

# Recurrent non–small-cell lung cancer in elderly patients: a case-based review of current clinical practice

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Management of recurrent non-small cell lung cancer (NSCLC) is a clinical challenge. Around one third of patients who are diagnosed with NSCLC will experience a local/regional or advanced stage recurrence. The median time to recurrence from initial diagnosis is 11.5 months. The median age of initial diagnosis of NSCLC is 71 years of age, patients with recurrent disease tend therefore to be even older. Treatment is a challenge, as this elderly patient population tends to have multiple comorbidities, polypharmacy and socioeconomic factors, that have not been accounted for in clinical trials in patients that define our current treatment recommendations. This case-based review outlines some of these challenges and outlines the need for further research.

**R**ecurrent non–small-cell lung cancer (NSCLC) is a common clinical challenge in the practice of geriatric oncology. About one-third of all patients who are diagnosed with lung cancer in the United States will experience a locoregional or advanced-stage recurrence of the disease after their initial diagnosis and treatment.<sup>1</sup> In a prospective study of 1,361 patients, the median time from initial diagnosis to recurrence was 11.5 months.<sup>2</sup> Patients in that study recurred with either an intrathoracic or an extrathoracic progression versus a second primary lesion, and the median length of survival after recurrence was 8.5 months. Such frequency of recurrence contributes to lung cancer's overall high mortality rate. In elderly patients—those who are older than 65 years—NSCLC remains the leading cause of cancer death in the United States.<sup>3</sup>

According to the National Cancer Institute's 2004–2008 Surveillance, Epidemiology, and End Results (SEER) database, the median age during that period for all NSCLC patients at initial diagnosis was 71 years.<sup>4</sup> The median age of cancer death was 72 years. The elderly population accounts for 68.4% of all newly diagnosed lung cancers; 31.1% of those patients were between the ages of 65 and 74 years, 29% between 75 and 84 years, and 8.3% older than age 85. With the rapid

growth of the elderly population in the United States, a corresponding increase in the number of advanced-age lung cancer patients is expected within the 70 million people who will be older than 65 years by 2030.<sup>5</sup>

According to the 2004 World Health Organization classification, NSCLC tumors are divided into squamous and nonsquamous subtypes. Among nonsquamous cancers, the adenocarcinoma variant is the most frequently recurrent NSCLC in elderly patients. The standard recommended clinical procedure for the diagnosis of disease recurrence is to establish the histopathologic and molecular diagnosis.<sup>6</sup> New treatment algorithms demand this differentiation because treatment and outcome differ according to these subtypes. In adenocarcinoma subtypes, a mutation analysis of the echinoderm microtubule-associated protein-like 4 (EML4), anaplastic lymphoma kinase (ALK), and epidermal growth factor receptor has become standard of care.<sup>7</sup>

Treatment recommendations for recurrent local and systemic disease are similar to recommendations for the initial primary diagnosis of NSCLC.<sup>3</sup> Recommendations for the elderly are mostly extrapolated from the data of younger patients,<sup>8,9</sup> because elderly patients are historically underrepresented in clinical trials for cancer treatments, especially those for recurrent lung cancers,<sup>10,11</sup> at least in part because treating elderly patients is likely to be complicated by polyphar-

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macy and their having comorbidities and/or functional impairments.<sup>12</sup> Geriatric syndromes, such as frailty or fragility, also present a challenge to enrolling and stratifying older patients in clinical trials.<sup>13</sup>

However multiple studies have shown that—depending on whether their functional status is independent, partially dependent, or frail—senior patients may respond to chemotherapeutic regimens with success levels similar to those in younger patient populations.<sup>3,14</sup> The Comprehensive Geriatrics Assessment (CGA) is the mainstay for obtaining a thorough evaluation of senior patients with cancer.<sup>15</sup> The assessment tool can detect multiple problems in senior cancer patients. Moreover, it is an excellent tool for stratifying patients as healthy and independent or frail and in need of care. The CGA has also been used as a precise prognostic tool in oncology settings,<sup>14</sup> and that approach is encouraged and recommended by National Comprehensive Cancer Network (NCCN) guidelines.<sup>3</sup> The actual compliance rate in clinical practice is unknown. Other screening tools, such as performance status, are more frequently used in busy oncology practices because of time constraints and staffing issues.

This article reviews management strategies for recurrent non—small cell lung cancer in elderly patients.

### Case presentation

An 88-year-old man was referred to the oncology clinic by his geriatrician for further evaluation of progressive hemoptysis because previous a cytology workup, including sputum cytology, had been highly suggestive of malignancy. Some 7 years before the onset of suspected hemoptysis, the patient had been diagnosed with right-sided stage IB NSCLC. He underwent a lobectomy and at the time was thought to have been cured. The histologic subtype was undifferentiated adenocarcinoma.

After the lobectomy, the patient was supposed to be followed with annual computed tomographic (CT) imaging, although he was followed for only 4 years after his initial diagnosis. He was a retired shipyard laborer, with a 60 pack-year smoking history. He had quit smoking about 14 years before he came to our clinic. His past medical history was significant for oxygen-dependent chronic obstructive pulmonary disease, ischemic cardiomyopathy (ejection fraction, 25%), coronary artery disease, atrial fibrillation, hypertension, diabetes mellitus, peripheral vascular disease, hypothyroidism, chronic renal impairment, and depression. His active medication list included 22 different drugs. He had been widowed for a year and admitted having decreased interest in social interactions. His daily activities consisted mainly of watching TV. He lived in an apartment adjacent to his

son's house. Because of his limited functionality, he required help in most instrumental activities of daily living (IADLs) and partial help in activities of daily living (ADLs).

### Organ systems and physical examination

During the 3 months before coming to our clinic, the patient had noticed that his sputum was tinged with blood and reported those findings to his son, who informed the father's geriatrician. The geriatrician ruled out an infectious etiology. However, a chest x-ray showed a right lung mass. Given the patient's history of lung cancer, the geriatrician sent the sputum for a cytology workup. The cytology report noted fragments highly suspicious for malignancy. Physical examination during the oncology consultation revealed a frail-appearing, oriented male who needed help in transferring from his stretcher to the exam chair. As his son was unable to escort him to the clinic, he was transferred there via ambulance from his home. His breathing was normal and not labored, with reduced breathing sounds on the right base. He had no peripheral lymphadenopathy, no pain on palpation of his chest wall, and no focal neurologic deficits.

Overall, the patient presented clinically with an Eastern Cooperative Oncology Group (ECOG) performance status of 3. As his sputum cytology was highly suggestive of malignancy and a chest x-ray revealed a mass lesion, we ordered a CT scan of the chest to define the anatomical location and mass characteristics more precisely. A non-contrast CT was chosen because his impaired kidney function allowed for no contrast. The scan confirmed a 6-cm central-right mass with spiculated edges and enlarged bilateral mediastinal lymph nodes. In conjunction with the highly suggestive sputum cytology for NSCLC, this patient was felt to have a slow-growing recurrence of his primary lung cancer rather than a new lung primary. We reviewed the imaging and pathology and discussed treatment options. His son was present during this discussion. We explained that given the patient's overall limited performance status, neither surgery nor aggressive chemotherapy would be of benefit. Instead, options for treatment would include palliative radiation therapy or targeted therapy with a receptor tyrosine kinase inhibitor (TKI). The TKI would possibly require further diagnostic procedures. The patient and his son were adamant that he would refuse further invasive diagnostic testing. The patient was also not interested in chemotherapy options. However, both voiced interest in palliative radiation to reduce the frequency and amount of hemoptysis. The patient was therefore referred and seen in radiation oncology consultation, at which point the radiation oncologist insisted on a biopsy to confirm the diagnosis before

offering radiation treatment. The patient and his son declined the invasive procedure and opted in the interim for home palliative-care management.

## Discussion

Surgery is the standard of care for localized primary- and recurrent-stage NSCLC in elderly patients. There is no difference in outcome in early-stage disease between primary and secondary primary lung cancers.<sup>16</sup> A retrospective analysis that compared pneumonectomy and sleeve resection for non-small cell lung carcinoma in 60 patients aged older than 70 years showed no statistical differences in mortality, local recurrence, or distant metastases between the two surgical interventions.<sup>17</sup> The 5-year survival and mean survival rates for sleeve resection were 59% and 51.9 months, respectively, compared with 0% and 30.1 months for pneumonectomy. The investigators in that study found that sleeve resection may be a better option in early NSCLC.

Radiation therapy for localized early-stage disease has been used in elderly patients who do not qualify for surgery because of poor performance status and comorbidities.<sup>18,19</sup> According to the NCCN guidelines, the level of evidence for this recommendation is a category 2B. In a small study, investigators reviewed responses in 36 patients who had been treated with hypofractionated stereotactic body radiation therapy (SBRT)<sup>20</sup>; median follow-up time was 13.8 months, and the local tumor control after 1 year was 100%. There were no postradiation reductions in performance status. The authors concluded that SBRT is an effective and appropriate treatment for elderly patients with early-stage NSCLC who have low performance status.<sup>20</sup> In a separate study, investigators reviewed chest irradiation with external beam radiotherapy as an option in locally recurrent NSCLC and concluded that reirradiation could be an option for recurrent disease.<sup>21</sup>

Combination therapies of surgical intervention and radiation have also been studied. Yano et al<sup>22</sup> used the combination of radiotherapy and surgery as first-line treatment in patients with postoperative oligometastasis. This particular study included 93 patients with distant metastasis whose 2- and 5-year survival rates after recurrence were 43.9% and 38.7%, respectively. In all, 44 patients first received local treatment—31 patients received radiotherapy, and 13 patients underwent surgical intervention. Metastatic organs included brain, bone, lungs, and other organs. The 2- and 5-year survival rates after recurrence were 43.9% and 38.7%, respectively.

Chemotherapy with concurrent or adjuvant radiotherapy has also been suggested for advanced NSCLC in elderly patients (NCCN category 1 disease).<sup>23</sup> Radiosen-

sitizing platinum doublets are favored, and cisplatin is preferred over carboplatin because of cisplatin's trend of better overall survival.<sup>24</sup> The NCCN level of evidence for the combination of paclitaxel and carboplatin is 2B. Takigawa et al<sup>25</sup> studied 99 patients in a docetaxel plus cisplatin arm (DP) and 101 patients in a mitomycin C, vindesine, and cisplatin arm (MVP). Both arms were concurrently treated with radiotherapy. The authors found longer overall survival and progression-free survival in the DP arm. Radiation intensity was similar for the 2 groups in the study. Severe toxicity did not differ between the 2 groups. Toxicity in the concurrent radiation and chemotherapy approach has been described in other studies as initially more severe. In the concurrent treatment arms of the Radiation Therapy Oncology Group (RTOG) 94-10 study and the Cancer and Leukemia Group B (CALGB) 9130 study, elderly patients were found to experience more myelosuppression, esophagitis, pneumonitis, and/or renal toxicity.<sup>26</sup> However, the higher incidence of recorded toxicity had no effect on response rate and overall survival.<sup>27</sup>

Chemotherapy regimens for elderly patients have been studied by different groups.<sup>28</sup> The Hellenic Oncology Research Group (HORG) studied the feasibility of chemotherapy treatment for older NSCLC patients by comparing younger patients (younger than 70 years) and older patients (older than 70 years) from the pooled data of 5 clinical trials. In all, 23% (424) of the trial's patients were older patients. The authors did not find any differences in overall response rates, times to tumor progression, or objective survival, but did note higher rates of toxicity in senior patients. The group eventually confirmed the feasibility of chemotherapy regimens in senior patients, but insisted on the need for elderly-specific further prospective trials.<sup>29</sup> The overall risk for chemotherapy-related toxicity is higher among elderly patients, and that fact should be discussed with patients. Reduced metabolism, decreased organ reserve, altered cancer biology, and polypharmacy are all contributory factors to the increased risk.<sup>3,13</sup> Although toxicity is higher in the elderly, studies have shown similar benefits of chemotherapy regardless of age in patients with good performance status.<sup>27</sup> Data on the treatment of patients with poor performance status are insufficient, and the prediction of toxicity and efficacy of chemotherapy treatment in the elderly continues to be an active subject of research.

Platinum doublets have been the backbone of NSCLC cancer treatment (NCCN category 1). The efficacy of platinum doublets (cisplatin plus gemcitabine or vinorelbine) in elderly patients has been studied by Ozkaya et al and others.<sup>30,31</sup> Gemcitabine plus cisplatin regimens have been shown to be superior in the treatment of

squamous cell histology, whereas pemetrexed-based regimens showed superior outcomes in nonsquamous histology (NCCN category 1).<sup>16</sup> Regimens of cisplatin plus gemcitabine versus vinorelbine have been studied in patients with advanced NSCLC who are 70 years and older. Both regimens are feasible and active in elderly patients according to the authors Gridelli et al.<sup>32</sup>

The combination of docetaxel plus gemcitabine has also been studied in elderly patients. Compared with docetaxel alone, it showed a modest improvement in time to progression but without changes in survival.<sup>33</sup> Pallis et al<sup>29</sup> found that this regimen has similar efficacy (overall response, 30.3% for patients younger than 70 years; 30.2% for those older than 70 years) and tolerance in 858 patients (666 younger than 70; 192 older than 70). Chemotherapy was well tolerated, but the incidence of mucositis was higher in the older group.

The addition of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab to chemotherapy regimens in the elderly has been studied in advanced and recurrent NSCLC, but its use remains controversial. Leigh et al<sup>34</sup> showed improvement in progression-free and overall survival in a cohort of 304 elderly patients. The investigators did not find any concerning issues relating to tolerability or adverse events with the use of bevacizumab. In contrast, a subset analysis<sup>35</sup> of the ECOG 4599 trial showed increased toxicity and no overall survival benefit in patients when bevacizumab was added to standard carboplatin and paclitaxel.

Pemetrexed, docetaxel, and erlotinib have been approved by the Food and Drug Administration as second-line chemotherapy single agents. Erlotinib is a TKI that acts on the epidermal growth factor receptor (EGFR). This TKI can also be used as the primary regimen in advanced disease if the EGFR is mutated (NCCN category 1)<sup>36</sup>; however, mutation-status analysis is obligatory before starting this medication as first-line therapy (NCCN category 1). Adding a TKI to chemotherapy in the first-line setting has an NCCN category 2B level of evidence.

Cetuximab, a chimeric monoclonal antibody against the EGFR, has also been tested and approved for the treatment of locally advanced or metastatic NSCLC. In the FLEX trial,<sup>37</sup> investigators compared the response among patients with advanced NSCL to cisplatin plus vinorelbine with or without cetuximab, and found an overall survival (OS) benefit for the combination of cisplatin plus vinorelbine with cetuximab (OS, 11.1 and 10.3 months respectively; NCCN category 2B). Other studies used cetuximab in the second-line therapy. A prospective study<sup>38</sup> enrolled 18 patients, who were followed for response. The median progression-free survival was 1.8

months, and median overall survival was 7.5 months. Response rate was 0.18%. The authors did not find any clinical response from this combination.

Multiple regimens in relapsed disease have been attempted in conjunction with the standard treatment with monotherapy alternatives, such as docetaxel or pemetrexed. No combination chemotherapy regimens used as adjuncts to these two agents have shown benefit.

In the past decade, biomarkers have emerged as prognostic and predictive markers; they continue to have a dynamic influence on treatment options. Besides the EGFR expression, EML4-ALK mutation status has been found to affect treatment and outcome. The ALK inhibitor crizotinib showed significant progression-free survival and overall response rates in patients with these mutations, compared with the rates for standard second-line chemotherapy, leading to its FDA approval.<sup>39</sup> Patients who have cancers with ALK mutations tend to be younger and male, with a history of nonsmoking or light smoking. The mutation is found in patients' adenocarcinoma. Testing for the mutation status in a tumor specimen of patients with squamous or large cell histology is not recommended.<sup>40</sup> The future of treatment algorithms for NSCLC is expected to change with further advancement of these findings.

Reasonable treatment alternatives include symptomatic treatment with comfort care or added palliative-care services. Studies have shown that in patients with NSCLC, early palliative care actually improved mood and quality of life. In a study by Temel et al,<sup>41</sup> 151 patients were randomized to receive either early palliative care integrated into standard oncologic care, or standard oncologic care alone. Patients with the palliative care intervention had less-aggressive care at the end of life and a longer survival. The surgical literature also supports the benefit of palliative care. The integration of palliative care into routine clinical care after surgical interventions in lung cancer patients has been shown to be essential in preserving function and optimizing quality of life through survivorship.<sup>42</sup> This interdisciplinary care model is helpful; it can link patients and their families with the appropriate supportive services in a time-effective manner. As these patients approach death, they and their families have been increasingly receptive to comfort care, although many continue to die in severe pain.<sup>43</sup> Other treatment modalities that are geared toward symptom control include interventions such as endobronchial tamponade or stent insertion, transcatheter arterial embolization, and palliative external vs. internal (brachy-) radiation treatments.<sup>44</sup> Most of these modalities lack prospective, randomized data to support their efficacy in elderly, frail

patients. Their utilization in this patient population thus needs an individualized decision-making process.

## Conclusion

Recurrent NSCLC remains a commonly encountered clinical scenario in elderly patients. The role of comprehensive geriatric assessment to stratify independent versus frail patients, and to determine future treatment (curative versus palliative) needs to be further studied. Treatment options are limited because of performance-status limitations, multimorbidity, and polypharmacy, combined with a continued underrepresentation of this patient population in randomized clinical trials. Chemotherapy options appear to be of limited success, and new trials have showed that monotherapy alternatives do not improve survival. The role of biomarkers in diagnosis and treatment in recurrent lung cancer in elderly patients needs to be elucidated.

The role of palliative care and hospice in recurrent lung cancer has not been studied in depth. It appears that, as in our case presentation, patients may find this modality of care useful. The roles of further interventions in terms of treatment for frail patients have not been evaluated in clinical trials. We therefore advocate for trial design and enrollment of this patient population (both frail and independent elderly patients) into clinical trials to investigate their best treatment options. In our view, it is important that specialized geriatricians, oncologists, and pulmonologists be involved in the complex care of this vulnerable patient population. More research into these issues is clearly needed.

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