Treatment of the Elderly When Cure is the Goal

The Influence of Age on Treatment Selection and Efficacy for Stage III Non-small Cell Lung Cancer

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Background: Treatment of elderly patients with stage III NSCLC is controversial. Limited data exist, as the elderly are underrepresented in clinical trials.

Methods: After ethics approval, we performed a retrospective review of 1372 stage III NSCLC patients treated at our institution during the period 1997–2007. Patients with malignant effusions and microscopic N2 discovered only postoperatively were excluded, leaving 740 who were classified by treatment plan: palliative (palliative chemotherapy or radiation [≤40 Gy]); nonsurgical multimodality (>40 Gy radiation ± chemotherapy); or surgical multimodality (chemotherapy, radiation, and surgery). Demographics, treatment, toxicity, and survival were analyzed by age, 0 to 65 years, $n = 384$; 66 to 75 years, $n = 256$; 76+ years, $n = 100$, and compared using log-rank, univariate, and multivariate statistical tests.

Results: Patients older than 65 years were more likely to have poor performance status ($p < 0.0001$), multiple comorbidities ($p < 0.0001$), and to receive palliative therapy only ($p < 0.0001$). Older and younger patients treated with curative intent with nonsurgical bimodality therapy or trimodality therapy including surgery had similar rates of grade 3/4 toxicity (0–65 years, 39%; 66–75 years, 43%; 76+ years, 5%; $p = 0.18$) and toxic death (0–65 years, 4%; 66–75 years, 4%; 76+ years, 0%; $p = 0.76$). Survival was worse with increasing age ($p < 0.0001$), likely due to greater use of palliative treatment in the elderly. When survival was analyzed for patients treated with curative intent, there was no difference between age groups for nonsurgical ($p = 0.32$) or surgical ($p = 0.53$) therapy.

Conclusion: In select fit elderly patients, combined modality therapy is tolerable and is associated with survival similar to that of younger patients.

Key Words: Locally advanced, Non-small cell lung cancer, Elderly, Combined modality treatment, Trimodality, Stage III NSCLC.

(*J Thorac Oncol.* 2011;6: 537–544)

Non-small cell lung cancer (NSCLC), the leading cause of cancer-related death in the industrialized world,[1] is primarily a disease of older people with a median age of approximately 70 years at diagnosis.[2,3] In the United States, an estimated 109,720 individuals older than 70 years were diagnosed with lung cancer in 2009.

Cancer clinical practice is guided by the results of clinical trials, yet the elderly often are underrepresented or excluded from these studies.[4] This means that oncologists must extrapolate evidence from trials of younger patients and apply the results to what may be a very different patient group biologically. Alternatively, they may rely on post hoc unplanned subset analyses of older patients from larger trials,[5,6] which also may not be representative of the entire elderly population.

Locally advanced, stage III lung cancer may be treated with curative intent with radical radiation alone, chemoradiation, or chemoradiation and surgery. Several randomized trials comparing radiation alone to sequential and/or concurrent chemoradiotherapy have demonstrated the superiority of combined modality therapy.[7] Sequential chemotherapy and radiotherapy has been compared with concurrent chemoradiotherapy, with concurrent therapy demonstrating superior survival.[8] However, combined modality treatment may be significantly more toxic than radiation alone and may be less tolerable in elderly patients. Regarding specific analyses of elderly patients receiving combined modality therapy for locally advanced NSCLC, the evidence is inconsistent. Some studies have shown greater toxicity and less benefit[9,10] in elderly subgroup analyses. However, more modern studies have confirmed the feasibility and efficacy of combined modality treatment, although more than one study has

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/11/0603-0537

demonstrated that this is at the cost of increased toxicity in the elderly.[11]

Within the bounds of tolerability, bimodality therapy with concurrent or sequential chemoradiation is widely accepted as a standard of care for locally advanced NSCLC. More controversial is the role of surgery in stage IIIA. A large European randomized trial was negative,[12] showing no survival benefit for surgery compared with radiation after induction chemotherapy. In contrast, a North American trial reported a potential benefit for surgery in patients who required only lobectomy,[13] although no overall survival benefit for the addition of surgery to chemoradiation in the overall study group.

No consensus definition of elderly exists.[14] Some investigators use age 65 years as a cut off, but the majority of Western analyses specify 70 years, as it has been described as the lower limit of senescence, being the age at which the incidence of comorbidity increases sharply.[15]

Given the paucity of data to guide treatment of elderly patients with locally advanced NSCLC, and the complex and potentially toxic nature of such treatment, we performed this retrospective analysis of 11 years of patient experience at the University Health Network (UHN), including the Princess Margaret Hospital, to examine the following question: in locally advanced NSCLC, how should the elderly be treated when cure is the goal?

PATIENTS AND METHODS

After Research Ethics Board approval, 1372 patients were identified as presenting to the UHN with a diagnosis of stage III NSCLC during the period 1997–2007 (Supplemental Figure 1, http://links.lww.com/JTO/A58). All patients included in the analysis received some of their treatment at UHN. The electronic and when necessary paper records of these patients were examined by four medical practitioners (L.E.C., A.S., K.B., and A.J.H.). Patients staged as IIIB NSCLC on the basis of a malignant effusion (pleural or pericardial) and those with stage III based on a postoperative pathological diagnosis of microscopic N2 involvement were excluded. This was to ensure that only clinical stage III patients at point of initial treatment planning were included in the analysis.

Data were abstracted into predesigned electronic data collection forms (Access, Microsoft, CA). Demographics, including performance status (PS) and comorbidity (classified according to Charlson comorbidity index [CCI], modified according to Asmis et al.[16]), treatment intent, treatment delivery, and clinical outcomes, including toxicity and survival, were collected.

Patients were classified as being planned for palliative therapy (radiation with a radiation dose $\leq$40 Gy or chemotherapy or both), radical radiation alone ($>$40 Gy), or nonsurgical multimodality therapy (platinum-based chemotherapy and radiation $>$40 Gy), which was further subdivided into concurrent or sequential and surgical multimodality therapy, which consisted of concurrent platinum-based chemoradiation as induction therapy with a dose 45 Gy, followed by surgical resection. Most patients receiving bimodality or trimodality therapy were treated in the manner of the Intergroup 0139 trial[13] (Supplemental Table 1) with concurrent etoposide/cisplatin and thoracic radiation followed by two further cycles of platinum-based chemotherapy alone after radiation and/or surgery.

Treatment delivery was recorded in terms of radiation dose, chemotherapy cycles planned and received, and surgical procedure performed. Toxicity was recorded according to the Common Terminology Criteria for Adverse Events v3.0 as well as surgical complications. Relapse and site of relapse were recorded. Progression-free survival and overall survival were measured from time of diagnosis.

Statistics

All analyses were generated using SAS software, Version 9.2 TS Level 2MO of the SAS System for Windows, copyright 2002–2008 (SAS Institute Inc., Cary, NC). Cases with missing values were excluded.

Variable summaries were generated using proc freq and proc means. Associations between age groups (0–65, 66–75, and 76+ years), patient demographics, and treatment-related variables were tested using the trend test for binary variables, the row mean score test for nominal variables with more than two levels, and the correlation test for ordinal variables. Fisher exact test and its extension, the Freeman-Halton test, were used to test for associations between nominal variables. The stratified Mantel-Haenszel mean score test was implemented to control for CCI category when testing for association between age group and treatment plan. Spearman's correlation was used to test for associations between continuous variables.

Univariate associations between age and survival were analyzed using the log-rank test, Kaplan-Meier plots, and Cox models. Cox models were implemented to perform multivariate analyses with age effects adjusted for Eastern Cooperative Oncology Group PS (PS 1 versus $\geq$2), smoking (never versus ever), sex, CCI (adapted for lung cancer according to Asmis et al.[16]; 0 versus 1–2 versus $\geq$3), weight loss ($<$5% versus $\geq$5%), and histologic type (adenocarcinoma versus other). Two versions of each model were implemented, one with age in its categorical form and one with age in its continuous form. Linearity and proportional hazards assumptions were tested with quadratic terms and time-varying covariates, respectively.

RESULTS

Demographics and Treatment Selection

Of 1372 charts examined, 740 patients met the inclusion criteria (Table 1, Supplemental Figure 1). Age-specific analyses were based on three age groups: 0 to 65 years, n = 384; 66 to 75 years, n = 256; 76+ years, n = 100. There was an association between increasing CCI and increasing age ($p < 0.0001$), and older patients were significantly more likely to have worse PS ($p < 0.0001$).

Fifteen patients, all older than 65 years, were offered no anticancer therapy whatsoever (66–75 years, 2.7%; 76+ years, 8%; $p < 0.0001$) (Table 2, Supplemental Table 2). Older patients also were more likely to be planned for palliative treatment only ($p < 0.0001$), most frequently palliative-dose radiation rather than chemotherapy. In addition to age, PS, CCI, and weight loss all were important determi-