P<.05$). In elderly patients, definitive treatment ($P<.05$), chemotherapy administration ($P<.05$), and ECOG PS of 0 to 1 ($P<.05$) were associated with improved outcome. In another study of 389 patients, the elderly group ($\geq$75 years old), had a median survival of 19.9 months in the combined modality group versus 7.8 months in the other treatments group ($P = .0048$), suggesting that elderly patients likely derive benefit from combined modality therapy if their PS is adequate.[32] Better methods of risk stratification for these elderly are therefore needed.

Advanced Disease: Management Principles

Importance of histology and molecular markers

It is imperative to classify lung cancer beyond small cell or non–small cell histologies. Within NSCLC, it is important to determine squamous versus adenocarcinoma histology. Two of the commonly used agents in NSCLC are not used in the squamous subtype (pemetrexed because of lack of efficacy and bevacizumab because of higher risk of toxicity). Further, adenocarcinoma tumors should be tested for molecular markers that offer options for treatment with targeted agents, especially mutations in the epidermal growth factor receptor (EGFR) and the EML-ALK genes (echinoderm microtubule-associated protein-like 4 [EML4] - anaplastic lymphoma kinase [ALK]). Those with proven mutations can be treated with tyrosine kinase inhibitors like erlotinib or afatinib and crizotinib or ceritinib for EGFR and EML-ALK mutations respectively. Thus, cytotoxic chemotherapy can be delayed in these patients in favor of these oral agents. About 10% to 15% of patients with adenocarcinoma may harbor such actionable mutations, with the likelihood being highest in nonsmokers. Commonly used oral agents with frequently encountered adverse events are listed in **Table 3**.

Cytotoxic chemotherapy in advanced disease

The standard of care for most patients with advanced, recurrent, or metastatic NSCLC is platinum-based combination chemotherapy. There is no specific age cutoff for the use of combination therapy but the use is generally restricted to patients with PS of 0 to 1. Toxicity associated with chemotherapy is higher with combination regimens and typically increases with age because of the decline in physiologic function with age as well as the increase in comorbidity burden. Thus, whether to treat an older patient with advanced lung cancer with a platinum-based combination regimen to maximize efficacy versus single-agent chemotherapy to minimize toxicity and maintain function and quality of life (QoL) is a question commonly encountered in clinical practice. Elderly patients have largely been excluded from practice-changing studies in

Table 3
Targeted therapies in lung cancer

Mutation	Prevalence (%)	Treatment Options	Common Side Effects
EGFR (exon 21 and L858R)	15	Erlotinib, gefitinib, afatinib	Diarrhea, acneiform rash, ocular toxicity, pulmonary toxicity (dyspnea, ILD)
ALK	5	Crizotinib, ceritinib	Myelosuppression, QTc prolongation, bradycardia, hepatotoxicity, pulmonary toxicity (ILD)
ROS1	1–2	Crizotinib	Myelosuppression, QTc prolongation, bradycardia, hepatotoxicity, pulmonary toxicity (ILD)

Abbreviations: ALK, anaplastic lymphoma kinase; ILD, interstitial lung disease; ROS1, proto-oncogene tyrosine-protein kinase reactive oxygen species.

advanced NSCLC. Among the 100 most cited trials between 1980 and 2010, 33% specifically excluded elderly patients in their trial design (age exclusion ranged from >65 to >75 years of age). The average patient median age reported in these trials was 60.9 years. The average age for trials that did not exclude elderly patients was not significantly different at 61.0 (P = .97). The average median age of patients was 61 years (95% CI, 60.4–61.6) in all trials. There have been several clinical trials and subset analyses that have been reported over the past decade to address this issue. The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) randomized 161 patients greater than or equal to 70 years of age with stage IIIB or IV NSCLC (PS, 0–2) to single-agent vinorelbine or best supportive care. Vinorelbine-treated patients scored better than control patients on QoL functioning scales, and they reported fewer lung cancer–related symptoms but reported worse toxicity-related symptoms. There was a statistically significant (2-sided P = .03) survival advantage for patients receiving vinorelbine; median survival increased from 21 to 28 weeks in the vinorelbine-treated group. The relative hazard of death for vinorelbine-treated patients was 0.65 (95% CI, 0.45–0.93).[33] This study established the role of palliative single-agent chemotherapy in advanced NSCLC. The follow-up study, the MILES (Multicenter Italian Lung Cancer in the Elderly Study) trial, assessed the superiority of a nonplatinum chemotherapy combination compared with single agents in a 3-arm phase III design in patients aged 70 years or older.[34] A total of 698 patients were randomized to vinorelbine, gemcitabine, or a combination of gemcitabine and vinorelbine administered up to a maximum of 6 cycles. There was no statistically significant difference between the 3 arms in terms of median OS (36 weeks for vinorelbine, P = .93; 28 weeks for gemcitabine, P = .65) compared with the combination median OS of 30 weeks but with higher toxicity in the combination arm. The Southern Italy Cooperative Oncology Group (SICOG) similarly randomized 120 patients (>70 years old) to vinorelbine or a combination of gemcitabine and vinorelbine on days 1 and 8 every 3 weeks for a maximum of 6 cycles. Median survival was better with the combination (29 vs 18 weeks; P<.01), with higher QoL scores for the combination arm, albeit with 3 toxic deaths in the combination arm compared with 1 in the vinorelbine arm.[35] The West Japan Thoracic Oncology Group Trial (WJTOG 9904) was a phase III trial that compared 2 single agents. Patients aged more than 70 years (n = 182) with stage IIIB/IV NSCLC were randomized to docetaxel (60 mg/m^2 every 21 days) or vinorelbine (25 mg/m^2 on days 1 and 8 of a 21-day cycle).[36] Response rates were significantly higher for docetaxel (22.7% vs 9.9%). Median survival was 14.3 months for docetaxel and 9.9 months for vinorelbine (P = .138). Grade 3 or 4 neutropenia was higher in the docetaxel arm, but there was no difference in grade 3 or febrile neutropenia or infection. Docetaxel was associated with an improved symptom score compared with vinorelbine. In addition, in a recent randomized phase III study, 451 patients (aged 70–89 years; PS, 0–2) with advanced NSCLC were randomized to single-agent gemcitabine (1150 mg/m^2 days 1 and 8 every 21 days), single-agent vinorelbine (25 mg/m^2 days 1 and 8 every 21 days), or carboplatin (area under the curve, 6) plus paclitaxel (90 mg/m^2) on days 1, 8, and 15 every 28 days.[37] Five cycles of single-agent or 4 cycles of combination therapy were allowed. Median survival was better with the combination (10.4 vs 6.2 months; P = .0001). Although there were more hematologic toxicities in the combination arm (54.1% vs 17.9%), there was no difference in early deaths.

Use of Targeted Therapy

Bevacizumab is a monoclonal antibody to the vascular endothelial growth factor that has been shown to improve OS when combined with paclitaxel and carboplatin in

patients with advanced (nonsquamous) NSCLC compared with the same chemotherapy alone. The median survival was 12.3 months in the group assigned to chemotherapy plus bevacizumab, compared with 10.3 months in the chemotherapy-alone group (HR for death, 0.79; $P = .003$). In a post hoc subset analysis of patients greater than or equal to 70 years old (n = 224; 26%), there was a trend toward higher response rate (29% vs 17%; $P = .067$) and progression-free survival (5.9 vs 4.9 months; $P = .063$) with bevacizumab compared with chemotherapy alone, although OS (11.3 months and 12.1 months, respectively; $P = .4$) was similar. However, grade 3 or worse adverse events, which included a greater number of deaths, were noted in 87% of elderly patients treated with bevacizumab versus 61% who were not ($P>.001$).[38] Other retrospective analyses limited to the elderly have also found no improvement in OS with the addition of bevacizumab to chemotherapy.[39–41]

Erlotinib is a tyrosine kinase inhibitor against the EGFR receptor pathway that has shown efficacy in patients with EGFR mutations. The elderly seem to gain as much benefit from this agent in terms of response and survival as younger patients but are most likely to have adverse events, especially rash, diarrhea, and dehydration, which can lead to earlier discontinuation of this agent.[42] Other common tumor-associated complications seen in patients with advanced lung cancer and their management are listed in **Table 4**.

Table 4
Commonly encountered complications in patients with advanced lung cancer

Complications of Lung Cancer	Incidence (%)	Symptoms/Signs	Management Outline
Brain metastasis	45–65 (over the course of patients with advanced lung cancer)	• Altered mental status • Seizures • Weakness and/or numbness	• Steroids • Radiation therapy and/or surgery • Can consider chemotherapy for asymptomatic brain metastasis with extensive systemic disease
Malignant pleural effusion	10–15	• Dyspnea • Cough • Chest pain	• Therapeutic thoracentesis • For patients with rapid accumulation: indwelling pleural catheter • Chemical pleurodesis alone or with an indwelling catheter
Superior vena cava syndrome	2–4 (more common in SCLC) Often related to central venous access devices	• Dyspnea • Facial/arm swelling • Distension of the veins in the neck and on the chest wall • Facial plethora	SCLC: chemotherapy NSCLC: • Radiation • Use of endovascular stents • Removal of central venous access devices if present, followed by anticoagulation

Abbreviation: SCLC, small cell lung cancer.

Risk Stratification Using Geriatric Assessment

Geriatric assessment (GA) has been used to a limited extent in NSCLC. Maione and colleagues[43] reported on the prognostic value for OS of baseline assessment of functional status, comorbidity, and QoL in 566 elderly patients with advanced NSCLC enrolled in the phase III randomized Multicenter Italian Lung Cancer in the Elderly Study (MILES). Functional status was measured as activities of daily living (ADL) and instrumental ADL (IADL). Comorbidity was summarized using the Charlson scale. Better values of baseline QoL ($P = .0003$) and IADL ($P = .04$) were significantly associated with better prognosis, whereas ADL ($P = .44$) and Charlson score ($P = .66$) had no prognostic value in this study. In the recent French study that evaluated the prognostic value of ADL, Mini–Mental State Examination, and Charlson Comorbidity Index, the investigators reported that a normal activities of daily living score was a significant independent favorable prognostic factor, whereas the Mini–Mental State Examination and Charlson Index were not prognostically useful.[37] In a novel Dutch study, 181 patients greater than or equal to 70 years old, PS of 0 to 2 with stage III to IV NSCLC were treated with 2 different carboplatin-based doublets.[44] The primary end point was change in global QoL from baseline compared with week 18. A pretreatment comprehensive GA and mini-GA during and after treatment were undertaken. A principal component (PC) analysis was performed to determine the underlying dimensions of CGA and QoL and was subsequently related to survival. There were no changes in QoL after treatment. CGA items were associated with neuropsychiatric toxicity. The PC analysis derived from CGA and QoL items had only 1 dominant underlying dimension, which had significant prognostic value. Physical and role functioning, frailty, and depression were the most prominent elements of this underlying structure. More recently the Cancer and Aging Research Group (CARG) incorporated CGA with patient-related and tumor-related factors to develop a composite score that is predictive of chemotherapy-associated toxicity in the elderly across tumor types and stages (**Fig. 2**).[45,46] In a study from China, 120 patients with lung cancer who were greater than or equal to 65 years of age were classified based on their CARG scores. Toxicity varied significantly among the risk groups ($P<.001$), but the incidence of toxicity did not vary significantly among the Karnofsky Performance Status (KPS)–based risk groups ($P = .322$), suggesting a better utility of this toxicity tool in predicting the risks

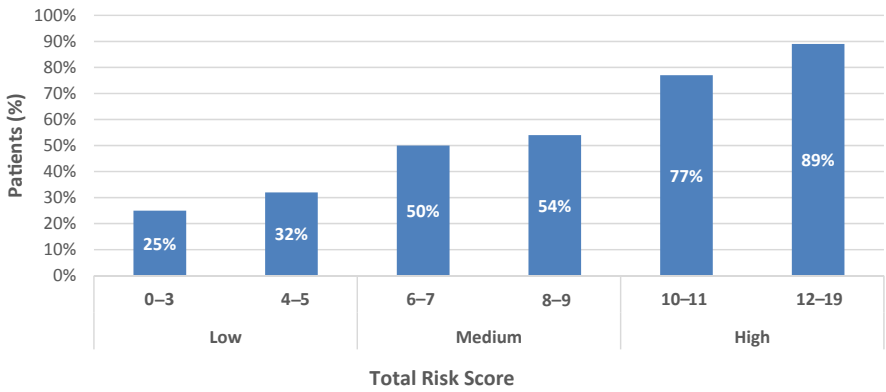

Fig. 2. Ability of CARG risk score to predict grade 3 to 5 chemotherapy toxicity. (*Adapted from* Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3463.)

of chemotherapy toxicity compared with KPS for older patients with lung cancer.[47] Because the elderly are particularly vulnerable to toxicity, it is vital to have the ability to assess the risk for toxicity before initiating therapy. The CARG retrospectively studied the factors associated with early discontinuation of chemotherapy (defined as chemotherapy duration of $\leq$6 weeks) in patients greater than or equal to 65 years old with stage IV NSCLC (n = 100). On multivariate analysis, factors independently associated with early discontinuation included second or higher line of chemotherapy (OR, 5.93; 95% CI, 2.25–15.61) and lower Medical Outcomes Study physical score of less than 70 (OR, 4.19; 95% CI, 1.56–11.29), the latter being a measure of physical function.[48] A potential paradigm for decision making in the clinic is presented in **Fig. 3**.

Patients' Preferences and Understanding of Goals of Therapy

Older patients may have goals or expectations that are different from those of younger patients, and this may be particularly true in the setting of a lethal disease such as lung cancer. In a novel study conducted in patients with advanced lung cancer after at least 1 cycle of chemotherapy, the median survival threshold for accepting chemotherapy was 4.5 months for mild toxicity and 9 months for severe toxicity. When given the choice between supportive care and chemotherapy, only 22% of patients chose chemotherapy for a survival benefit of 3 months; 68% of patients chose chemotherapy if it substantially reduced symptoms without prolonging life. Older patients tended to demand greater benefit before accepting chemotherapy and were more likely to accept supportive care instead of chemotherapy than younger patients.[49] A national, prospective, observational cohort study that included 1193 patients with newly diagnosed advanced lung or colorectal cancers treated with palliative intent chemotherapy sought to characterize the prevalence of the expectation that chemotherapy might be curative in these patients.[50] Of the 710 patients with lung cancer, 69% gave answers that were not consistent with understanding that chemotherapy was very unlikely to cure their cancer. In multivariable logistic regression, factors that were associated with a greater likelihood of this apparent misunderstanding were nonwhite race or

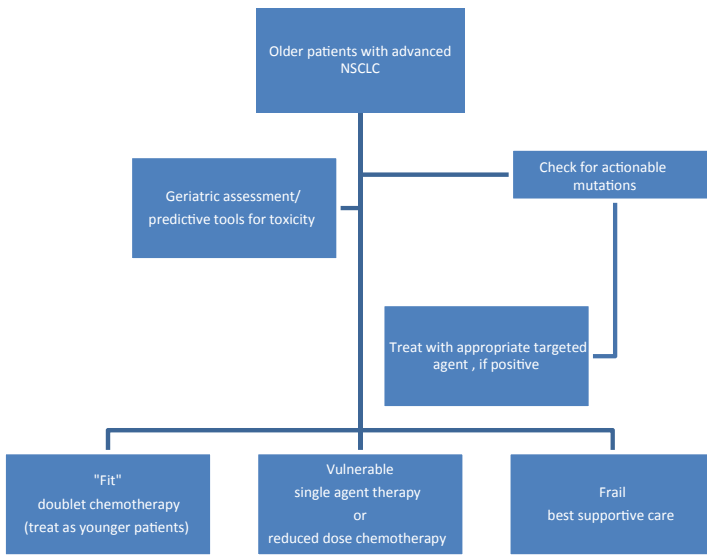

Fig. 3. Future paradigm for decision making in older adults with advanced NSCLC.

ethnic group compared with white race (OR for Hispanic patients, 2.82; 95% CI, 1.51–5.27; OR for black patients, 2.93; 95% CI, 1.80–4.78). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. There was a strong trend of worse understanding with age (OR 1.68 for patients in the age group 70–79 years; 95% CI, 1.10–2.59). Thus, goals of chemotherapy need to be conveyed clearly to patients and there is a high prevalence of misconceptions about the role of chemotherapy, with minority ethnic groups and older patients being at the greatest risk for such misunderstanding.

The Role of Palliative Care

A recent prospective randomized controlled study evaluated the effect of early palliative care after the diagnosis of metastatic NSCLC on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease. Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments.[51] Patients assigned to early palliative care had a better QoL than the patients assigned to standard care (mean score on the FACT-L (Functional Assessment of Cancer Therapy- Lung) scale [in which scores range from 0 to 136, with higher scores indicating better QoL], 98.0 vs 91.5; $P = .03$). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs 38%; $P = .01$). Despite there being fewer patients in the early palliative care group than in the standard care group receiving aggressive end-of-life care (33% vs 54%; $P = .05$), median survival was longer among patients receiving early palliative care (11.6 months vs 8.9 months; $P = .02$).

SUMMARY

Lung cancer is a disease of the elderly. Older patients with good functional status and PS can be treated similarly to younger patients, although data for octogenarians are scant. Integration of GA can help with better risk stratification of patients and improve clinical decision making in these patients.

REFERENCES

1. Siegel R, Jamal A. Cancer facts and figures 2015. Available at: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf. Accessed July 11, 2015.
2. World Health Organization. Available at: http://www.who.int/healthinfo/survey/ageingdefnolder/en/. Accessed July 11, 2015.
3. American Cancer Society. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics. Accessed July 11, 2015.
4. Mery C, Pappas A, Bueno R, et al. Similar long term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the Surveillance, Epidemiology, and End Results database. Chest 2005;128:237–45.
5. Shrivani S, Jiang J, Chang J, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060–70.
6. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–60.

7. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719–27.
8. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.
9. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004;26:173–82.
10. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. J Natl Cancer Inst 2003;95:1453–61.
11. Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043–51.
12. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552–9.
13. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010; 375:1267–77.
14. Wisnivesky J, Smith C, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study. BMJ 2011;343:d4013.
15. Cuffe S, Booth CM, Peng Y, et al. Adjuvant chemotherapy for non-small-cell lung cancer in the elderly: a population-based study in Ontario, Canada. J Clin Oncol 2012;30:1813–21.
16. Ganti AK, Williams CD, Gajra A, et al. Effect of age on the efficacy of adjuvant chemotherapy for resected non-small cell lung cancer. Cancer 2015. http://dx.doi.org/10.1002/cncr.29360.
17. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA(N2) and IIIB non–small cell lung cancer: Mature results of Southwest Oncology Group Phase II Study 8805. J Clin Oncol 1995;13:1880–92.
18. Albain KS, Crowley JJ, Turrisi AT 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol 2002;20(16): 3454–60.
19. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374(9687):379–86.
20. Jalal SI, Riggs HD, Melnyk A, et al. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. Ann Oncol 2012 Jul;23(7):1730–8.
21. Vokes EE, Herndon JE 2nd, Kelley MJ, et al, Cancer and Leukemia Group B. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-

small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007;25(13): 1698–704.
22. Stinchcombe TE, Hodgson L, Herndon JE 2nd, et al, Cancer and Leukemia Group B. Treatment outcomes of different prognostic groups of patients on cancer and leukemia group B trial 39801: induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for unresectable stage III non-small cell lung cancer. J Thorac Oncol 2009;4(9):1117–25.
23. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 2005; 23(25):5883–91 [Erratum appears in J Clin Oncol 2006;24(12):1966].
24. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16(2):187–99.
25. Atagi S, Kawahara M, Yokoyama A, et al. Japan Clinical Oncology Group Lung Cancer Study Group. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol 2012;13(7):671–8.
26. Schild SE, Mandrekar SJ, Jatoi A, et al. The value of combined-modality therapy in elderly patients with stage III nonsmall cell lung cancer. Cancer 2007;110: 363–8.
27. Rocha Lima CM, Herndon JE II, Kosty M, et al. Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. Cancer 2002;94:181–7.
28. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90.
29. Sigel K, Lurslurchachai L, Bonomi M, et al. Effectiveness of radiation therapy alone for elderly patients with unresected stage III non-small cell lung cancer. Lung Cancer 2013;82:266–70.
30. Davidoff AJ, Gardner JF, Seal B, et al. Population-based estimates of survival benefit associated with combined modality therapy in elderly patients with locally advanced non-small cell lung cancer. J Thorac Oncol 2011;6:934–41.
31. Aridgides PD, Janik A, Bogart JA, et al. Radiotherapy for stage III non-small-cell lung carcinoma in the elderly (age $\geq$ 70 years). Clin Lung Cancer 2013;14:674–9.
32. Pirapati H, Karlin NJ, Schild SE, et al. Multimodality therapy improves survival in elderly patients with locally advanced non-small cell lung cancer–A retrospective analysis. J Geriatr Oncol 2012;3:104–10.
33. 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.
34. Gridelli 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.
35. 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.

36. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006; 24:3657–63.
37. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011; 378:1079–88.
38. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab in non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
39. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 2008;26:60–5.
40. Leighl NB, Zatlouka P, Mezger J, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). J Thorac Oncol 2010; 5:1970–6.
41. Laskin J, Crino L, Felip E, et al. Safety and efficacy of first-line bevacizumab in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer: safety of Avastin in lung trial (MO19390). J Thorac Oncol 2012;7:203–11.
42. Wheatley-Price P, Ding K, Seymour L, et al. Erlotinib for advanced non-small cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008;26:2350–7.
43. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian Lung Cancer in the Elderly study. J Clin Oncol 2005;23: 6865–72.
44. Biesma B, Wymenga AN, Vincent A, et al. Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. Ann Oncol 2011;22:1520–7.
45. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. J Clin Oncol 2011;29: 1290–6.
46. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29: 3457–65.
47. Nie X, Liu D, Li Q, et al. Predicting chemotherapy toxicity in older adults with lung cancer. J Geriatr Oncol 2013;4:334–9.
48. Gajra A, Tew WP, Hardt M, et al. Predictors of early discontinuation of chemotherapy (EDC) in patients (pts) age 65 or older with stage IV non-small cell lung cancer (NSCLC). J Clin Oncol 2012;30(Suppl) [abstract: e18133].
49. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ 1998;317:771–5.
50. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med 2012;367:1616–25.
51. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–42.