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Non-Small Cell Lung Cancer in the Elderly: a Practical Approach to Screening, Diagnosis, and Treatment

Michal J. Sobieszczyk[1] · Whittney A. Warren[2] · Andrew P. Polito[1] · William S. Krimsky[3] · Sy Sarkar[3]

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Abstract

Purpose of Review Lung cancer is primarily a disease of the elderly. We summarize the literature on screening, diagnosis, and treatment of early non-small cell lung cancer in the elderly population.

Recent Findings Lung cancer screening has resulted in a reduction in lung cancer mortality and is recommended in some patients up to 80 years old. Minimally invasive techniques, such as endobronchial ultrasound guided biopsy, have allowed for low diagnostic complications rates in elderly patients. Surgical treatment remains the standard of care; however, stereotactic body radiation therapy in non-operative candidates has similar outcomes with less morbidity. Decision to treat and choice of treatment should not be based on age alone, but should incorporate functional status, comorbid disease, and patient preference.

Summary Advances in screening, diagnostic techniques, and radiation therapies have transformed the management of early non-small cell lung cancer in the elderly. Further studies are needed incorporating larger numbers of geriatric patients in a disease that primarily affects the elderly.

Keywords Non-small cell lung cancer · Stereotactic body radiation therapy · Elderly patients · Lung cancer

Introduction and Epidemiology

Non-small cell lung cancer (NSCLC) remains the second most common malignancy in the USA and is the leading cause of cancer-related death among US adults. There were 222,500 new cases of lung cancer diagnosed in 2017 which accounts for approximately 14% of all new cancer diagnosis. It remains predominately a disease of the elderly, with more than 50% of all cases occurring in patients older than 70 years; of those patients, 14% were older than 80 years [1]. By the second half of the century, more than 20% of the population will be 65 years or older. As the population shifts toward older age, the incidence of lung cancer in the elderly will continue to grow.

Although the overall trend in mortality has decreased for younger patients, it continues to increase in the elderly population, especially in older female patients. The overall 5-year survival for patients older than 75 years is 12.2%, in comparison, the survival rate for patients under 45 years of age is more than twice that rate (27.4%) [2]. One UK study analyzed the effects of age in 25,261 patients with NSCLC and found that odds of having a histopathologic diagnosis and treatment decreased with age, despite adjustments for stage, performance status, and comorbidities [3].

Despite the noted difference in diagnosis and treatment, there is little difference in initial presentation of early NSCLC between younger and older patients (≥ 70 years); the time between initial symptoms and the type of diagnosis is similar [4]. Early stage lung cancer is diagnosed more commonly in the elderly with higher percentage of resectability at initial diagnosis versus patients younger than 65 years [5]. One retrospective series investigated differences between clinical characteristics, pathological features, and disease course in 383 patients with resected NSCLC [6]. In the 15-year follow-up period, the rates of recurrence and disease-free

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✉ Sy Sarkar
sysarkar@yahoo.com

[1] San Antonio Military Medical Center, Department of Pulmonary, Critical Care and Sleep Medicine, San Antonio, TX, USA

[2] Walter Reed National Military Medical Center, Department of Pulmonary, Critical Care and Sleep Medicine, Bethesda, MD, USA

[3] Interventional Pulmonology, Medstar Franklin Square Medical Center, 9103 Franklin Square Drive, Suite 309, Baltimore, MD 21237, USA

survival did not vary between younger and older patients (< 70 years vs ≥ 70 years). Another study by Goodgame et al. conducted a retrospective review of 781 patients diagnosed with stage I NSCLC after surgical resection. The clinical and pathological characteristics (tumor classification, tumor size, histology, and grade) were not statistically different between older and younger patients. Although the overall 5-year survival rates differed (52% in < 70 years vs 67% in ≥ 70 years, $p < 0.001$), the estimated disease recurrence was identical (24%) [7]. Although different ages require different considerations, the above studies suggest that age should not be the only consideration when approaching an elderly patient with early NSCLC. The elderly remain underrepresented in large clinical trials and this results in lack of evidence based clinical recommendations.

Lung Cancer Screening in Elderly Patients

It has been established that the risk of lung cancer increases with age, male gender, chronic obstructive pulmonary disease, pulmonary fibrosis, and tobacco smoking. Until recently, there was less evidence regarding the utility of screening for pulmonary malignancies even among these otherwise high-risk patient populations [8–11]. Historically, the false positive rate of radiographic screening has approached or exceeded 90% with both CT and plain chest films; uncertainty regarding the diagnosis and morbidity associated with invasive diagnostic procedures seemingly decreased the appeal of screening, especially among elderly patients [8, 9]. The National Lung Cancer Screening Trial published in 2011 demonstrated a 20% relative risk reduction in cancer-related mortality as well as a 6.7% reduction in all-cause mortality among patients aged 55–74 screened annually with low-dose CT when compared to plain chest radiography [12••]. Subsequent analysis of seven randomized controlled trials including the NLST by the United States Preventive Services Task Force led to updated guidelines for screening in 2013. Currently, patients between the age of 55–80 who continue to smoke with a greater than 30-pack-year history or who have quit within the preceding 15 years are recommended for annual screening with low-dose CT. Screening should continue until the patient has not smoked for 15 years or if life expectancy is limited by comorbidities [9]. Screening may also be discontinued if the patient is not fit or willing for invasive investigations or treatments if an abnormality is identified—features that may become more important in later screening years as patients age with greater associated co-morbid disease.

While guidelines highlight favorable results in younger patients, the benefit of lung cancer screening in the elderly has been insufficiently evaluated. The European studies contemporary with the NLST excluded patients older than 70–74 years [12••, 13]. The Multicenter Italian Lung Detection (MILD—2012) study included all patients older than 49 with at least a 20-pack-year history and found a non-significant trend toward increased mortality [14]. This study had problems with design, however, and is largely regarded as a poor quality study. A retrospective series of patients aged 75–84 years found that elderly patients had a significantly higher incidence of lung cancer as well as higher cancer-related mortality when compared to younger groups, concordant with existing epidemiologic data [15]. Given that the mortality benefit of screening lies in detection of early cancers that may be amenable to definitive operative or ablative therapies, more aggressive screening and treatment of elderly patients may result in similar reductions in lung cancer mortality [16]. Interestingly, the NLST found that the overall rate of complications related to invasive diagnostic procedures was low; serious adverse events and death were more common in patients determined not to have lung cancer, ostensibly representing younger age groups [17]. While there are no specific guidelines or recommendations for patients greater than 80 years of age, probably the most important determination for screening candidacy is whether the patient is sufficiently healthy to undergo definitive therapy if an early cancer is identified: Functional status, comorbidities, life expectancy, and the patient's willingness to comply with subsequent diagnostic and therapeutic procedures should also be taken into consideration.

Diagnostic Evaluation

An accurate diagnosis and staging of NSCLC is essential in developing an appropriate treatment plan. The diagnostic pathway selected must take into account anticipated life expectancy, performance status, quality of life, and potential complications of any invasive diagnostic procedures. In patients with suspected NSCLC the diagnostic modality is dictated by extent and presumed stage of disease. When evaluating a suspicious lung nodule, the least invasive approach should be taken, and the patient's individual clinical presentation must be taken into account.

Over the last 20 years, there has been an emergence of new minimally invasive approaches in the diagnosis of early lung cancer that employ either bronchoscopic or percutaneous approaches. Electromagnetic navigation bronchoscopy (ENB), radial endobronchial ultrasound (rEBUS), and image-guided transthoracic biopsy are the most common minimally invasive modalities in the diagnosis of early stage NSCLC. The selection of the appropriate modality is dependent on lesion size and location and patient comorbidities. ENB combines conventional and virtual bronchoscopy to enable the guidance of bronchoscopic instruments to target peripheral parenchymal lesions (Fig. 1). It utilizes a low-dose electromagnetic field and a sensor device to create a three-dimensional virtual

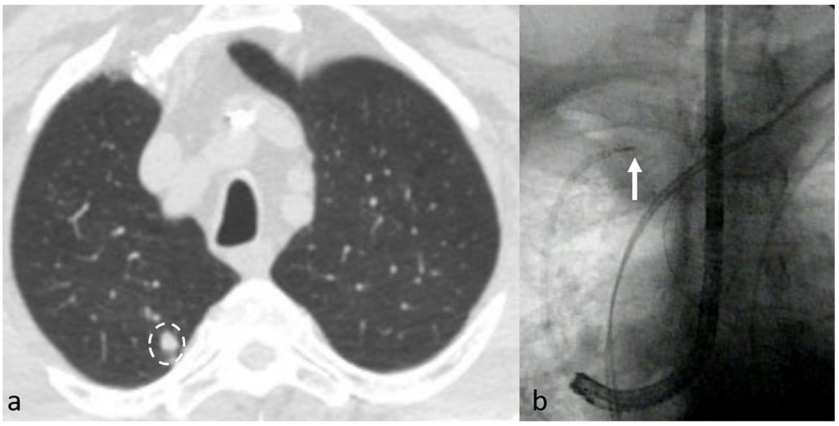

Fig. 1 **a** Chest computed tomography demonstrating right upper lobe pulmonary nodule (hashed circle). **b** Chest radiograph demonstrating electromagnetic navigational bronchoscopy guided transbronchial biopsy (arrow) of the right upper lobe pulmonary nodule

bronchial tree that allows the bronchoscopist to navigate to a lesion without direct visualization. Diagnostic yield varies between 60 and 80% and is dependent on size, location, and proximity to a radiographically visible airway [18–20]. The safety of ENB has been evaluated in several studies, the largest of which was a prospective multicenter investigation of 1000 patients with suspicious peripheral lung lesions (average size of 2 cm). The study demonstrated a pneumothorax rate of 4.9%, bronchopulmonary hemorrhage rate of 2.3%, and a respiratory failure rate of 0.6%. Only one death was reported (0.1%). Although, it must be noted that the study did not report complication rates by age, the average age of participants was 67 years [21].

An additional bronchoscopic tool, the radial EBUS, is a rotating ultrasound transducer at the end of a probe that is passed through the working channel of a bronchoscope. It can be used in conjunction with ENB or by itself to facilitate localization of a peripheral lung lesion. When used independently with a bronchoscope, a guide sheath is utilized to enable confirmation of the location of a lesion and repeated sampling of tissue from the same position. In a recent meta-analysis, the use of radial EBUS with a guide sheath resulted in a pooled diagnostic yield of 73.2% [22]. The rate of successful yield was affected by the size and presence of existing airway leading to the lesion "air bronchus sign," but not by the age of the patient. The safety of radial EBUS has been evaluated in a single-center retrospective review of 965 patients (average age of 69). The reported complication rate was 1.3% and included pneumothorax (0.8%) and respiratory infection (0.5%) [23].

Biopsy of a peripheral lung nodule by transthoracic needle biopsy (TTNB) involves passing a needle percutaneously to obtain either core needle biopsy (CNB) or fine-needle aspiration (FNA). It is typically performed under computed tomographic (CT) guidance. TTNB has a reported sensitivity of 74 to 90% for the definitive diagnosis of lung lesions [24]. Most of the time, the procedure requires the needle to traverse the pleural space and the lung parenchyma. The procedure requires very little sedation and is typically well-tolerated but can result in a pneumothorax or pulmonary hemorrhage. The incident of pneumothorax has been reported to be between 10 and 15%, and 5–18% of cases complicated by pneumothorax will require chest tube placement for drainage [25–28]. Factors influencing risk are increased patient age (> 75 years), presence of emphysema, depth of traversed lung parenchyma, duration of procedure, smaller lesion size, and the number of passes [29]. The second most common complication of CT-guided biopsy is pulmonary hemorrhage and occurs in 4–27% of cases [30]. Hemothorax occurs in < 0.1% of cases and may be higher risk in patients with preexisting pulmonary arterial hypertension.

A major factor in determining the treatment of NSCLC is the staging of intrathoracic lymph nodes. Disease limited to the ipsilateral hilar and/or intrapulmonary lymph nodes does not preclude surgical resection (stage I-III). Lymph node involvement beyond these stations often indicates advanced stage and excludes surgical cure. Two recent retrospective population-based studies in the UK demonstrated that 52% of lung cancer patients are categorized as stage I-III at the time of diagnosis [31, 32]. This highlights the importance of thorough and accurate lymph node staging prior to treatment decisions. Non-invasive nodal staging with imaging alone in the elderly is an attractive option; however, it has limitations. A meta-analysis of CT and positron emission tomography (PET) scan demonstrated sensitivity and specificity of 55% and 81% and 77% and 86% respectively for lymph node staging. Although PET scan has a higher specificity, the high false positive rate requires tissue biopsy to confirm positive findings [33]. Until recently, this required invasive surgical staging via mediastinoscopy. A large meta-analysis of 9267 patients undergoing mediastinoscopy for suspected NSCLC reported a median sensitivity of 78% and negative predictive value of 91% [24]. The disadvantages of mediastinoscopy include lack of reliable access to hilar lymph nodes and requirement for general anesthesia. With the advent of curvilinear EBUS (a bronchoscope with a longitudinal convex

ultrasound transducer that provides sonographic imaging of mediastinal and hilar lymph nodes), the identification and sampling of mediastinal and hilar lymph nodes can be performed endoscopically, often times under moderate sedation (Fig. 2). The reported diagnostic yield of endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) of lymph nodes is variable; a large meta-analysis that pooled 2756 patients reported a median sensitivity of 89%. When compared with mediastinoscopy, multiple studies have shown EBUS to be comparable if not superior [33–35]. In the elderly, EBUS may provide a minimally invasive, well-tolerated option for diagnosis and staging of NSCLC. A prospective study undertaken in the UK analyzed the safety and efficacy of EBUS in 451 patients across two age groups (< 70 years vs ≥ 70 years) over a two-year period. Despite poorer performance status than their younger peers, older patients tolerated the procedure well with equivalent complication rates (8.7% in < 70 years vs 6.1% in ≥ 70 years $p = 0.13$). Sensitivity was equivalent between the groups (92.9% vs 86.4%; $p = 0.12$); however, the negative predictive value (91.8% vs 73.9%; $p = 0.001$) and diagnostic accuracy (96.0% vs 90.2%; $p = 0.02$) in patients with proven or suspected NSCLC favored the ≥ 70-year-old cohort. The study also showed that the overall prevalence of nodal malignancy was significantly lower in the older cohort (55.9% vs 72.2%, $p = 0.0004$) [36]. The authors suggest that the low prevalence of nodal malignancy in the elderly patients may indicate selection bias where physicians were more likely to refer older patients for tissue confirmation with radiographic evidence of early N0 or N1 disease rather that those with radiographic N2 or N3 disease. This suggests reliance on non-invasive staging in the elderly presenting with radiographic evidence of advanced disease. With PET specificity of only 86%, a lack of tissue confirmation may inappropriately upstage elderly patients. Age should not be the only factor in the approach to diagnosis and staging; associated comorbidities, lesion location, size, and depth, and patient preferences should be considered and discussed in a multidisciplinary setting.

Therapeutic Options for Treatment of Early NSCLC

Therapeutic options for the treatment of early NSCLC in the elderly have traditionally encompassed surgery, chemotherapy, and radiation, or a combination of these modalities depending on the stage of NSCLC, comorbidities, and performance status of the patient. Recently, stereotactic body radiosurgery has emerged as a less invasive, yet curative treatment for early stage NSCLC. Immunotherapy and targeted therapy drugs have also become options for first line therapy in patients who are not candidates for the previously mentioned more traditional forms of NSCLC therapy. A multidisciplinary team including the patient, primary care provider, oncologist, pulmonologist, radiation oncologist, and cardiothoracic surgeon is recommended for determining which patients should be treated, as well as the appropriate treatment strategy.

After the decision has been made that treatment is appropriate, the next decision point in the management of stage I and II NSCLC is the determination of surgical candidacy. Surgical treatment is the first line curative therapy for early NSCLC, gold standard therapy option, though precision radiotherapeutic techniques may be equivalent in some situations and are discussed below. Determination of surgical candidacy incorporates underlying comorbidities as well as postoperative predictive lung function. Assessment of comorbidity is discussed below. Postoperative-predicted lung function can be calculated based on preoperative spirometry and is the major determinant of surgical candidacy. In the preoperative evaluation, comorbid cardiovascular disease should be evaluated based on American College of Cardiology/American Heart Association guidelines for a patient undergoing an intermediate risk surgery [37]. Smoking cessation is key to decreasing perioperative risk in all patients undergoing thoracic surgery [38].

Anatomic resection is the surgical treatment of choice for early stage NSCLC and most often involves lobectomy; however, pneumonectomy may be necessary when less extensive

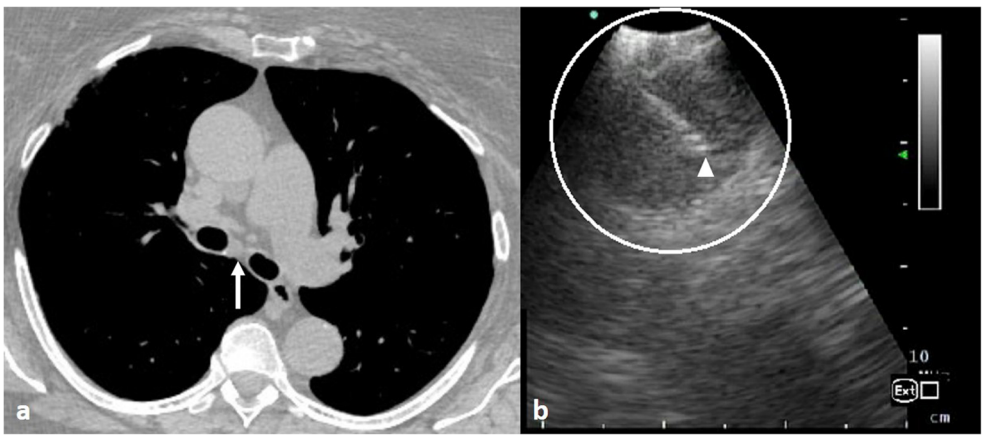

Fig. 2 **a** Chest computed tomography demonstrating subcarinal lymph node (arrow). **b** Endobronchial ultrasound-guided transbronchial needle aspiration of the subcarinal lymph node (solid circle denotes lymph node, arrowhead indicates needle tip)

surgical resection is not feasible [39]. Pneumonectomy for treatment of early NSCLC has declined over the last decade and current guideline-based recommendations advocate for lung sparing resection, such as sleeve lobectomy over pneumonectomy in appropriate candidates [39, 40]. Older patients undergoing pneumonectomy have significantly elevated postoperative risk and truncated 5-year survival. In a study of 5701 patients undergoing pneumonectomy for early NSCLC, patients < 70 years had overall survival of 46.3% versus 25.8% in patients aged > 70 years [40]. In this study, for patients where pneumonectomy was recommended but declined by the patient or surrogate decision maker, standard radiation therapy had inferior overall survival at 12.2% in patients aged > 70 years. The authors concluded that carefully selected elders may be offered pneumonectomy for survival benefit; however, this benefit may be diminished by newer radiation techniques discussed below.

Lobectomy is the surgical treatment of choice in early NSCLC when technically feasible. Among 2690 patients aged 65–80, postoperative 30-day mortality was 2.34% overall and decreased to 1.19% among patients undergoing lobectomy via video-assisted thoracoscopic surgery (VATs) versus open thoracotomy [41••]. In the older subgroup of patients represented in this study (aged 75–80), mortality was 1.56% when VATs was used to perform lobectomy compared to 1.27% in those aged 65–69. This data suggests that in appropriately selected elders, curative lobectomy should be offered as a treatment modality with relatively low postoperative mortality. Though age should not be used to preclude surgical therapy, there is evidence that advancing age may contribute to worse outcomes. In patients at least 80 years old, postoperative morbidity and mortality increased to 48.0% and 6% respectively for lobectomy [42]. VATs lobectomy may improve outcomes in octogenarian and older patient populations versus open thoracotomy.

Despite improvements in surgical technique allowing for lower postoperative morbidity and mortality in older patient populations, comorbid disease and preexisting pulmonary pathology may prohibit lobectomy. Lung-sparing techniques have broadened the number of patients who are operative candidates. Sublobar resections including segmentectomy and wedge resection are surgically curative options that allow for preservation of lung function and lower morbidity in patients who are not candidates for lobectomy. In patients aged 65–74 years, sublobar resection has shown inferior long-term survival and lung cancer-specific survival versus lobar resection [43]. However, several recent studies have demonstrated fewer complications and no difference in overall survival in patients aged ≥ 75 years with early NSCLC undergoing sublobar resection [43, 44••, 45]. Smaller tumors (< 2 cm) and tumors with favorable histopathology (adenocarcinoma) have also demonstrated comparable overall survival and lung cancer-specific survival with sublobar resection versus lobectomy [46].

Current guidelines recommend that for early stage NSCLC patients who are not operable, definitive radiation therapy using either conventional fractionation or stereotactic body radiation therapy (SBRT) should be offered [39]. For stage I and selected node negative stage II NSCLCs, SBRT allows for the delivery of high-dose radiation to a limited treatment field, over 1–10 fractionations, maximizing treatment effect with minimal toxicity to the surrounding lung and organs. Fiducial tracking with the bronchoscopic placement of gold or platinum markers at the sight of the lesion are not required for SBRT but may improve treatment accuracy and further minimize radiation-induced damage to surrounding normal lung (Fig. 3) [47]. In non-operable candidates with small peripheral lesions, SBRT has demonstrated excellent local control rates (90–95%) [48••]. Though the sample size was small, a study comparing SBRT to lobectomy in operative candidates found improved survival and lower, less severe post treatment complications [49]. The average age in that study was 67, and in an older patient population with higher comorbid disease, the results would likely have been even more pronounced. Until larger, randomized controlled trials are available comparing surgery to SBRT in early operable NSCLC, surgery remains the treatment of choice. When conventional fractionation has been compared to SBRT, overall survival is similar in some studies and decreased in others; however, less toxicity and higher quality of life scores are noted in the SBRT group [50, 51]. For patients whose lesions are not amenable to SBRT, conventional radiation therapy remains an option and provides survival benefit versus no therapy [51].

For patients with stage II NSCLC and high-risk stage Ib cancers, adjuvant chemotherapy using a cisplatin-based regimen may provide survival benefit after surgical resection [39, 52, 53]. Adjuvant chemotherapy is advocated due to the high rates of recurrence and cancer-related death in these groups even when the primary tumor was completely resected [54]. Older adults have been underrepresented in the majority of clinical trials exploring the benefits of adjuvant chemotherapy. Several subgroup analyses have, however, demonstrated benefit of adjuvant chemotherapy in the older patient population [55]. In patients aged ≥ 70 years, a similar survival benefit was noted with adjuvant chemotherapy despite receiving fewer cycles and lower doses of chemotherapy than younger patients [56]. This again emphasizes that treatment decisions should not be made based on age alone, but should be made based on functional status with adjustments for comorbid disease. Adjuvant radiation may also be necessary in patients with early NSCLC and positive surgical margins after resection [39].

Driver genetic mutations have recently been identified as therapeutic targets in the treatment of advanced NSCLC.

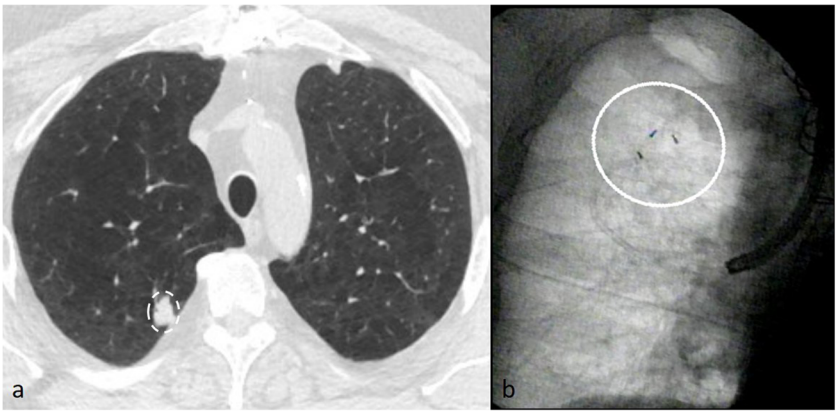

Fig. 3 **a** Chest computed tomography demonstrating right upper lobe pulmonary nodule (hashed circle). **b** Chest radiograph demonstrated bronchoscopically placed fiducial markers (solid circle)

Epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and several other less common driver mutations now have targeted therapies that provide improved survival versus traditional chemotherapy with a substantially lower toxicity profile [57]. In elderly patients with poor performance status, inhibitors of driver mutations are a well-tolerated therapy in a patient population that might otherwise be offered no therapy. The role for these therapies as adjuvant treatment in early NSCLC is not yet defined though preliminary studies suggest benefit and clinical trials are underway to determine appropriate candidates for these therapies (ALCHEMIST trial, NCT02194738) [58, 59].

For patients without driver mutations, immunotherapy has emerged as a treatment option for advanced NSCLC. Tumor inhibition of T cell pathways involving PD-1 and its ligand PD-L1 allow for immune system evasion and proliferation. In patients with advanced NSCLC and significant PD-1 expression, antibodies against PD-1 have provided survival benefit with less toxicity than systemic chemotherapy [60]. Immunotherapy has not been validated for treatment of early NSCLC; however, the ALCHEMIST trial (NCT02194738) has recently incorporated a study arm randomizing driver mutation negative patients with early NSCLC to receive immunotherapy or placebo. If validated, immunotherapy may provide another less toxic adjuvant treatment option for elders with early NSCLC.

Decision to Treat—Appropriate Selection of the Elderly Patient

The initial decision point after diagnosis of stage I or II NSCLC in older patients should assess whether treatment is appropriate for the individual patient. Decisions regarding treatment based solely on patient age should be avoided [61]. Instead, treatment should be offered based on performance status, expected survival with and without treatment considering the patient's comorbid disease, and the patient's personal goals and expectations [62]. In rare circumstances, performance status and comorbid disease may limit diagnostic capabilities and treatment without definitive diagnosis may be warranted.

Performance status should be assessed objectively to determine tolerance of specific therapies such as chemotherapy. Activities of daily living (ADL) and instrumental activities of daily living (IADL) are associated with treatment tolerance as well as survival and may be used to guide decision making [63]. Based on a study of 200 geriatric patients with cancer, a comprehensive geriatric assessment which incorporates ADLs and IADLs was more sensitive than physician judgment for classifying patients as fit or frail with regard to cancer treatment [64]. The Karnofsky Performance Status or Eastern Cooperative Oncology scale can be used to objectively assess ADL and IADL [65]. Comorbidities should be assessed independently of functional status when considering cancer treatment in older patient populations as comorbid disease does not always correlate with functional status and can have significant influence on tolerance of therapy [66]. The Charlson Comorbidity Index has been used to objectively quantify the effect of comorbid disease on outcomes in older patients with NSCLC [67].

For some patients, comorbid disease and the location of the pulmonary abnormality may preclude definitive diagnosis. Nodules that are not amenable to bronchoscopy or computed tomography-guided biopsy may be difficult to the diagnosis in patients who are not surgical candidates. Because of the minimally invasive treatment options, such as SBRT that are now available, with relatively well-tolerated side effects, these patients may be candidates for treatment without definitive diagnosis. The decision to treat without tissue diagnosis should be made by a multidisciplinary team and several risk stratification tools are available to estimate the risk of malignancy for a solitary pulmonary nodule. The Brock University cancer prediction equation incorporates age, sex, family history of lung cancer, and radiographic characteristics of the nodule to predict malignancy risk associated with a solitary pulmonary nodule [68]. The Mayo Clinic model also incorporates similar features as well as prior smoking status and history of extrathoracic cancer to determine risk of malignancy for a pulmonary nodule [69].

Conclusion

The advent of lung cancer screening has resulted in the earlier detection of NSCLC in patients up to 80 years of age. The development of minimally invasive diagnostic modalities, advances in surgical techniques as well as development of non-operative therapies such as SBRT has created a wider range of options for this patient population. It is important to note that age should not be the sole determining factor in evaluation and treatment of NSCLC. A multidisciplinary approach should be taken that considers not only the age, but patient wishes, functional and emotional status, and their co-morbidities. Although few studies investigate the topic of diagnostic and therapeutic techniques in the elderly population with NSCLC, the existing trials demonstrate the feasibility of studying this population and that further effort should be made to investigate the best approaches to management of elderly patients with early NSCLC.

Disclaimer The views reflected in this manuscript are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

Compliance with Ethical Standards

Conflict of Interest Michal Sobieszczyk, Whittney Warren, Andrew Polito, and Sy Sarkar declare no conflict of interest.

William Krimsky is a part-time employee for the Medtronic corporation. He is also a consultant/CSO for Gala Therapeutics, consultant for Innovital Systems, and consultant for Peytant Solutions.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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