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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Older Patients with Lung Cancer: a Summary of Seminal Contributions to Optimal Patient Care

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Abstract

Purpose of Review This review aspires to summarize the landmark advancements in the management of the non-small cell lung cancer (NSCLC), both historically and contemporarily with special focus in older adults.

Recent Findings The past two decades have witnessed remarkable improvements in the diagnosis and management of lung cancer. Screening recommendations now facilitate earlier diagnosis in high-risk individuals, PET/CT scans have improved radiologic accuracy in identifying sites of disease, and surgical management with minimally invasive techniques has rendered surgery safer in those with limited physiologic reserve. Radiation enhancements, especially radiosurgery, have extended the reach and safety of radiation among high-risk populations. Finally, the revolution in precision medicine with identification of numerous actionable mutations, the advent of immunotherapy, and enhanced supportive care have revolutionized the outcomes in patients with advanced lung cancer.

Summary Older adults who represent a majority of patients battling lung cancer have not benefitted to the same extent as their younger counterparts. This special population is only expected to grow in coming days. Hence, addressing major gaps in the management of older adults with NSCLC and optimizing the care are much needed.

Keywords Lung cancer · Non-small cell lung cancer · Geriatric assessment · Older adults · Targeted therapy · Immune checkpoint inhibitors · Screening · Stereotactic ablative radiotherapy · Chronological age · Driver mutations · Palliative care

Introduction

Despite remarkable progress in the screening, radiologic, molecular diagnostics, surgical, radiation, and systemic therapies, lung cancer remains the leading cause of cancer-related deaths in the USA [1]. In 2021, of the estimated 235,760 new cases of lung cancer diagnosed in the USA, 131,880 will die from the disease [1]. Lung cancer is a disease of older adults: with a median age of 71 years at diagnosis, over two-thirds of men and women diagnosed with lung cancers are above age 65 with over a quarter over age 75 [2]. Similarly, the median age of death is 72 with higher mortality in those above age 65: 32.4% of those between the ages 65 and 74 and 28.3% for those 75 and 84 compared to 20.3% for age 55–64 years [2]. Thus, while lung cancer disproportionately affects older adults, their outcomes are poorer than younger counterparts. The reasons for these are multifactorial and in addition to disease biology, likely affected by delays or absence of screening, advanced stage at diagnosis, and lower likelihood of being offered curative therapies. Definition of "older adult" based on chronologic age is an evolving concept and can vary geographically and culturally across the globe. It is imperative to consider the functional status, cognition, psychological state, comorbidity, medication burden, nutrition, and social support to estimate the biological age [3]. There have been significant strides in the management of older adults with cancer as evidenced by guidelines from organizations such as the National Comprehensive Cancer Network (NCCN) and

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American Society of Clinical Oncology (ASCO). These principles are especially relevant to older adults with lung cancer—a malignancy with high mortality and often associated with tobacco-induced comorbid conditions [4, 5]. Below we review the typical outcomes of older patients with lung cancer in a stage-based manner and make recommendations on how to improve their care by incorporating established principles from geriatric oncology.

Screening in Older Adults—Guidelines and Practice

Tobacco use accounts for approximately 80% of all lung cancer and is a major modifiable risk factor. Multiple prospective trials and pooled analyses have demonstrated a reduction in mortality by 15–25% among high-risk current and former smokers when screened with low-dose computed tomography (LDCT) [6–8]. Thus, the United States Preventive Services Task Force (USPSTF) recommendations first issued in 2013 were to screen adults 55 to 80 years with a 30-pack per year (PPY) smoking history and current smoker or have quit within the past 15 years and were broadened to include those with 20 PPY history in 2021 [9]. Similar recommendations have been made by other professional societies [10–12]. Adherence to lung cancer screening in real-world data has been low with only 14% of the patients above age 70 undergoing lung cancer screening [8, 13]. Older adults were underrepresented in screening trials: in the NLST trial, only 25% of patients enrolled in the screening arms were of age 65–74 years and less than 1% were 75 years or older. Notably, over 96% of the patients with a positive screen led to a false-positive result after further work-up [8]. Diagnostic work-up, especially invasive procedures, can lead to additional complications in older adults with multiple comorbid conditions. The USPSTF guidelines do state that screening should be discontinued "once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery." Thus, one way to improve lung cancer–related outcomes among older adults is to offer appropriate screening especially to those with good physiologic function. Education of primary care providers is crucial in this context. Given paucity of representation of older adults in screening trials, assessment of real-world datasets can help fill the gaps.

Management Decisions in Older Adults with Lung Cancer

A simplified approach to lung cancer management includes a stage-based paradigm: surgery for early-stage disease followed by adjuvant systemic therapy in higher risk disease; concurrent chemoradiotherapy (CCRT) for locally advanced disease followed by immunotherapy for responding and stable disease; systemic therapy for metastatic disease including with targeted therapy; and immune checkpoint inhibitors (ICIs) and/or chemotherapy. Older adults have long been underrepresented in cancer treatment trials and age-based disparities persist despite efforts to increase representation [14, 15•]. The stringent eligibility criteria of traditional clinical trials tend to exclude most older adults with their higher comorbid burden and worse performance status (PS). The over-reliance on PS in clinical trial eligibility is ill-founded since this broad assessment applies to all adult patients with cancer regardless of age and does not account for the heterogeneity among older adults. Geriatric assessment (GA) refers to the evaluation of functional, cognitive, psychological, and nutritional status; physical performance; falls; comorbid medical conditions; and social support using validated tools to identify geriatric impairments that are not routinely captured in oncology assessments. [4, 5].

Surgery for Localized Disease (Stages I–IIIA)

Curative surgery, the standard of care for early-stage disease (stages I, II, and select IIIA) which includes lobectomy with mediastinal lymph node dissection, is performed less frequently in elderly patients: 92% of the patients who were < 65 years of age were offered curative surgery versus only 70% for the patients who were more than 75 years of age [16]. No difference in survival between lobectomies and limited resections in terms of survival was observed for the elderly population. Similarly, the percentage of patients receiving lobectomy decreased with increasing age, 31% at the age of 70 to 74 years versus 18% for more than 80 years ($p < 0.001$) [17]. Resectable stage IIIA includes a minority of patients, typically with T1-2 tumors with the single station non-bulky N2 involvement and, less commonly, those with T3N1 or T4N0 tumors treated with neoadjuvant therapy. In a seminal trial by Albain et al., with stage IIIA (N2) NSCLC—396 patients, disease-free survival (DFS) benefit of [hazard ratio (HR) 0.77, 95% CI 0.62–0.96, $p = 0.017$] was observed with neoadjuvant CCRT followed by surgery versus surgery without overall survival (OS) benefit (HR 0.87, 95% CI 0.70–1.10, $p = 0.24$) [18]. Only 15.9% of the patients in this trial were 70 years and older though half of the population in this study was over 60 years.

Thus, surgery should be offered to fit older adults since outcomes are similar to those in younger patients. Although age is reported as an independent predictor for post-surgical survival in patients with NSCLC, chronologic age alone should not be used as a basis to assess surgical risk. The guidelines from the American College of Surgeons recommend an interdisciplinary care model to

improve outcomes of surgery in older adults [19]. Accumulating evidence suggests that pre-operative GA and its components can assist in better stratifying patients suited for surgery assessing for frailty [20•].

Non-surgical Treatment Approaches for Localized Lung Cancer (Stage I, Stage IIA-cT2bN0)

For patients deemed not to be surgical candidates, radiation therapy has been accepted as an alternative option for localized NSCLC. Age has not shown to be a factor in acute or late toxicity of conventional radiation therapy, although weight loss, more common in older adults with NSCLC, is associated with worse outcomes [21]. Modern radiation techniques such as stereotactic ablative radiotherapy (SABR) have demonstrated better primary tumor control and OS than conventionally fractionated radiotherapy although not proven equivalent to lobectomy. It is considered an appropriate option for patients with high surgical risk unable to tolerate sub-lobar resection, age > 75, and poor lung function [22]. In a pooled analysis of the two prospective trials STARS and ROSEL with 58 patients evaluating cT1-2a (< 4 cm), N0M0 operable NSCLC randomized to SABR or lobectomy with mediastinal lymph node dissection or sampling, OS at 3 years was 95% and 79% in the SABR and surgery groups (hazard ratio [HR] 0.14 [95% CI 0.017–1.190], log-rank $p = 0.037$) and recurrence-free survival at 3 years was 86% and 80% in the SABR and surgery group (HR 0.69 [95% CI 0.21–2.29], log-rank $p = 0.54$), respectively [23]. In the SABR group, 10% of patients had grade 3 treatment-related adverse events, with no grade 4 or 5 events compared to 44% with grade 3–4 events in the surgical arm. In an Amsterdam-based cancer registry of stage I NSCLC, 875 patients age 75 and older documented increase in the use of RT from the period 1999 through 2007 by 16%, with a 12% absolute decrease in the number of untreated patients, indicating an ability to offer more curative treatment to elderly patients and with improvement in OS coincident with the implementation of SBRT [24]. Surveillance, Epidemiology, and End Results (SEER) linked to a Medicare database study of more than 9000 patients with early-stage node-negative NSCLC patients after propensity score matching analysis demonstrated similar OS between SABR vs lobectomy in elderly patients of 66 and older although OS was better for lobectomy at 75% versus 55% for SABR [17]. Thus, radiation therapy, especially SABR, is an accepted current standard for older adults with localized NSCLC who are not candidates for surgical resection due to cardiorespiratory factors or other comorbidities.

Role of Adjuvant Therapy Post-surgery

The post-surgical treatment includes adjuvant systemic therapy and radiation therapy in certain clinical circumstances [25, 26]. The LACE meta-analysis has established the survival benefit for the adjuvant chemotherapy doublet cisplatin based in NSCLC for stage II–IIIA NSCLC [26]. Although older adults (≥ 70 years) represented only 9% of the total patients included, the survival benefit of adjuvant chemotherapy was confirmed in this population [26]. A declining benefit of adjuvant chemotherapy with increasing age was noted in the International Adjuvant Lung Cancer Trial (IALT) [27]. In a retrospective subset analysis of the JBR.10 trial, adults > 65 years demonstrated prolonged OS with chemotherapy versus observation (HR 0.61; 95% CI 0.38–0.98; $p = 0.04$), despite lower doses of the drugs and fewer cycles administered [28]. Hence, adjuvant chemotherapy should not be withheld from older adults based on the age alone. In the contemporary ADAURA trial with the use of adjuvant osimertinib in patients with resected epidermal growth factor receptor (EGFR) mutation positive NSCLC stage IB-IIIA, age (30–86) years, 2-year OS rate was 98% for osimertinib versus 85% for placebo (95% CI, 80 to 89). (1) The median age on this trial was 64 years. Use of osimertinib improved OS in patients ≥ 65 years with HR 0.22 (95% CI 0.13–0.36) [29•]. The recently reported IMpower010 showed disease-free survival (DFS) benefit with atezolizumab versus best supportive care (BSC) after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC, with pronounced benefit in the subgroup whose tumors expressed PD-L1 on 1% or more of tumor cells [3]. Thirty-seven to 43% of the patients on this trial were age ≥ 65. HR for DFS in age ≥ 65 years was 0.64 (0.41–1.01) compared to 0.67 (0.46–0.96) for age < 65 years [30•]. Thus, adjuvant osimertinib should be offered for EGFR mutant NSCLC and adjuvant atezolizumab for PD-L1-expressing NSCLC post-resection. The role of radiation therapy in adjuvant setting is limited to only N2 + disease with improved OS in a non-randomized analysis. RT is administered concurrently with chemotherapy for positive resection margin.

Non-surgical Treatment Modality for Locally Advanced Disease

Stage IIIB and stage IIIC NSCLC are considered unresectable along with stage IIIA with multi-level nodal involvement, bulky disease, and unresectable T3 and T4 due to local extension [25]. The current treatment for this stage of NSCLC consisted of CCRT with the more recent addition

of durvalumab in patients with stable or responsive disease [22, 31]. In the pre-durvalumab era, many US-based studies and pooled analyses evaluating the safety and efficacy of CCRT in older adults found similar benefit, albeit with greater toxicity [32–34]. Similarly, two Japanese trials demonstrated the benefit of CCRT over radiation therapy (RT) alone in patients over 70 years of age with similar findings reported in a meta-analysis [35–37]. Higher incidence of hematological toxicity and infection was seen in the combination arm whereas grade 3 pneumonitis and lung toxicity were similar [37]. Weekly chemotherapy regimen including carboplatin and paclitaxel was associated with better tolerability and equal efficacy compared to cisplatin and etoposide and, hence, especially preferred for older adults [38, 39]. When considering sequential versus CCRT approach, OS advantage was observed with CCRT (HR, 0.84; 95% CI, 0.74 to 0.95; $p = 0.004$), with an absolute benefit of 5.7% (from 18.1 to 23.8%) at 3 years and 4.5% at 5 years. There was increase in acute esophageal toxicity. Notably, the proportion of patients ≥ 70 years included in this meta-analysis was low as noted in the primary trials of older adults representing with 13% in the concurrent regimen and 19% in the sequence of regimen [40]. Recent development involves incorporating consolidation immunotherapy with anti-programmed cell death ligand 1 (PDL-1) systemic therapy with durvalumab for 12 months after definitive CCRT [31]. Updated results show durable OS benefits with durvalumab (HR = 0.71; 95% CI: 0.57–0.88) with a median OS of 47.5 months for durvalumab vs 29.1 months in the placebo arm [41••]. In the PACIFIC trial, 45% of the patients were age 65 or older but age did not impact outcomes [41••]. Thus, the current standard of care for older adults with locally advanced unresectable NSCLC is CCRT followed by durvalumab.

Advanced Disease

For decades, palliative treatments with platinum-based doublets have been the standard of care as first-line therapy in NSCLC, showing improved survival and quality of life among fit older patients [42]. Accelerated developments of targeted therapies against identified oncogenic driver mutations and immune checkpoint inhibitors (ICIs) have changed the treatment of advanced NSCLC [43]. Initial comprehensive molecular testing of the tumor sample, including PD-L1 immunohistochemistry (IHC), to determine therapy in NSCLC is the current standard of care and considered first step to determining therapy [44, 45]. However, a significant proportion of patients cannot undergo tissue molecular testing, especially in the relapsed and metastatic settings, because of lack of tissue for testing or suboptimal conditions prevent invasive procedures [46]. Incorporation of liquid biopsy using circulating tumor DNA (ctDNA) into clinical practice emerged as a clinically useful, less invasive, rapid, and convenient diagnostic test to increase the availability of molecular testing to many patients including elderly [47].

EGFR sensitizing mutations, exon 19 deletions and the exon 21 L858R substitution, are the first established and the most frequent oncogenic mutations that started the era of personalized medicine in NSCLC. Since then, the list of targetable molecular alterations in NSCLC expanded and multiple effective matched targeted therapies are developed and approved by the FDA in the first- and second-line settings [48]. Targeting EGFR mutation or ALK fusion with tyrosine kinase inhibitors (TKI) showed superior outcomes and improved quality of life compared to standard chemotherapy. For those with less common molecular alterations as ROS1 or RET rearrangement, MET abnormalities, BRAF V600E or HER2 mutation, KRAS G12C mutation, or Exon 20 EGFR insertion, single arm phase II studies showed high efficacy and favorable toxicity profile that led to their approval. The evidence of efficacy among older adults can be retrieved from subgroup analysis, with key trials of latest targeted therapy in advanced NSCLC summarized in Table 1.

In the absence of molecular alteration, early incorporation of ICI either as monotherapy, doublet or in combination with chemotherapy is currently the standard of care in advanced-stage NSCLC, guided by PD-L1 tumor proportion score (TPS) (Table 2). In NSCLC with PDL1 > 50%, monotherapy with ICI showed superior response and OS benefit compared to systemic chemotherapy in all age subgroups [49••, 50, 51]. Around 45–53% of patients enrolled in the studies were > 65 years old. A recent pooled analysis of three clinical trials included 264 elderly patients (≥ 75 years) with PD-L1 TPS ≥ 1% confirmed the clinical efficacy and safety of pembrolizumab in comparison to chemotherapy. Nosaki et al. demonstrated that pembrolizumab as first-line therapy in elderly patients with PD-L1 TPS ≥ 50% ($n = 132$) has a superior OS compared with chemotherapy (HR, 0.41 [95% CI, 0.23−0.73]). It also has a lower frequency of severe adverse events (grade ≥ 3) in elderly patients (24.2.5%) compared to chemotherapy (61%) [52••]. Unlike chemotherapy, ICIs are associated with distinguished autoimmune reactions named immunotherapy-related adverse events (irAEs). IrAEs can affect one or multiple organs at any time during treatment, with the skin being the most common site of irAE, followed by the endocrine and gastrointestinal systems [53].

For patients with PD-L1 < 50%, platinum-based chemotherapy remains the mainstay of treatment in routine clinical practice. Multiple trials showed the superiority of the combination of ICI and platinum-based chemotherapy (based on tumor histology) compared to platinum-based chemotherapy alone, establishing the combination of ICI

Table 1 Biomarker-driven treatments in NSCLC

Biomarker/molecular alteration	Treatment regimens	Clinical efficacy		
		Age	HR (95% CI)	Overall clinical efficacy
Approved in first line settings				
EGFR sensitizing mutation	Osimertinib [81]	< 65 = 298/556 (53.6%)	PFS 0.44 (0.33–0.58)	ORR 80% mPFS of 18.9 m vs. 10.2 m (HR 0.46, 95% CI 0.64–0.96; $p = 0.02$) mOS of 38.6 m vs. 31.8 m (HR, 0.80, 95.05% CI, 0.64 to 1.00; $p = 0.046$)
		≥ 65 = 258/556 (46.4%)	PFS 0.49 (0.35–0.67)	
ALK rearrangement	Alectinib [82]	< 65 = 233/303 (77%)	PFS 0.48 (0.34–0.70)	ORR 82.9% mPFS of 34.8 m vs. 10.9 m (HR 0.43, 95% CI 0. 0.32–0.58)
		≥ 65 = 70/303 (23%)	mPFS 0.45 (0.24–0.87)	
	Brigatinib [83]	< 65 = 93/137 (68%)	PFS 0.42 (0.29–0.63)	ORR 71% mPFS of 24.0 m vs. 11.1 m (HR 0.48, 95% CI, 0.35–0.66; $p < 0.0001$)
		≥ 65 = 44/137 (32%)	PFS 0.58 (0.33–1.01)	
ROS1 gene rearrangement	Crizotinib [84]	NR		ORR 72% mPFS of 19.3 m (95% CI, 15.2–39) mOS of 51.4 months (95% CI, 29.3 to not reached)
BRAF V600E mutation	Dabrafenib plus trametinib [85]	< 65 = 29/57 (51%) ≥ 65 = 28/57 (49%)		Treatment naïve: ORR 63.9% mPFS of 10·8 months (95% CI; 7.0–14.5)
				Pretreated: ORR 68.4% mPFS of 10.2 months (95% CI: 6.9–16.7)
RET rearrangement	Selpercatinib [86]	NR		Pretreated: ORR 64% mDoR of 17.5 months (95% CI, 12.0–NE)
				Treatment naïve: ORR 85% DOR at 6 months: 90%
	Pralsetinib [87]	NR		Pretreated: ORR 70% mDOR NR (15·2–NE)
				Treatment naïve: ORR 85% mDOR 9.0 (6.3–NE)
MET exon 14 skipping mutations	Capmatinib [88]	NR		**Pretreated:** ORR 41% mDoR of 9.7 m (95% CI, 5.6 to 13.0)
				Treatment-naive: ORR 68% mDOR 12.6 m (95% CI, 5.6 to NE)
	Tepotinib [89]	NR		ORR 46% mDOR of 11.1 months (95% CI, 7.2 to NE)
HER2 mutation	Trastuzumab deruxtecan [90]	NR		ORR 55% mDOR 9.3 months (95% CI, 5.7 to 14.7) mOS 7.8 months (95% CI, 13.8 to 22.1)
	Ado-trastuzumab emtansine [91]	NR		ORR 44% mPFS of 5 months (95% CI, 3 to 9)
Approved in subsequent settings				
EGFR Ex 20 insertion	Amivantamab [92]	< 65 = 48/81	ORR 44% (95% CI, 30 to 59)	ORR 40% mDOR of 11.1 months (95% CI, 6.9 to NE) mPFS of 8.3 months (95% CI, 6.5 to 10.9)
		≥ 65 = 33/81	ORR 33% (95% CI, 18 to 52)	
	Mobocertinib [93]	< 65 = 72/114 (63.2%)	ORR 31.9% (95% CI, 21.4 to 44)	Overall ORR 28% DCR 78% mDOR of 17.5 months (95% CI, 7.4–20.3) mPFS of 7.3 months (95% CI, 5.5–9.2)
		≥ 65 = 42/114(36.8%)	ORR 21.4 (95% CI, 11.2 TO 37.1)	
KRAS G12C	Sotorasib [94]	NR		ORR 37.1% DCR 80.6% mDOR of 11.1 months (95% CI, 6.9 to NE) mPFS of 6.8 months (95% CI, 5.1 to 8.2)

EGFR, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *ROS1*, c-ROS oncogene 1; *RET*, rearranged during transfection gene; *HER2*, human epidermal growth factor receptor 2; *NR*, not reported; *NE*, not estimated; *TKI*, tyrosine kinase inhibitor; *ORR*, objective response rate; *DCR*, disease control rate; *mOS*, median overall survival; *mPFS*, median progression free survival; *m*, months; *mDOR*, median duration of response; *CI*, confidence interval; *HR*, hazards ratio; *vs*, versus

Table 2 Immune checkpoint inhibitors in advanced NSCLC

Biomarker	Treatment regimens	Clinical efficacy		
		Age	HR (95% CI)	Overall clinical efficacy
PD-L1 tumor proportion score (TPS) ≥ 50%	Pembrolizumab [49••]	< 65 = 141/305 (46.2%)	PFS 0.61 (0.40–0.92)	ORR 45% mPFS of 10.3 vs. 6 m (HR, 0.50, 95% CI 0. 0.37 to 0.68; $p < 0.001$) mOS of 30 m vs. 14.2 m (HR, 0.60; 95% CI, 0.41 to 0.89; $p = 0.005$)
		≥ 65 = 164/305 (53.8%)	PFS 0.45 (0.29–0.70)	
	Atezolizumab [50]	< 65 = 102/205 (49.8%)	OS 0.59 (0.34–1.04)	mPFS of 8.1 m vs. 5 m (H, 0.63; 95% CI, 0.45 to 0.88) mOS of 20.2 m vs. 13.1 m (HR, 0.59; 95% CI, 0.40 to 0.89; $p = 0.01$)
		65–74 = 80/205 (39%)	0.63 (.34–1.19)	
		≥ 75 = 23/205 (11.2%)	0.79 (0.18–3.56)	
	Cemiplimab [51]	< 65 = 157/280 (55%)	OS 0.66 (0.44–1)	ORR 39% mPFS of 8.2 m vs. 5.7 m (HR 0.54, 95% CI 0.43 to 0.68; $p < 0.0001$) mOS was not reached vs. 14.2 m (HR 0.57; 95% CI 0.42 to 0.77; $p = 0.0002$)
		≥ 65 = 126/280 (45%)	OS 0.48 (0.3–0.76)	
Non-squamous NSCLC with PD-L1 TPS < 50%	Pemetrexed and platinum-based chemotherapy with or without pembrolizumab (2, 7)	< 65 = 312/616 (50.6%)	OS 0.43 (0.31–0.61)	ORR 48% mOS of not reached vs. 11.3 m (HR, 0.49; 95% CI, 0.38–0.64; $p = < 0.001$)
		≥ 65 = 304/616 (49.4)	OS 0.64 (0.43–0.95)	
	Carboplatin, paclitaxel, and bevacizumab with or without atezolizumab (4, 8)	< 65 = 375/692 (54%)	PFS 0.65	ORR 64% mOS 19.2 m vs. 14.7 m (HR 0.78; 95% CI, 0.64–0.96; $p = 0.02$)
		65–74 = 248/692 (36%)	PFS 0.52	
		75–84 = 64/692 (9%)	PFS 0.78	
	Carboplatin and nab-paclitaxel with or without atezolizumab [58]	< 65 = 341/679 (50.2%)	OS 0.79 (0.58–1.08)	mPFS of 7.0 m vs. 5.5 m (HR 0.64; 95% CI 0.54 to 0.77; $p < 0{\cdot}000$) mOS of 18.6 m vs. 13·m (HR 0.79; 95% CI 0.64 to 0.98; $p = 0.033$) and median progression-free survival (])
		≥ 65 = 338/679 (49.8%)	OS 0.78 (0.58–1.05)	
Squamous NSCLC with PD-L1 TPS < 50%	Carboplatin and paclitaxel or nab-paclitaxel, with or without pembrolizumab [95]	< 65 = 254/559 (45.4%)	PFS 0.50 (0.37–0.69)	ORR 58% mOS of 15.9 m vs. 11.3 m (HR, 0.64; 95% CI, 0.49–0.85; $p < 0.001$)
		≥ 65 = 305/559 (54.6%)	PFS 0.63 (0.47–0.84)	
Regardless of PDL1 expression	Nivolumab plus ipilimumab (CheckMate-227) [96]	< 65 = 406/793 (51.2%)	OS 0.70 (0.55–0.89)	PDL1 > 1%: ORR 35.9% mOS of 17.1 m vs. 14.9 m (HR 0.79; CI 95% 0.65–0.96; $p = 0.007$)
		65–74 = 306/793 (38.6%)	OS 0.91 (0.70–1.19)	
		≥ 75 = 81/793 (10.2%)	`OS 0.92 (0.57–1.48)	
	Nivolumab plus ipilimumab combined with two cycles of chemotherapy (9LA) [97]	< 65 = 354/719 (49%)	OS 0.61 (0.47–0.8)	Regardless of PDL1 expression: ORR 37.7% mPFS of 6.8 m vs. 5.0 m [HR 0.70; 97.48% CI 0.57–0.86; $p = 0.00012$) mOS of 14.1 m vs. 10.7 m (HR 0.69; 96.71% CI 0.55–0.87; $p = 0.00065$)
		65–74 = 295/719 (41%)	OS 0.62 (0.46–0.85)	
		≥ 75 = 70/719 (10%)	OS 1.21 (0.69–2.12)	

and platinum-based chemotherapy as the current standard of care for PD-L1 < 50% in the absence of ICI contraindication (2–5). Patients aged > 65 years constitute around 45–55% of the clinical trial population, and they derive similar survival advantage with slightly higher frequency of grade 3 to 4 adverse events in comparison to doublet chemotherapy. However, compared to younger patients, older adults may obtain less benefit with ICI therapy [54]. For patients with contraindication to ICI, age should not preclude histology appropriate chemotherapy. Historically, single-agent chemotherapy improved survival and quality of life among elderly over BSC [55]. The IFCT-0501 trial demonstrated that the platinum-based chemotherapy offers a significant survival advantage to elderly patient aged ≥ 70 with NSCLC regardless of histology over single-agent chemotherapy [42]. Currently, pemetrexed-based regimen is preferred in non-squamous histology NSLCL based on better clinical outcomes [56]. On the other hand, weekly nab-paclitaxel-based chemotherapy, when compared to every 3 weeks of solvent-bound paclitaxel-based chemotherapy, showed a superior response rate in the squamous cell histology (41% vs. 24%; $p < 0.001$). Although there was no statistically significant difference in OS in the whole population, patients aged ≥ 70 years in the nab-paclitaxel-based chemotherapy had a more prolonged OS of 19.9 months compared to 10.4 months in the solvent-bound paclitaxel arm (HR 0.583; $p = 0.009$) [57]. This observed OS benefit in the elderly could be attributed to the tolerability of the weekly schedule.

Integrating Palliative and Best Supportive Care

The goals of therapy in older adults can span from curative intent of therapy which may include chemotherapy, biologic agents, surgery, and radiation to palliative intent systemic therapy, targeted radiation, and BSC for the control of pain and respiratory symptoms. Multiple prospective trials support the early use of palliative care (EPC) to improve quality of life without the loss of quantity of life in NSCLC [58–60]. The study by Temel et al. showed statistically and clinically meaningful improvements in quality of life and depression at 12 weeks. Patients enrolled had more accurate understanding of prognosis, higher rates of documentation of resuscitation preferences, and less aggressive care at the end of life. Further EPC also demonstrated longer OS over standard oncology care (11.6 months vs. 8.9 months, $p = 0.02$, respectively) [58].

Integrating EPC is considered a quality care benchmark in cancer care. This is especially true for NSCLC, older adults, and those with poor PS [22, 61]. Palliative care should be offered in addition to standard oncology care with the goal of managing distressing symptoms throughout the cancer care continuum in accordance with patient and caregiver social, cultural, and spiritual beliefs to help personalize treatment decisions and minimize risks of therapy-associated toxicity. The risk of polypharmacy and the drug interaction should be seriously considered while prescribing multiple medications. The palliative care team is best rendered by multidisciplinary team that has many of the same critical representation as a geriatric multidisciplinary team, e.g., social workers, nutritionists, pharmacists, and chaplains in addition the clinical team of physicians, advanced practice providers, and nurses. Supportive care for patients undergoing or not going antineoplastic therapy includes transfusion of blood products, nutritional support, growth factor support, antinausea medications, and antidiarrheal medications.

Role of Geriatric Assessment in the Management of Elderly Lung Cancer Patient, Current Status, and Recent Advances

Aging is associated with an overall decline physiologic function: older adults are at greater risk for sarcopenia, associated with adipose deposition in different organs, and decreased hepatic and renal drug clearance which leads to lower tolerance for chemical challenges such as antineoplastic therapy. The aging bone marrow can be further impacted due to increased half-life of lipophilic drugs leading to greater hematologic toxicity in the elderly [3]. Frailty means a state of increased vulnerability for morbidity and/or mortality when exposed to a stressor. Frailty has been associated with increased chemotherapy-related toxicity among older adults with advanced NSCLC [62•]. While frailty increases with age, it is independent of the chronological age and is evaluated in a multidisciplinary team [63].

Incorporating GA can help with better risk stratification than PS alone [64]. There are various validated tools for assessing GA as well as more comprehensive, abbreviated, and patient-reported versions [64–66, 67••]. While there can be subtle benefits to one instrument over another in a given clinical circumstance, any instrument that includes assessment of critical domains of function, mobility, falls, cognition, nutrition, social support, depression, comorbidity, polypharmacy, and geriatric syndromes can be used. Multiple studies have demonstrated the importance of GA in the management of patients with advanced cancer [65]. Initial studies were non-randomized studies demonstrating feasibility and validating GA instruments in diverse populations [67••, 68••, 69].

The elderly patients with ≥ 70 years, performance status of 0–2, and a stage IV NSCLC in the ESOGIA-GFPC-GECP 08–02 study were assigned between single vs doublet chemotherapy based on performance status and age. The study failed to demonstrate improvement in treatment

failure–free survival (TFFS) or OS with treatment allocation based on CGA but with reduced treatment toxicity and fewer treatment failures as a result of toxicity, which were considered significant secondary outcomes [70, 71]. Furthermore, body mass index of less than 20 kg/m^2, Charlson Comorbidity Index of ≥ 2, and existence of geriatric syndrome were associated with poor TFFS. The NVALT study analyzed pre-therapy comprehensive GA for association with adverse effects. GA-detected factors associated with toxicity included physical and role functioning, depression, and frailty [72]. Similarly, frailty was associated with worse outcomes in older adults treated with 2nd-line chemotherapy after progression on platinum-based chemotherapy [73]. In a pooled analysis of two trials in older adults of chemotherapy in advanced NSCLC, cognition assesses by the Mini-Mental State Examination scores were associated with OS (median OS of 21.2, 13.5, and 12.2 months for scores 30, 29–24, and ≤ 23 respectively) [74]. Furthermore, recent prospective studies have demonstrated the benefit of GA in reducing treatment-related toxicity, decreasing acute care utilization, and improving quality of life and survival in older adults with solid tumors including lung cancer [75–78]. Despite the evidence to the support its use, GA utilization and adoption is limited [79, 80]. There is greater need for education of providers to promote adoption and utilization of GA in the management of older adults with lung cancer.

Conclusions

Older adults who represent a majority of patients with lung cancer stand to benefit from the many recent advancements in treatment, especially the newer pharmacologic agents with favorable toxicity profiles compared to conventional chemotherapy. The checkpoint inhibitors have improved outcomes in stage III and IV disease; the widespread availability of testing for actionable mutations and the newer therapeutic options for mutant NSCLC has also facilitated management of care among older adults. Timely integration of palliative care is especially important in older adults with advanced disease or declining PS. Incorporating GA to better risk-stratify older adults and individualize management decisions is the current standard although not always met in practice. Ongoing efforts at education regarding the value of GA and incorporating GA into routine clinical practice can further improve patient outcomes in older adults with NSCLC.

Declarations

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.

Conflict of Interest Alina R. Basnet declares that she has no conflict of interest. Asrar Alahmadi declares that he has no conflict of interest. Ajeet Gajra has been an employee of and has owned stock in Cardinal Health, and has also been an employee of ICON plc.

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•• Of major importance

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