Treatment of Stage I-III Non-Small-Cell Lung Cancer in the Elderly

Elderly patients with stage I-III non-small-cell lung cancer (NSCLC) constitute a peculiar patient population and need specific therapeutic approaches. Limited resections are an attractive alternative for elderly patients with resectable NSCLC because of the potential reduction in postoperative complications. Curative radiation therapy is an acceptable alternative for elderly patients who are unfit for or refuse surgery. Hypofractionated stereotactic body radiation therapy is of particular interest for this population because of its favorable tolerance.

More than two-thirds of the patients who die of lung cancer in the United States are over 65 years old.[1] Specific approaches to the treatment of elderly patients with non-small-cell lung cancer (NSCLC) are needed. In fact, many elderly patients tolerate all treatment modalities poorly because of comorbidity and organ failure. The prevalence of these comorbid conditions is about twice as high as in the general population.[2] The most important coexisting pathologies in lung cancer patients are cardiovascular and pulmonary diseases, which are common among heavy cigarettes smokers. Moreover, among elderly persons it is common to find a condition known as "frailty," in which most functional reserve is exhausted. Decreased hepatic, renal, and bone marrow functions have a negative impact on the degree of toxicity—in particular, on cisplatin toxicity. In order to plan the treatment of elderly NSCLC patients, a multidimensional geriatric evaluation, including not only assessment of comorbidities but also of functional, mental, and nutritional status, is needed.

Surgery
The dilemma that elderly patients with lung cancer and their physicians face is that of balancing the increased risk of surgery with conventional open thoracotomy techniques and improved long-term survival when surgery is successful. Twenty-five years ago, several authors[3] concluded that age beyond 70 years was a prohibitory factor for thoracotomy. Although small series have since suggested that carefully selected elderly patients can safely undergo thoracotomy,[4] it is still common practice to provide fewer surgical options to the elderly patient with lung cancer. Nugent et al.[5] came to this conclusion after reporting data from a series of 1,802 patients collected in the United States from 1983 to 1993. Although the incidence of stage I-II cancer was five times higher in the elderly group (6% among younger patients and 33% among older patients), the resection rate was 32% for the younger group and only 6% for the elderly. Similarly, in Europe, Damhuis and Schutte[6] found a 26% resection rate for patients who had lung cancer and were younger than 70 years, compared with a 14% rate for those who were older than 70 years. Both groups in this report had comparable operative mortality (3.2% vs 4.0%), probably indicating careful preoperative selection of elderly patients.
Some authors[7] believe that many elderly patients who have lung cancer and undergo standard anatomic pulmonary resections (lobectomy or pneumonectomy) with posterolateral thoracotomy have a higher incidence of postoperative mortality than younger individuals. The Lung Cancer Study Group (LCSG) quantified this observation in a multi-institutional study conducted in the late 1970s and early 1980s. Patients who were aged 70 years or older had a 30-day postoperative mortality of 7.1% compared with 1.3% for patients who were younger than 60 years and 4.1% for those between ages 60 and 69 years.[8] In 14 reports from Italy, the United Kingdom, the United States, and Finland published after the LCSG data, the operative mortality after lung resection with an open thoracotomy technique has ranged from 1% to 22%, with an average of 5.9%.[8] These data compare poorly with video-assisted thoracic surgery (VATS) techniques for removal of stage I lung cancer in elderly patients. In six recent reports of 378 patients from Canada, the United States, Japan, and Hong Kong, the average operative mortality was 1.1%.[9]

Limited Resections
The operative risk of death after thoracotomy in elderly patients is due to two major anatomic
Treatment of Stage I-II Non-Small-Cell Lung Cancer in the Elderly

Lonardi et al treated 48 elderly (≥ 75 years) patients with stage IIIA or IIIB, inoperable, symptomatic advanced disease, the 1-year survival rate approached 44%.[21] In a study by Gava et al, for 38 patients aged at least 70 years with locally unresectable NSCLC in elderly patients, and globally, such treatment was well tolerated by this older population. In a study by Gava et al, for 38 patients aged at least 70 years with locally advanced disease, the 1-year survival rate approached 44%.[21]

Several retrospective studies have been reported on radiotherapy as curative treatment of unresectable NSCLC in elderly patients, and globally, such treatment was well tolerated by this older population. Zachariah et al reported on radiotherapy in lung cancer in patients ≥ 80 years old.[14] Of 36 patients, 21 were treated with conventional radiotherapy doses ranging from 59.40 to 66 Gy. Response to radiotherapy was observed in 9 patients (43%). The treatment was well tolerated by this very old population. In a study by Gava et al, for 38 patients aged at least 70 years with locally advanced disease, the 1-year survival rate approached 44%.[21]

Lonardi et al treated 48 elderly (≥ 75 years) patients with stage IIIA or IIIB, inoperable, symptomatic NSCLC using 1.8 to 2.5 Gy per fraction to a median dose of 50 Gy. These investigators observed a 2-year survival rate of 10% and a median survival of 5 months.[22] Of 47 assessable patients, 21 had a partial remission, 17 stable disease, and 9 had progressive disease. Despite the short overall median survival, dose-related survival was much better in patients given at least 50 Gy than in those with lesser doses. This finding has shown 5-year survival rates of 5% to 30%.[16,17] Although some patients are not offered therapy because of comorbid disease or advanced age, in a review by McGarry et al,[18] cancer was the cause of death for 53% of inoperable patients who received no specific cancer therapy at time of diagnosis for stage I NSCLC. Poor performance status and comorbid conditions that preclude surgery at least partially account for the poor survival of patients with early-stage lung cancer treated with radiotherapy. Complication rates of definitive radiation therapy are low, despite poor pulmonary function and performance status.[17]

Pergolizzi et al performed a prospective study on curative radiotherapy alone in 40 elderly patients with stage IIIA disease.[19] Radiotherapy was directed toward gross tumor burden with a median of 60 Gy (conventionally fractionated). No treatment-related mortality was observed, and no clinically significant acute morbidity was scored. The median survival was 19 months and the 5-year survival rate was 12%.

Patients who are unfit for surgery or refuse surgery are typically treated with radiation therapy, which has shown 5-year survival rates of 5% to 30%.[16,17] Although some patients are not offered therapy because of comorbid disease or advanced age, in a review by McGarry et al,[18] cancer was the cause of death for 53% of inoperable patients who received no specific cancer therapy at time of diagnosis for stage I NSCLC. Poor performance status and comorbid conditions that preclude surgery at least partially account for the poor survival of patients with early-stage lung cancer treated with radiotherapy. Complication rates of definitive radiation therapy are low, despite poor pulmonary function and performance status.[17]

Results database, these investigators showed that for patients who are 74 years or younger, the survival curves of the two groups were nearly identical for the first 3 years after surgery. On the basis of these data, some authors have shown an institutional bias toward wedge resection for elderly patients with early-stage lung cancer.[7,11] Limited resections are an attractive alternative for elderly patients with lung cancer because of the potential reduction in postoperative complications, the rapid recovery, and the increased prevalence of early-stage disease in this group.[15] Because long-term survival is the same after lobectomy or limited resection for the first several postoperative years, the elderly, with a lower remaining life expectancy than younger patients, may benefit the most from this strategy. Some authors[7] believe that there is an age above which lobectomy is no longer the gold standard.

Mery et al confirmed the hypothesis that at some threshold of age, lobectomy no longer provides a population survival advantage.[15] In fact, analyzing the Surveillance, Epidemiology, and End Results database, these investigators showed that for patients who are 74 years or younger, the survival curves between lobectomy and limited resection diverge after 25 months. Overall median survival after lobectomy was 66 months, compared with 50 months after limited resection (P < .0001). Kaplan-Meier curves for long-term survival after limited resection and lobectomy among patients who were 75 years or older, however, never deviated from each other.

Radiotherapy
Patients who are unfit for surgery or refuse surgery are typically treated with radiation therapy, which has shown 5-year survival rates of 5% to 30%.[16,17] Although some patients are not offered therapy because of comorbid disease or advanced age, in a review by McGarry et al,[18] cancer was the cause of death for 53% of inoperable patients who received no specific cancer therapy at time of diagnosis for stage I NSCLC. Poor performance status and comorbid conditions that preclude surgery at least partially account for the poor survival of patients with early-stage lung cancer treated with radiotherapy. Complication rates of definitive radiation therapy are low, despite poor pulmonary function and performance status.[17]
treated with lower doses: 52% vs 35% at 6 months, and 28% vs 4% at 13 months. Most symptoms were successfully palliated. Toxicity was negligible, mainly consisting of World Health Organization (WHO) grade 1/2 esophagitis.

Tombolini et al used radiotherapy alone in 41 patients ≥ 70 years with medically inoperable IIIA and IIIB NSCLC. These patients received a conventionally fractionated radiotherapy dose of 50 to 60 Gy plus a 10-Gy boost to the gross tumor volume.[23] Two-year survival and disease-free survival rates were 27% and 14.6%, respectively.

Thus, although at least two studies have found advanced age to be a negative prognostic factor for stage I disease,[17,24] the toxicity of radiation therapy alone for inoperable lung cancer in elderly patients is not greater than toxicity in younger patients.[25,26] It is interesting to note that Gauden and Tripcony[26] showed a general trend for elderly patients (≥ 70 years vs < 70 years) to have better 5-year survival (34% vs 22%), median survival (26 vs 22 months), and recurrence-free survival (30% vs 18%). The cohort of patients aged 80 years or older had the smallest proportion of medical disease precluding surgery (53%) and the largest proportion with good performance status (80%). Good performance status and fewer comorbid conditions may explain the trend for a favorable outcome in the older patient subgroup.

Novel Approaches

Severe esophagitis and radiation-induced lung injury are the primary acute and subacute side effects of most concern in elderly patients with NSCLC treated with radiation. These side effects can be life-threatening. Therefore, newer treatments that will improve the therapeutic ratio (tumor control/toxicity) are needed.

This may include employing novel radiotherapy techniques.[27] Older patients with reduced pulmonary capacity can have a difficult time tolerating the traditional, large treatment fields. Newer techniques, including three-dimensional conformal radiotherapy (3D-CRT) and stereotactic body radiation therapy, allow for greater precision and radiotherapy delivery. Regarding the latter, the Radiation Therapy Oncology Group (RTOG) has initiated a study (RTOG 0236) incorporating stereotactic body radiation therapy for patients with medically inoperable early-stage disease (stage I/II). This study, which utilizes elements of 3D-CRT in addition to stereotactic targeting, incorporates a variety of systems for decreasing the effects of lung and other organ motion.

Timmerman et al recently reported the results of a phase I dose-escalation protocol for the treatment of medically inoperable patients with stage I lung cancer at Indiana University.[28] The starting dose was 8 GY X 3 (24 Gy total), with escalations of 2 Gy per fraction for each cohort. Perhaps delivering radiotherapy this way would provide a favorable option for elderly patients who, for reasons of reduced performance status or transportation difficulties, might have problems coming for a traditional 6-week course of treatment. Tolerance and control rates in this study were excellent.

These preliminary data are the basis for RTOG L-0236, which is evaluating treatment with 60 Gy in three fractions over 1.5 to 2 weeks. Hypofractionated stereotactic body radiation therapy of lung tumors is of particular interest for elderly or frail patients who may feel overwhelmed psychologically and financially by a prolonged course of daily radiation.

Chemotherapy

Lessons From Advanced Disease

The main clinical data on chemotherapy for elderly NSCLC patients come from cases of advanced disease. These data are useful for administering chemotherapy and designing clinical trials in patients with early-stage disease as well. A phase III multicenter trial in 191 patients (the Elderly Lung Cancer Vinorelbine Italian Study, or ELVIS) showed that single-agent vinorelbine improved quality of life and survival compared to supportive care alone (median survival: 27 vs 21 weeks, P = .04).[29] Therefore, in elderly patients with advanced NSCLC, palliative chemotherapy should be considered.

To improve these results obtained with single-agent chemotherapy, some non-platinum-based combinations have been developed. The most studied regimen is gemcitabine (Gemzar) plus vinorelbine. A large randomized phase III trial (the Multicenter Italian Lung Cancer in the Elderly Study, or MILES) including about 700 elderly patients showed that the combination of vinorelbine plus gemcitabine is not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC (Table 1).[30] Based on this background, and until results are available from prospective randomized trials of platinum-based chemotherapy, single-agent chemotherapy should be considered a reasonable treatment choice in unselected elderly patients with advanced NSCLC.
Overall, few prospective clinical experiences with cisplatin-based chemotherapy in elderly NSCLC patients have been reported. Cisplatin is particularly difficult to use in elderly patients because of renal and neurologic side effects and potential hydration-related problems. Nevertheless, the issue of cisplatin- and carboplatin-based therapy for elderly patients with advanced NSCLC has recently been addressed in some retrospective analyses of large randomized trials.[31-36] Treatment outcomes of patients younger and older than 70 years enrolled in these trials were compared. Globally, these analyses found no differences in survival between older and younger patients, with a small increase in toxicity in the elderly, suggesting that advanced age alone should not preclude platinum-based chemotherapy for NSCLC.

That said, the aforementioned analyses could suffer from selection bias. In fact, elderly patients enrolled in this sort of trial could be representative not of the whole elderly population, but rather, of a small subgroup thought by investigators to be eligible for aggressive treatments.[37]

Prospective clinical trials of platinum-based chemotherapy with inclusion criteria limited to the elderly population are needed. A topic of interest is the exploration of innovative schedules and attenuated doses of cisplatin that could be more suitable in elderly patients. Feliu et al reported good tolerability and activity with low-dose cisplatin (50 mg/m2) plus gemcitabine,[38] and Maestu et al, with low-dose carboplatin (area under the concentration-time curve [AUC] 5) plus gemcitabine.[39]

Chemotherapy of Stage I-III NSCLC

Adjuvant Chemotherapy Overview—A meta-analysis evaluating data available from 4,357 patients included in clinical trials comparing surgery alone to surgery plus chemotherapy showed a survival benefit of 5% at 5 years for adjuvant cisplatin-based chemotherapy.[40] These results have stimulated clinical research in this field.[41-45] The Adjuvant Lung Project of Italy (ALPI) randomly assigned 1,209 patients with stage I, II, or IIIA NSCLC to receive surgery alone or surgery plus adjuvant chemotherapy consisting of mitomycin, vindesine, and cisplatin. This trial failed to demonstrate a statistically significant survival benefit for adjuvant chemotherapy in completely resected NSCLC.[41] Similarly, the Big Lung Trial, with only 381 patients enrolled, failed to observe a survival benefit with adjuvant chemotherapy.[42]

The International Adjuvant Lung Cancer Trial (IALT) enrolled 1,867 stage I-IIIA NSCLC patients who were randomly assigned to receive surgery alone or surgery followed by cisplatin-based chemotherapy consisting of cisplatin plus etoposide (56%), cisplatin plus vinorelbine (27%), cisplatin plus vindesine (6%), or cisplatin plus vinblastine (11%). Patients assigned to chemotherapy had a significantly higher 5-year survival rate than those assigned to observation (44.5% vs 40.4%; hazard ratio for death [HR] = 0.86; P < .03).[43] The IALT trial was the first study to observe a survival
benefit for adjuvant cisplatin-containing chemotherapy. Very recently, two large randomized trials of adjuvant third-generation platinum-based chemotherapy have been reported, with positive results. The National Cancer Institute of Canada (NCIC) BR10 trial randomized 482 stage IB and II NSCLC patients to receive surgery alone or surgery followed by chemotherapy with cisplatin plus vinorelbine. Overall survival was significantly prolonged for cisplatin plus vinorelbine (94 vs 73 months; HR = 0.69; P = .011).[44] Similarly, a Cancer and Leukemia Group B (CALGB) trial in 344 stage IB NSCLC patients observed a statistically significant survival benefit for adjuvant chemotherapy with carboplatin plus paclitaxel (overall survival at 4 years = 71% vs 59% in chemotherapy and observation groups, respectively; HR = 0.62, P = .028).[45]

Some randomized trials and a meta-analysis of data from 2,000 patients have shown that adjuvant single-agent chemotherapy with uracil/tegafur (UFT) significantly improves the survival of completely resected early-stage NSCLC patients (in the meta-analysis, the 5-year survival rate was 81.8% vs 77.2% for UFT and observation, respectively; HR = 0.77; P = .011).[46,47] Moreover, a meta-analysis of data from 5,716 patients has confirmed the importance of cisplatin-based chemotherapy and single-agent UFT as adjuvant chemotherapy in the treatment of resected NSCLC (HR = 0.891, P = .012 for cisplatin-based chemotherapy; and HR = 0.799, P = .015 for single-agent UFT).[48] Taken globally, these data suggest that postoperative chemotherapy improves survival after surgery in patients with stage IB-IIIA NSCLC, and the awareness of the efficacy of this approach is progressively growing in the scientific community, although the topic remains controversial.

Adjuvant Chemotherapy in the Elderly—Clinical data obtained in the younger population cannot be automatically adopted in the elderly counterpart. In fact, elderly patients tolerate chemotherapy poorly because of comorbidity and organ failure, and after lung surgery they must be considered at higher risk of chemotherapy-induced toxicity. Thus, there are many doubts as to whether the platinum-based chemotherapy used in positive adjuvant trials is feasible in resected elderly patients. In fact, the survival benefit obtained with platinum-based chemotherapy may vanish or decrease in the elderly due to a potential higher toxic death rate or lower compliance to treatment. Modified schedules or attenuated doses of platinum-containing chemotherapy should be investigated in this clinical setting by specifically designed trials.

The survival benefit yielded in the UFT adjuvant trials[46-48] at least suggests that newer-generation single-agent chemotherapy (vinorelbine, gemcitabine, taxanes) may be investigated in future adjuvant trials for patients who are unsuitable for even modified or attenuated platinum-containing chemotherapy, including resected elderly NSCLC patients. Specific prospective data on adjuvant chemotherapy in elderly patients are not available. A subgroup analysis of the famous meta-analysis[40] showed no evidence that any age group benefited more or less from adjuvant chemotherapy. The ongoing Adjuvant Navelbine International Trialist Association (ANITA) 02 study of adjuvant single-agent vinorelbine (30 mg/m2 weekly for a total of 16 administrations) in patients who cannot receive cisplatin-based chemotherapy may produce useful data along these lines. As with the large randomized trials of platinum-based chemotherapy in advanced disease, retrospective subgroup analyses of data from elderly patients enrolled in the above-mentioned adjuvant trials will likely be presented in the near future. Although this sort of analysis could suffer from selection bias, in the next years they might be the unique source of scientific data on adjuvant chemotherapy for elderly NSCLC patients. In fact, although specifically designed prospective trials are warranted and to be encouraged as the only tool for elucidating the role of this approach in the elderly, the potential low accrual to surgical adjuvant trials could be a serious limitation.

Neoadjuvant Chemotherapy—Randomized trials of neoadjuvant chemotherapy specifically in elderly NSCLC patients have never been performed. A French randomized trial in the general population of patients with resectable stage I, II, and IIIA NSCLC compared preoperative chemotherapy (mitomycin, ifosfamide, and cisplatin) to surgery alone. Survival was superior in the preoperative chemotherapy group and was 9% to 10% higher in this group at years 3 through 5. However, the probability value showed only a trend toward superiority (P = .09), because the study was underpowered to show an improvement of this magnitude.[49] Survival differences were statistically significant only for the subgroup of patients with stage I and II disease. Some large randomized trials on neoadjuvant chemotherapy are ongoing in the United States and Europe, and these studies will elucidate the role of this approach in the general population. Very recently, the results of a phase III trial of surgery alone or surgery plus preoperative paclitaxel/carboplatin chemotherapy in early-stage NSCLC were reported.[50] About 350 patients were accrued. The study closed early due to the positive data obtained in the adjuvant trials, but it is
one of the largest randomized trials to examine preoperative chemotherapy in early-stage NSCLC, representing a landmark regarding the feasibility of this approach. A trend in progression-free survival and overall survival favoring preoperative chemotherapy was reported.

Accrual to neoadjuvant trials is traditionally difficult. At the moment, therefore, specific trials for elderly patients are not planned. New neoadjuvant data reported in the younger population should be considered with interest for the elderly, because preoperative chemotherapy is generally safer than postoperative chemotherapy, and thus, potentially more suitable for elderly patients than adjuvant chemotherapy. Nevertheless, the feasibility of neoadjuvant chemotherapy used in younger patients must be confirmed in the elderly population.

Combined Chemoradiotherapy—Several randomized trials comparing sequential and concurrent chemoradiotherapy to radiation alone have demonstrated the superiority of the combined approaches. More recently, randomized trials compared sequential to concurrent approaches, demonstrating a survival benefit in favor of concurrent chemoradiotherapy.[51,52]

Few specific prospective data are available on combined chemoradiotherapy in the treatment of locally advanced NSCLC in the elderly. Although based on limited population samples, these phase II trials are interesting because they investigate alternative schedules of treatment more suitable for older patients, mainly administering low-dose chemotherapy. These regimens were demonstrated to

### Table 2
Possibilities for Future Research in the Medical Treatment of Older Patients With Stage I–III NSCLC

<table>
<thead>
<tr>
<th>Postoperative Setting</th>
<th>Preoperative Setting</th>
<th>Locally Advanced Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenuated-dose platinum-based chemotherapy</td>
<td>Attenuated-dose platinum-based chemotherapy combined with radiotherapy (sequential or concurrent)</td>
<td>Attenuated-dose platinum-based chemotherapy combined with radiotherapy (sequential or concurrent)</td>
</tr>
<tr>
<td>Third-generation single-agent chemotherapy (vinorelbine, gemcitabine, taxanes)</td>
<td>Chemotherapy combined with targeted therapies</td>
<td>Third-generation single-agent chemotherapy (vinorelbine, gemcitabine, taxanes) combined with radiotherapy (sequential or concurrent)</td>
</tr>
<tr>
<td>Targeted therapies (± chemotherapy)</td>
<td></td>
<td>Combination of chemoradiotherapy with targeted therapies</td>
</tr>
</tbody>
</table>
be active and feasible in the elderly.[53,54] Retrospective analyses on randomized trials of chemoradiotherapy have compared treatment outcomes between elderly patients and their younger counterparts.[55-59] Results are globally ambiguous, with some analyses showing an excess of toxicity and a lack of survival benefit in the elderly subgroup,[55-57] others supporting both feasibility and efficacy of combined treatment (including a concurrent schedule) in this population,[58] and others finding increased toxicity but survival rates equivalent to younger individuals.[59]

The Radiation Therapy Oncology Group (RTOG) performed a retrospective analysis of patients included in phase II/III trials. A quality-adjusted survival analysis of 979 patients treated with radiotherapy alone or combined chemoradiotherapy showed a critical relationship between age and ability to tolerate combined treatment. In fact, elderly patients aged more than 70 years achieved the best quality-adjusted survival with standard radiotherapy only.[55] Moreover, a large analysis of survival data from 1,999 patients enrolled in different Radiation Therapy Oncology Group trials treated with or without chemotherapy found a negative influence of older age on survival.[56]

These results have been confirmed in another RTOG retrospective analysis of 749 locally advanced NSCLC patients enrolled in three separate trials and randomized to radiotherapy alone vs combined sequential or concurrent chemoradiotherapy. As therapy intensified, the incidence of grade 3-5 toxicities increased in the elderly group (>70 years). Unlike the overall patient population, elderly patients did not benefit from combined treatment, and the authors concluded that specific trials are indicated.[57]

Two years later, the same authors retrospectively evaluated treatment outcomes in elderly vs younger patients enrolled in a randomized RTOG trial of concurrent vs sequential chemoradiotherapy. They concluded not only that combined treatment was feasible, but also that the concurrent approach was superior to the sequential one, in the elderly population as well as overall. Indeed, the median survival of elderly patients favored concurrent chemoradiation over sequential chemoradiation (22.4 vs 10.8 months respectively; \(P = .069\)). Long-term toxicities were similar between patients aged less and more than 70 years, but short-term toxicities (grade \(\geq 3\) neutropenia and grade \(\geq 3\) esophagitis) were more pronounced in the elderly compared with patients under age 70.[58]

To examine the relationship between patient age and outcome, the North Central Cancer Treatment Group recently performed a secondary analysis of a phase III trial on two different schedules of radiation therapy (twice daily vs daily) combined with chemotherapy in stage III NSCLC. This retrospective analysis compared the outcomes of patients aged \(\geq 70\) years with those of younger individuals. Of the 244 assessable patients, 63 (26%) were elderly, and 181 (74%) were younger. The 2- and 5-year survival rates were 39% and 18%, respectively, in patients younger than 70 years, compared with 36% and 13%, respectively, in elderly patients (\(P = .4\)). Toxicity \(\geq 4\) occurred in 62% of patients younger than 70 years, compared with 81% of elderly patients (\(P = .007\)). Hematologic toxicity \(\geq 4\) occurred in 56% of patients younger than 70 years, compared with 78% of elderly patients (\(P = .003\)). Pneumonitis \(\geq 4\) occurred in 1% of those younger than 70 years, compared with 6% of elderly patients (\(P = .02\)). In summary, despite increased toxicity, elderly patients treated with combined chemoradiotherapy had survival rates equivalent to younger individuals. Therefore, the authors concluded that fit, elderly patients with locally advanced NSCLC should be encouraged to receive combined-modality therapy, but preferably on clinical trials with cautious, judicious monitoring.[59]

Only specifically designed prospective studies will elucidate the real role and feasibility of combined chemoradiotherapy in the treatment of elderly patients with locally advanced NSCLC. Evidence from retrospective analyses could suffer from selection bias. In fact, elderly patients enrolled in such trials could not be representative of the whole elderly population, but only of a small subgroup thought to be eligible for aggressive treatments by investigators. The percentage of elderly patients among those diagnosed with lung cancer in clinical practice is much higher than the percentage of elderly patients among those enrolled in non-age-specific clinical trials for lung cancer treatment. As a consequence, the generalizability of these results is poor, potentially putting many elderly patients at risk until large prospective trials are performed to address this issue.[37]

A variety of treatment options could be considered as of potential interest in the elderly—for example, single-agent chemotherapy and sequential radiotherapy; attenuated-dose platinum-based chemotherapy and sequential radiotherapy; single-agent chemotherapy and concurrent radiotherapy; attenuated-dose platinum-based chemotherapy and concurrent radiotherapy. Until trials of combined chemoradiotherapy are conducted specifically in the elderly, however, the aggressive concurrent approach should be considered for selected patients only.
Conclusions
Elderly patients with early-stage lung cancer are at risk of morbidity and mortality from untreated disease. Thus, all treatment modalities should be considered when indicated. That said, elderly patients who have lung cancer and undergo standard anatomic pulmonary resections (lobectomy or pneumonectomy) with posterolateral thoracotomy probably have a higher incidence of postoperative mortality than younger individuals. Although there are not enough data to support the use of limited resections for every patient with early lung cancer, these procedures are certainly reasonable alternatives for older patients with high operative risk, cardiopulmonary impairment, and other comorbid diseases.

Curative radiation therapy is an acceptable alternative for patients who are unfit for or refuse surgery. Radiation therapy may be safely delivered to very aged patients with NSCLC at not merely palliative doses, both to achieve better local control and to confer likely survival benefits. Shorter radiation therapy regimens may have similar control rates to those of standard fractionated radiation therapy and should be considered to decrease the treatment burden. Hypofractionated stereotactic body radiation therapy is of particular interest for elderly patients due to its favorable tolerance. Although now considered almost standard in the treatment of early-stage NSCLC, adjuvant chemotherapy should be recommended in selected elderly patients only, until prospective data on feasible regimens in this setting are available. Neoadjuvant chemotherapy in the early stages of disease is an experimental approach under investigation in the general patient population and, consequently, should not be considered in clinical practice for elderly patients.

Retrospective analyses on chemoradiotherapy in the treatment of elderly patients with locally advanced NSCLC are to be considered globally ambiguous and at risk of selection bias. Only specifically designed prospective studies will elucidate the true role and feasibility of combined chemoradiotherapy—mainly a concurrent approach—in the treatment of locally advanced NSCLC elderly patients.

Future investigations in the medical treatment of older patients with stage I-III NSCLC (Table 2) will include the evaluation of alternative schedules of chemotherapy and chemoradiotherapy more suitable for the elderly and the introduction of new, well-tolerated targeted therapies.

Disclosures:
Dr. Gridelli is a speaker and consultant for Eli Lilly and Roche, and a speaker for Pierre Fabre.

References:


**Source URL:**
http://www.patientcareonline.com/printpdf/treatment-stage-i-iii-non-small-cell-lung-cancer-elderly/page/0/1

**Links:**