Treatment at Twilight: An Analysis of Therapy Patterns and Outcomes in Adults 80 Years and Older With Advanced or Metastatic NSCLC

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ABSTRACT

Introduction: The aim of this study is to evaluate treatment patterns, survival outcomes, and factors influencing systemic treatment decisions in adults 80 years and older with NSCLC.

Methods: This was a retrospective National Cancer Database study evaluating outcomes in adults aged 80 years and older with advanced NSCLC. Patients were analyzed on the basis of systemic therapy, including none, chemotherapy or immunotherapy (IO) alone, and chemotherapy plus IO (chemotherapy + IO). Median overall survival (OS) was compared using Kaplan-Meier methodology. Hazard ratio with 95% confidence interval (CI) was used to assess differences in outcomes, and OR with 95% CI was used to assess factors contributing to systemic therapy provision.

Results: Patients 80 years and older (OR = 1.135 [95% CI: 1.127–1.142], $p = 0.000$), females (OR = 1.129 [95% CI: 1.085–1.175], $p < 0.001$), blacks (OR = 1.272 [95% CI: 1.179–1.372], $p < 0.001$), non-Hispanic whites (OR = 1.210 [95% CI: 1.075–1.362], $p = 0.002$), and those with increasing Charlson-Deyo Comorbidity Index score ($p < 0.001$) were less likely to receive systemic therapy. Median OS for no therapy, IO alone, chemotherapy alone, and chemotherapy plus IO was 2.63 (95% CI: 2.57–2.69), 10.68 (95% CI: 9.96–11.39), 12.35 (95% CI: 11.98–12.72), and 14.03 (95% CI: 13.87–14.88) months, respectively. In chemotherapy alone, mean OS was 1.12 months (95% CI: 0.55–1.70) ($p < 0.001$) longer with multiagent versus single agent. There was no difference between IO plus single agent versus IO plus multiagent chemotherapy (0.67 mo [95% CI −1.18 to 2.54], $p = 1.00$).

Conclusions: Age, comorbidities, patient race, and sex affected systemic therapy provision. Multiagent chemotherapy and chemotherapy plus IO significantly improved survival; with the latter, survival was similar with IO plus single or multiagent chemotherapy.

Introduction

NSCLC accounts for greater than 85% of lung cancer cases and is often considered a disease of older individuals, with many cases diagnosed after age 70 years and in an advanced stage.[1] In recent years, multiple trials, including KEYNOTE-021 (cohort G), KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, and KEYNOTE-407, revealed the efficacy and survival benefit of treating advanced or metastatic NSCLC with either

immunotherapy (IO) alone in patients who have a programmed death-ligand 1 (PD-L1) greater than or equal to 50% or in combination with doublet chemotherapy.[2–7] Despite the evolving treatment landscape, these therapies are not always feasible for the geriatric aged cohort, who were underrepresented in these pivotal trials. In addition to poor clinical trial recruitment, a myriad of factors including poor performance status, medical comorbidities, and treatment-limiting toxicities often requires a highly heterogeneous and individualized treatment approach. Moreover, elderly patients may have diminished therapeutic response to IO arising from immunosenescence, an unfortunate consequence of aging.[8] Although there may be a subset of elderly patients who may endure and attain a survival benefit from the current standard-of-care chemotherapy plus IO, efficacy may be limited to the ability to tolerate therapy.[9,10]

In an era where IO is commonplace in the thoracic oncology treatment repertoire, identifying treatment patterns and outcomes in older patients with NSCLC is needed to inform on therapeutic strategies and to optimize patient outcomes. This study aims to evaluate treatment patterns and outcomes in patients 80 years and older with NSCLC through data provided by the National Cancer Database (NCDB).

Materials and Methods

National Cancer Database

This was a retrospective analysis using data provided by the NCDB. Release of deidentified patient data was provided by the NCDB after approval of the requested study protocol and data analysis plan. Because this was a retrospective database studied involving an aggregate of deidentified patient data from across the country, informed patient consent and approval from an institutional review board were not necessary. The NCDB is a large, hospital-based database with information reported in patients in the United States who received treatment by American College of Surgeons' Commission on Cancer (CoC)–accredited program and coded according to the Facility Oncology Registry Data Standards Manual. Patient inclusion into this database is dependent on CoC accreditation, which is held by more than 1500 cancer centers ranging from community to academic facilities. The NCDB is jointly administered by the American Cancer Society and the American College of Surgeons CoC and is estimated to encompass approximately 80% of all newly diagnosed cases of lung cancer in the United States and Puerto Rico.[11–13]

Study Design

Following written protocol approval by the NCDB, a Participant Use Data File was provided for all patients diagnosed with NSCLC from 2004 to 2018 with coding in accordance with the International Classification of Diseases for Oncology, third edition. The primary aim of this study was to compare outcomes between patients who received no therapy, chemotherapy alone, chemotherapy plus IO, or IO alone. Secondary objectives included assessment of whether there was a difference in outcomes for patients who received single-agent chemotherapy versus combination chemotherapy in the chemotherapy and chemotherapy plus IO arms, and whether the additional supplementation of nonsystemic therapies further improved survival outcomes. Finally, assessment of demographic, geographic, and socioeconomic factors and their relationship to systemic therapy provision and outcomes was assessed.

Adults 80 years and older with advanced-stage (III or IV) NSCLC diagnosed between 2015 and 2018 were included. Patients were excluded if they had stage I or II disease, unknown stage, unknown systemic treatment status, missing/unknown pathologic confirmation of NSCLC, neuroendocrine or epithelial tumors, year of diagnosis between 2004 and 2014, and unknown last follow-up status (Fig. 1). Pertinent demographic factors assessed included biological sex (male/female), race (non-Hispanic white, black, Hispanic, Asian, other), insurance status (Medicare, Medicaid, private, uninsured, "other government," unknown), treatment center (community hospital, community network, academic, integrated cancer network), geographic location (West, Midwest, South, Northeast), and the Charlson-Deyo Comorbidity Index (CDCC), an age-independent prognostic calculator with scores of 0, 1, 2, and greater than or equal to 3.[14] The CDCC score is based on reported International Classification of Diseases, Ninth Revision, and International Classification of Diseases, Tenth Revision, scores and includes the following diagnoses: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia/paraplegia, renal disease, moderate or severe liver disease, and acquired immunodeficiency syndrome. Geographic location was allocated into four distinct regions as follows: West (Pacific/Mountain); South (West South Central/East South Central/South Atlantic); Northeast: (New England/Middle Atlantic); and Midwest (West North Central/East North Central). Cancer-specific information included reported stage group (III/IV), NSCLC subtype (squamous cell carcinoma [SCC], adenocarcinoma, large cell carcinoma, adenosquamous carcinoma, NSCLC not otherwise specified [NOS]), and metastatic regions at diagnosis (distant lymph nodes, bones, brain, liver, distant lung, and other generalized
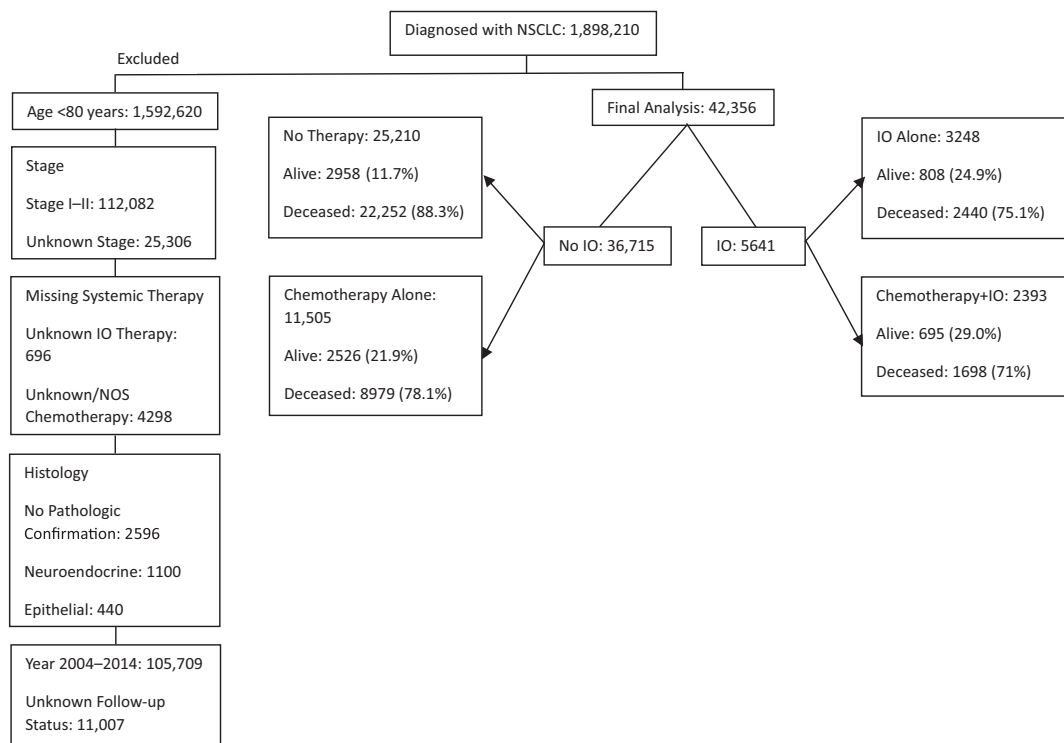
Figure 1. Consort diagram. IO, immunotherapy; NOS, not otherwise specified.

metastatic regions, which were reported from 2016 onward).

Patients were dichotomized according to their initial systemic treatment status, including none, IO alone, chemotherapy alone, and chemotherapy plus IO. Treatment subgroup analysis also included whether the chemotherapy-alone group received single-agent or multiagent therapy and whether chemotherapy plus IO received single-agent or multiagent chemotherapy with IO and the impact on survival differences. Additional individual supplemental provision of radiation, primary surgery, and non-primary surgeries were assessed. Demographic factors that increased the likelihood of withholding systemic therapies were also analyzed.

Statistical Analysis

Descriptive statistics were reported as medians for continuous variables and as frequencies and percentages for categorical variables. Differences in patient-level characteristics for NSCLC were compared with Pearson's chi-square test with continuity correction or Fisher's exact test. Cox proportional hazard model using hazard ratio (HR) was used to compare the association of survival times between patient-level characteristics and systemic therapies provided. OR assessed the association between patient demographic factors and the likelihood of withholding systemic therapies. The chi-square test was used to assess the significance of the differences. Median

overall survival (OS) was assessed through Kaplan-Meier methodology, and differences in survival were compared by the log-rank test. Assessment of mean OS difference between treatment arms including none, IO only, chemotherapy (both single agent and multiagent) only, and chemotherapy plus IO (both single agent and multiagent chemotherapy) was conducted by the Bonferroni method. Descriptive statistics using 95% confidence interval (CI) were used for OS and HR. For the above-reported comparisons, a two-sided p value of less than 0.05 was considered statistically significant.

Results

Of 1,898,210 patients with NSCLC, 42,356 (2.2%) met complete inclusion criteria (Fig. 1). Baseline demographics are reported in Table 1. The median age of the cohort was 83 (83–90) years, and 28,983 (68.4%) ranged from ages 80 to 85 years. There were 21,934 (51.8%) males, and 35,653 (84.2%) patients were white. A total of 37,738 (89.1%) were insured with Medicare, and 18,515 (43.7%) received treatment at a community network-based CoC-accredited institution. There were 24,311 (57.4%) that had a baseline CDCC score of 0, and 14,383 (33.9%) patients were geographically located in the Southern United States. The two most common NSCLC subtypes were SCC in 11,350 (26.8%) and adenocarcinoma in 26,314 (62.1%) patients. A total of 29,698 (70.1%) had stage IV disease. The most

Table 1. Baseline Demographics Dichotomized According to Systemic Therapy Received

Treatment History	IO Only (n = 3248)	Chemotherapy + IO (n = 2393)	Chemotherapy Alone (n = 11,505)	No Therapy (n = 25,210)	Total (N = 42,356)
Median age (y)	84 (80-90)	82 (80-90)	83 (80-90)	84 (80-90)	83 (80-90)
80-85 y	2173 (66.9)	1977 (82.6)	9110 (79.2)	15,723 (62.4)	28,983 (68.4)
86 to >90 y	1075 (33.1)	416 (17.4)	2395 (20.8)	9487 (37.6)	13,373 (31.6)
Sex					
Male	1643 (50.6)	1379 (57.6)	6135 (53.3)	12,777 (50.7)	21,934 (51.8)
Female	1605 (49.4)	1014 (42.4)	5370 (46.7)	12,433 (49.3)	20,422 (48.2)
Race					
White	2821 (86.9)	2075 (86.7)	9670 (84.1)	21,087 (83.6)	35,653 (84.2)
Black	189 (5.8)	149 (6.2)	870 (7.6)	2179 (8.6)	3387 (8.0)
Asian	124 (3.8)	76 (3.2)	495 (4.3)	806 (3.2)	1501 (3.5)
Hispanic	80 (2.5)	63 (2.6)	341 (2.9)	845 (3.4)	1329 (3.5)
Other	34 (1.0)	30 (1.2)	129 (1.1)	293 (1.2)	486 (1.1)
Insurance					
Medicare	2947 (90.7)	2168 (90.6)	10,260 (89.2)	22,363 (88.7)	37,738 (89.1)
Medicaid	32 (1.0)	20 (0.8)	128 (1.1)	381 (1.5)	561 (1.3)
Private	194 (6.0)	149 (6.2)	810 (7.0)	1699 (6.7)	2852 (6.7)
Other	37 (1.1)	26 (1.1)	157 (1.4)	306 (1.2)	526 (1.2)
Uninsured	12 (0.4)	8 (0.3)	38 (0.3)	153 (0.6)	211 (0.5)
Unknown	26 (0.8)	22 (0.9)	112 (0.9)	308 (1.2)	468 (1.2)
Hospital type					
Community	267 (8.2)	192 (8.0)	934 (8.1)	2364 (9.4)	3757 (8.9)
Comm/network	1335 (41.1)	1096 (45.8)	4861 (42.2)	11,223 (44.6)	18,515 (43.7)
Academic	958 (29.4)	634 (26.5)	3399 (29.5)	6064 (24.0)	11,055 (26.1)
Integrated network	688 (21.2)	471 (19.7)	2311 (20.1)	5559 (22.0)	9029 (21.3)
CDCC score					
0	1916 (59.0)	1489 (62.2)	7211 (62.7)	13,695 (54.3)	24,311 (57.4)
1	713 (21.9)	476 (19.9)	2483 (21.6)	5673 (22.5)	9345 (22.1)
2	318 (9.8)	240 (10.0)	1013 (8.8)	3074 (12.2)	4645 (10.9)
>3	301 (9.3)	188 (7.9)	798 (6.9)	2768 (10.9)	4055 (9.6)
Geographic regions[a]					
West	583 (18.0)	358 (14.9)	1839 (15.9)	4155 (16.5)	6935 (16.4)
Midwest	804 (24.7)	646 (27.0)	3061 (26.6)	6703 (26.6)	11,214 (26.5)
South	1008 (31.0)	854 (35.7)	3796 (33.0)	8725 (34.6)	14,383 (33.9)
Northeast	853 (26.3)	535 (22.4)	2809 (24.4)	5627 (22.3)	9824 (23.2)
NSCLC subtype					
SCC	788 (24.3)	471 (19.7)	3072 (26.7)	7019 (27.8)	11,350 (26.8)
Adenocarcinoma	2180 (67.1)	1755 (73.3)	7204 (62.6)	15,175 (60.2)	26,314 (62.1)
Adenosquamous	38 (1.2)	30 (1.2)	155 (1.3)	298 (1.2)	521 (1.2)
Large cell	86 (2.6)	62 (2.6)	416 (3.6)	914 (3.6)	1478 (3.5)
NSCLC, NOS	156 (4.8)	75 (3.1)	658 (5.7)	1804 (7.1)	2693 (6.4)
Analytical stage group					
3	545 (16.7)	647 (27.0)	4772 (41.5)	6692 (26.5)	12,656 (29.9)
4	2703 (82.2)	1746 (73.0)	6733 (58.5)	18,518 (73.5)	29,700 (70.1)
Metastatic sites					
Distant lymph nodes	361 (11.1)	200 (8.4)	576 (5.0)	1334 (5.3)	2471 (5.8)
Bone	982 (30.2)	639 (26.7)	1834 (15.9)	4720 (18.7)	8175 (19.3)
Brain	385 (11.8)	232 (9.7)	812 (7.0)	2135 (8.5)	3564 (8.4)
Liver	347 (10.7)	199 (8.3)	659 (5.7)	2166 (8.6)	3371 (7.9)
Distant lung	823 (25.3)	452 (18.9)	1555 (13.5)	4147 (16.4)	6977 (16.5)
Other sites	949 (29.2)	540 (22.5)	1761 (15.3)	5505 (21.8)	8755 (20.7)
Non-primary site surgery	104 (3.2)	70 (2.9)	295 (2.5)	600 (2.4)	1069 (25.2)
Primary site surgery	57 (1.7)	75 (3.1)	645 (5.6)	911 (3.6)	1688 (3.9)
Radiation	1345 (41.4)	974 (40.7)	4778 (41.5)	8176 (32.4)	15,273 (36.1)

*Note:* All values are n (%) unless otherwise specified.

[a]Geographic region is classified as follows: West: Pacific/Mountain; South: West South Central/East South Central/South Atlantic; Northeast: New England/Middle Atlantic (Northeast); Midwest: West North Central/East North Central.

CDCC, Charlson-Deyo Comorbidity Index; IO, immunotherapy; NOS, not otherwise specified; SCC, squamous cell carcinoma.

frequently reported metastatic sites were bone in 8175 (19.3%) and brain in 3564 (8.4%) patients (Table 1). Of 13,897 patients with documented metastatic sites, 2576 (18.5%) had three or more metastatic sites of disease at diagnosis. Descriptive demographic difference by sex and race can be found in Supplementary Tables 1 and 2, respectively.

A total of 3248 (7.7%) received IO alone, 11,505 (27.2%) received chemotherapy alone, 2393 (5.6%) received chemotherapy plus IO, and 25,210 (59.5%) received no systemic therapy. Of the 2393 who received chemotherapy plus IO, 342 (14.3%) received single-agent chemotherapy, and of the chemotherapy alone group, 3469 (30.1%) received single-agent chemotherapy. Between 2015 and 2018, the number of patients who did not receive systemic therapy decreased from 64.6% to 52.9%, and the number of patients who received chemotherapy only decreased from 31.7% to 20.6%, respectively (Fig. 2). Between 2015 and 2018, the number of patients who received IO alone increased from 1.1% to 14.3%, and that of patients who received chemotherapy plus IO rose from 2.2% to 12.0%, respectively (Fig. 2). Radiation was given to 32.4%, 41.5%, 41.4%, and 40.7%, and primary or non-primary surgery was performed in in 3.6%, 5.6%, 1.7%, and 3% of patients who received no systemic therapy, chemotherapy alone, IO alone, or chemotherapy plus IO, respectively (Table 1 and Supplementary Fig. 1). Rates of primary site surgery, non-primary site surgery, and radiation remained similar each year (Fig. 2). The median time from diagnosis to initiation of systemic therapy for chemotherapy alone was 134 (0–159) days, and for IO alone was 46 (0–449) days. For chemotherapy plus IO, median time was 42 (0–678) days for the

chemotherapy component and 68 (0–866) days for the IO component. When assessing median time to initiation by stage, initiation of chemotherapy and IO was 49 (2–676) days and 133 (6–866) days for stage III and 41 (0–442) and 53 (0–835) days for stage IV disease. Time to systemic therapy initiation by hospital type was 44 (0–449) days for community hospitals, 42 (0–474) days at comprehensive cancer networks, 43 (0–1159) days at integrated networks, and 46 (0–678) days at academic hospitals. A total of 1688 (3.9%) patients received a reported primary site surgery, of which 1268 (75.1%) were stage III. Of patients who received primary site surgery, 911 (53.8%) did not receive systemic therapy, 57 (3.4%) received IO alone, 645 (38.2%) received chemotherapy, and 75 (4.4%) received chemotherapy plus IO. Of these patients, 701 received therapy after surgery, 15 received perioperative therapy, and 61 received systemic therapy before surgery. Of the 911 who received a primary site surgery but no systemic therapy, 450 (49.4%) received radiation therapy. Of the 57 who received IO with surgery, 29 (50.9%) patients also received radiation. Of the 1069 patients who received non-primary site surgery, 1688 who received primary site surgery, and 15,199 who received radiation, 600 (56.1%), 911 (53.9%), and 8176 (53.5%), respectively, did not receive systemic therapy as front-line therapy (Supplementary Fig. 1). For patients who received radiation, 62 (0.40%) received treatment before surgery, 791 (52%) received it after surgery, and nine (0.06%) received radiation before and after surgery. A total of 3205 (21.9%) received palliative radiation therapy with palliative care intent, whereas 11,935 (78.1%) patients received radiation that was with non-palliative intent (Supplementary Table 3).
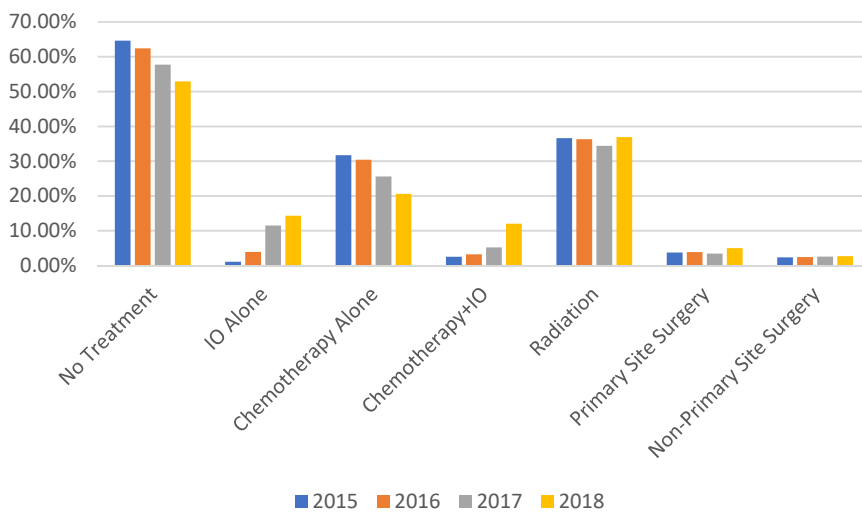
Figure 2. Proportion of patients who received systemic therapy, radiation, and surgical treatments over time. IO, immunotherapy.

Table 2. Demographic Factors Associated With Likelihood of Receiving Systemic Therapies

Covariate	OR	95% CI	p Value
Age[a]	1.135	1.127-1.142	0.000
Sex			
Male	Ref	Ref	Ref
Female	1.129	1.085-1.175	<0.001
Race			
Non-Hispanic white	Ref	Ref	Ref
Black	1.272	1.179-1.372	<0.001
Asian	0.779	0.698-0.870	<0.001
Other	1.142	0.947-1.378	0.165
Hispanic	1.210	1.075-1.362	<0.001
Treatment center			
Community	Ref	Ref	Ref
Community network	0.896	0.832-0.965	<0.001
Academic/research	0.727	0.672-0.786	<0.001
Integrated network	0.924	0.852-1.001	0.053
Geographic region			
Midwest	Ref	Ref	Ref
Northeast	0.925	0.873-0.979	0.007
South	1.047	0.993-1.103	0.088
West	1.002	0.939-1.070	0.944
Insurance status			
Uninsured	Ref	Ref	Ref
Private	0.534	0.388-0.733	<0.001
Medicaid	0.786	0.550-1.123	0.186
Medicare	0.495	0.363-0.674	<0.001
Other government	0.506	0.355-0.722	<0.001
Unknown	0.718	0.499-1.034	0.075
CDCC score			
0	Ref	Ref	Ref
1	1.232	1.172-1.294	<0.001
2	1.558	1.456-1.666	<0.001
≥3	1.669	1.580-1.827	<0.001

Note: Higher OR denotes a higher likelihood of withholding systemic therapies.
[a]Per year increase in age is associated with increasing likelihood of withholding systemic therapy.
CDCC, Charlson-Deyo Comorbidity Index; CI, confidence interval; Ref, reference.

There were 25,210 patients who did not receive any therapy. Median age of this cohort was 84 (80–90) years, of which 15,723 (62.4%) were aged 80 and 85 years. A total of 12,433 (49.3%) of these patients were females, 21,077 (83.6%) were white, and 22,363 (88.7%) were insured with Medicare. There were 11,223 (44.6%) patients treated at a community/network hospital, and 13,694 (54.3%) had a CDCC score of 0. Adenocarcinoma was the most common NSCLC subtype reported in 15,175 (60.2%), and 18,518 (73.5%) had stage IV disease. On assessment of factors that were associated with the decision to withhold treatment, factors that increased the likelihood of receiving no systemic therapy included increasing age at diagnosis (OR = 1.135 [95% CI: 1.127–1.142], $p = 0.000$), females (OR = 1.129 [95% CI: 1.085–1.175], $p < 0.001$), blacks (OR = 1.272 [95% CI: 1.179–1.372], $p < 0.001$),

Hispanics (OR = 1.210 [95% CI: 1.075–1.362), and CDCC score of 1 (OR = 1.232 [95% CI: 1.172–1.294], $p < 0.001$), 2 (OR = 1.558 [95% CI: 1.456–1.666], $p < 0.001$), and 3 (OR = 1.669 [95% CI: 1.580–1.827], $p < 0.001$). Asians (OR = 0.779 [95% CI: 0.698–0.870], $p < 0.001$), Medicare insurance (OR = 0.495 [95% CI: 0.363–0.674], $p < 0.001$), other government insurance (OR = 0.506 [95% CI: 0.355–0.722], $p < 0.001$), private insurance (OR = 0.534 [95% CI: 0.388–0.733], $p < 0.001$), treatment at an academic institution (OR = 0.727 [95% CI: 0.672–0.786], $p < 0.001$) or a comprehensive community network (OR = 0.896 [95% CI: 0.832–0.965], $p < 0.001$), and patients receiving treatment in the Northeastern United States (OR = 0.925 [95% CI: 0.873–0.979], $p = 0.007$) were less likely to have systemic therapy withheld (Table 2).

Outcomes

Median OS for no therapy, IO alone, chemotherapy alone, and chemotherapy plus IO was 2.63 (95% CI: 2.57–2.69), 10.68 (95% CI: 9.96–11.39), 12.35 (95% CI: 11.98–12.72), and 14.03 (95% CI: 13.87–14.88) months, respectively (Fig. 3A). Median OS for patients who received IO compared to those that did not was 12.250 (95% CI: 11.704–12.796) and 4.570 (95% CI: 4.470–4.670) ($p = 0.000$) months, respectively (Fig. 3B). Receipt of IO (HR = 0.377 [95% CI: 0.361–0.393], $p = 0.000$), chemotherapy (HR = 0.439 [95% CI: 0.426–0.452], $p = 0.000$), and chemotherapy plus IO (HR = 0.345 [95% CI: 0.328–0.363], $p = 0.000$) (Table 3) improved outcomes compared with no systemic therapy. When comparing mean survival differences between the systemic treatment arms, chemotherapy alone and chemotherapy plus IO had a 2.48 (95% CI: 1.82–3.13) ($p < 0.001$) and 1.9 (95% CI: 1.01–2.78) ($p < 0.001$) month longer mean OS, respectively, compared with IO alone. In patients treated with chemotherapy alone, patients who received multiagent chemotherapy lived on average 1.12 months (95% CI: 0.55–1.70) ($p < 0.001$) longer compared with single-agent chemotherapy. There was no survival difference in patients who received either chemotherapy alone or chemotherapy plus IO (0.57 mo [95% CI: 0.16–1.31], $p = 0.234$). Moreover, there was no mean survival difference found if patients received IO plus single-agent chemotherapy versus IO plus multiagent chemotherapy (0.67 mo [95% CI: −1.18 to 2.54], $p = 1.00$) (Fig. 4).

Median OS for patients who received systemic therapy plus radiation versus no radiation was 13.540 (95% CI: 13.004–14.076) and 11.530 (95% CI: 11.157–11.903) months; for patients who received systemic therapy plus primary site surgery versus no surgery was 30.190 (95% CI: 26.544–33.836) versus 11.860 (95% CI: 11.568–12.152) months; for patients who received
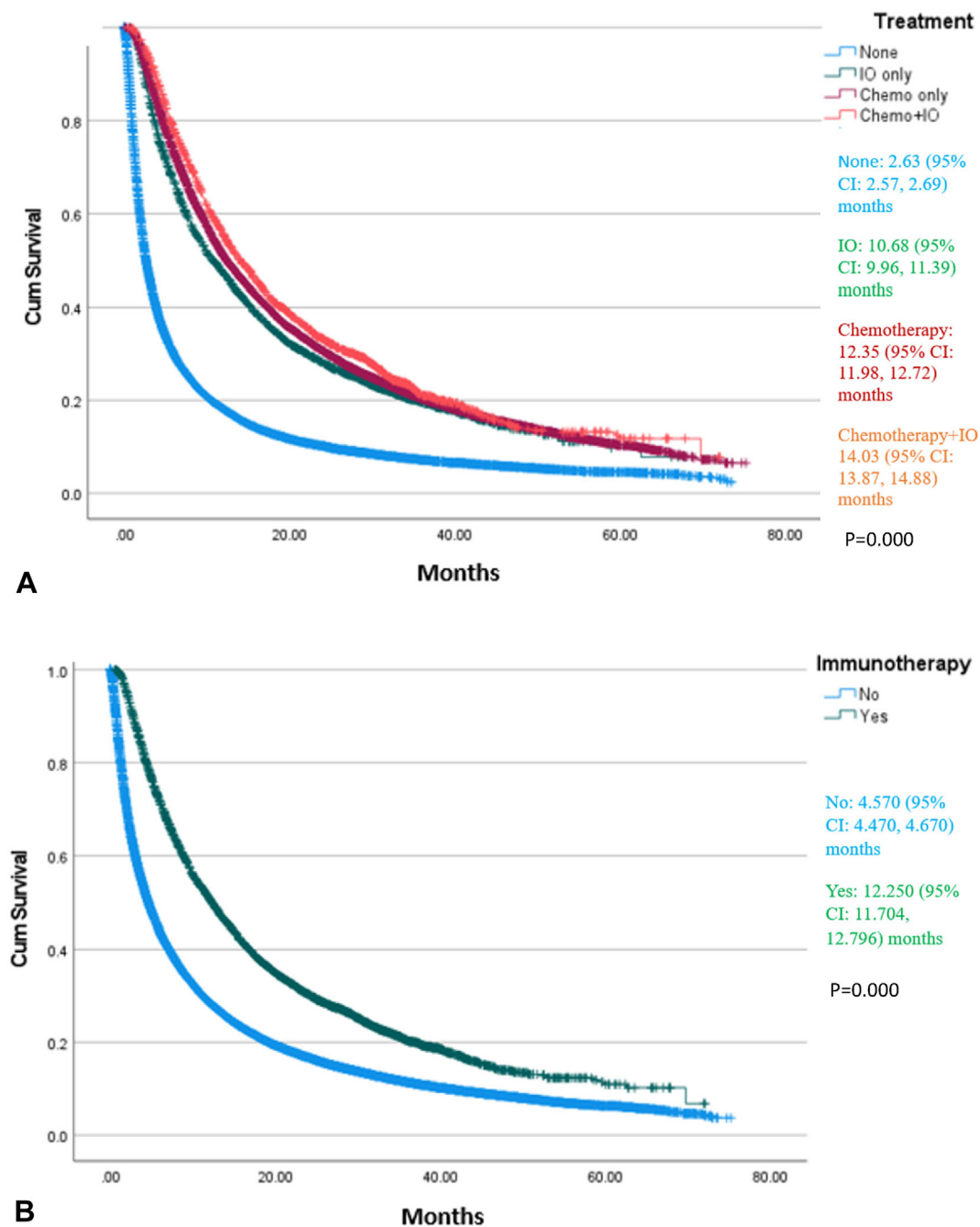
Figure 3. (*A*) Median OS for different systemic therapies. (*B*) Median OS difference with receipt of IO versus no IO. Chemo, chemotherapy; CI, confidence interval; IO, immunotherapy; OS, overall survival.

systemic therapy plus non-primary site surgery versus no surgery was 14.520 (95% CI: 12.613–16.427) versus 12.290 (95% CI: 11.980–12.600) (Supplementary Table 4). Treatment with radiation (HR: 0.664 [95% CI: 0.649–0.679], $p < 0.001$), primary site surgery (HR: 0.495 [95% CI: 0.465–0.527], $p < 0.001$), non-primary surgery (HR: 0.867 [95% CI: 0.811–0.927], $p < 0.001$), and receipt of IO versus no IO (HR: 0.912 [95% CI: 0.873–0.954], $p < 0.001$) improved the outcomes (Table 3 and Fig. 3*B*). For patients who did not receive any systemic therapy but received other treatment modalities, median OS improved with radiation versus no radiation (5.160 [95% CI: 4.968–5.352] versus 1.87 [95% CI: 1.827–1.913] mo, $p < 0.001$), primary site surgery versus no surgery (16.690 [95% CI: 14.411–18.969] versus 2.500 [95% CI: 2.444–2.556], $p < 0.001$), or non-primary site surgery versus no surgery (3.150 [95% CI: 2.817–3.483] versus 2.600 [95% CI: 2.540–

Table 3. Demographic and Treatment Prognostic Factors on Patient Outcomes

Covariate	HR	95% CI	p Value
Age[a]	1.009	1.006-1.013	<0.001
Sex			
Male	Ref	Ref	Ref
Female	0.825	0.808-0.843	<0.001
Race			
Non-Hispanic white	Ref	Ref	Ref
Black	0.917	0.882-0.954	<0.001
Asian	0.768	0.723-0.817	<0.001
Other	0.877	0.793-0.971	<0.001
Hispanic	0.827	0.776-0.882	<0.001
Treatment center			
Community	Ref	Ref	Ref
Community network	1.021	0.982-1.061	0.294
Academic/research	0.908	0.871-0.946	<0.001
Integrated network	1.034	0.992-1.07	0.115
Geographic region			
Midwest	Ref	Ref	Ref
Northeast	0.899	0.872-0.926	<0.001
South	0.921	0.896-0.946	<0.001
West	0.897	0.867-0.948	<0.001
Insurance status			
Uninsured	Ref	Ref	Ref
Private	0.866	0.740-1.014	0.75
Medicaid	0.775	0.648-0.927	0.005
Medicare	0.866	0.743-1.009	0.065
Other government	0.851	0.712-1.018	0.078
Unknown	0.924	0.770-1.107	0.391
CDCC score			
0	Ref	Ref	Ref
1	1.166	1.136-1.197	<0.001
2	1.224	1.183-1.266	<0.001
≥3	1.331	1.284-1.380	<0.001
NSCLC subtype			
Large cell	Ref	Ref	Ref
Adenocarcinoma	0.789	0.745-0.836	<0.001
SCC	0.845	0.797-0.897	<0.001
Adenosquamous	0.913	0.819-1.018	0.101
Other/NOS	0.944	0.882-1.011	0.102
Stage			
III	Ref	Ref	Ref
IV	1.833	1.787-1.879	0.000
Metastatic sites[a]			
Distant lymph nodes			
No	Ref	Ref	Ref
Yes	0.754	0.654-0.869	<0.001
Bone			
No	Ref	Ref	Ref
Yes	0.997	0.899-1.105	0.997
Brain			
No	Ref	Ref	Ref
Yes	0.740	0.516-1.061	0.101
Liver			
No	Ref	Ref	Ref
Yes	1.133	0.985-1.303	0.081
Contralateral lung			
No	Ref	Ref	Ref
Yes	0.804	0.728-0.888	<0.001

(continued)

Table 3. Continued

Covariate	HR	95% CI	p Value
Number of metastatic sites[a]			
1	Ref	Ref	Ref
2	1.263	1.122-1.421	<0.001
≥3	1.856	1.502-2.293	<0.001
Treatment			
None	Ref	Ref	Ref
IO alone	0.377	0.361-0.393	0.000
Chemotherapy alone	0.439	0.426-0.452	0.000
Chemotherapy + IO	0.345	0.328-0.363	0.000
Receipt of IO			
No	Ref	Ref	Ref
Yes	0.912	0.873-0.954	<0.001
Non-primary surgery			
No	Ref	Ref	Ref
Yes	0.867	0.811-0.927	<0.001
Unknown	0.856	0.488-1.503	0.589
Primary site surgery			
No	Ref	Ref	Ref
Yes	0.495	0.465-0.527	<0.001
Unknown	0.725	0.575-0.915	0.007
Radiation			
No	Ref	Ref	Ref
Yes	0.664	0.649-0.679	<0.001
Unknown	0.851	0.787-0.920	<0.001

[a]Analysis on specific metastatic sites and number of metastatic sites was only done in patients with reported stage IV disease.
CDCC, Charlson-Deyo Comorbidity Index; CI, confidence interval; HR, hazard ratio; IO, immunotherapy; NOS, not otherwise specified; Ref, reference.

2.660] mo, $p = 0.002$). Finally, median OS for patients who received no systemic therapy, radiation, or surgery compared with median OS for receipt of any type of therapy was 1.810 (95% CI: 1.767–1.853) versus 9.430 (95% CI: 9.232–9.628) months, respectively ($p = 0.000$). Additional survival differences can be found in Supplementary Figure 2*A* to *I* of the Supplementary Appendix.

Multiple factors influenced patient outcomes. Treatment at an academic hospital (HR: 0.91 [95% CI: 0.87–0.95], $p < 0.001$), females (HR = 0.82 [95% CI: 0.81–0.84], $p < 0.001$), and adenocarcinoma (HR = 0.79 [95% CI: 0.74–0.84], $p < 0.001$) and SCC (HR = 0.84 [95% CI: 0.80–0.90, $p < 0.001$] improved outcomes (Table 3). Geographically, patients in the Northeastern (HR = 0.90 [95% CI: 0.87–0.93], $p < 0.001$), Southern (HR = 0.92 [95% CI: 0.89–0.94], $p < 0.001$), and Western (HR = 0.89 [95% CI: 0.88–0.93], $p < 0.001$) United States had better OS compared with the patients in the Midwest. Compared with non-Hispanic whites, blacks (HR = 0.92 [95% CI: 0.88–0.85], $p < 0.001$), Asians (HR = 0.77 [95% CI: 0.72–0.82], $p < 0.001$), Hispanics (HR = 0.83 [95% CI: 0.78–0.88], $p < 0.001$), and others (HR = 0.88 [95% CI: 0.79–0.97]) had improved OS (Table 3). Per year increase in age (HR = 1.009 [95% CI:
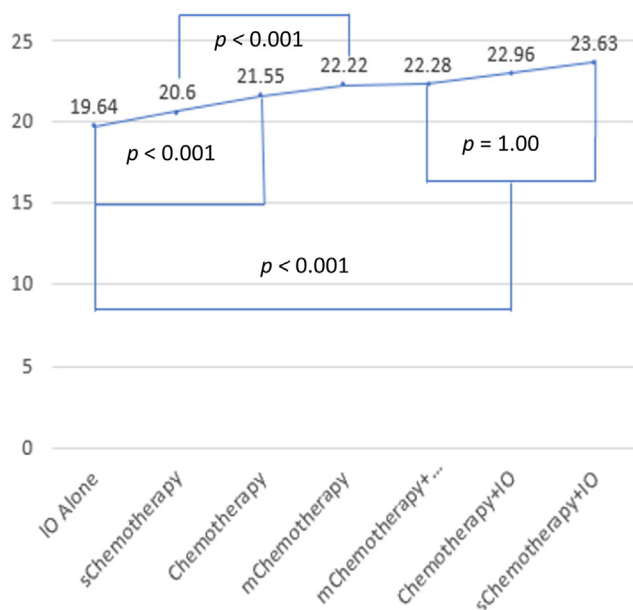
Figure 4. Mean differences in survival based on systemic therapy provisions. IO, immunotherapy; Mchemotherapy, multiagent chemotherapy; Schemotherapy, single-agent chemotherapy.

1.006–1.013], $p < 0.001$), patients with CDCC score of 1 (HR = 1.16 [95% CI: 1.14–1.19], $p < 0.001$), 2 (HR = 1.22 [95% CI: 1.18–1.27], $p < 0.001$), and 3 and higher (HR = 1.33 [95% CI: 1.284–1.380], $p < 0.001$) compared with 0, and stage IV NSCLC (HR = 1.83 [95% CI: 1.79–1.88], $p = 0.000$) had poorer survival (Table 3). Metastatic sites and number of metastatic sites also affected the outcomes; patients with distant lymph nodes (HR = 0.754 [95% CI: 0.654–0.869) compared with no lymph node metastasis ($p < 0.001$) and patients with contralateral lung metastasis (0.804 [95% CI: 0.728–0.88) versus no lung metastasis ($p < 0.001$) had better outcomes. Compared with a single metastatic site, patients with two (HR = 1.263 [95% CI: 1.122–1.421], $p < 0.001$) and three or more (HR = 1.856 [95% CI: 1.502–2.293], $p < 0.001$) metastatic sites had poorer outcomes (Table 3). Median OS for individual demographic factors can be found in Supplementary Table 4 and Supplementary Figure 2A to J.

Discussion

Our study of older individuals with advanced NSCLC was most notable for the following findings: (1) A large number (59.5%) of patients aged 80 years and older did not receive systemic therapy. (2) There was a clear survival advantage with utilization of any systemic therapy compared with no therapy. (3) There was no significant survival difference when using IO plus single-agent chemotherapy versus IO plus multiagent chemotherapy ($p = 1.00$), but there was a small yet significant benefit when using multiagent chemotherapy versus single-agent chemotherapy in the absence of IO ($p < 0.001$). (4) Radiation, primary site surgery, and non-primary site surgery resulted in a survival advantage, regardless if systemic therapy was used. (5) Increasing age, Hispanic and black individuals, females, a increasing CDCC score, and lack of insurance were factors that affected the decision to withhold therapies. (6) Although females and racial minorities were less likely to receive systemic therapy, these cohorts had better outcomes compared with males and non-Hispanic whites. In addition, outcomes were better for those treated at academic hospitals, those who had insurance, received treatment in non-Midwest regions of the United States of America, received IO as part of their systemic therapy, received radiation, or had any surgical interventions.

A growing number of studies are focusing on outcomes of elderly patients with NSCLC receiving systemic therapy. Several key trials emphasize the importance of providing systemic therapies to older patients. The ELVIS trial, which included patients with advanced NSCLC aged above or equal to 70 years, reported that single-agent vinorelbine improved OS by 7 weeks compared with best supportive care measures.[15] The IFCT-0501 phase 3 trial revealed that patients aged 70 to 89 years had significantly longer median OS (10.6 versus 6.2 mo) with platinum-based doublet chemotherapy compared with single-agent chemotherapy, but with an increased frequency of hematologic toxicities.[16] In a subgroup analysis of the ARIES cohort, treatment of bevacizumab with physician's choice chemotherapy improved outcomes in elderly patients including the cohort aged above or equal to 75 years, with similar adverse event rates across age cohorts.[17] These findings suggest that a multiagent regimen confers significant benefits to older patients. Our data further supports the benefit of multiagent therapy in patients aged 80 years and older; however, although statistically significant, patients who received a multiagent chemotherapy regimen lived on average 1.12 months (95% CI: 0.55–1.70) longer than those with single-agent therapy. This modest benefit in OS may have been a direct influence on multiagent therapy, but it may have been influenced by patient performance status, comorbidities, patient preference, patient age, or treatment tolerance. Additional studies in this patient age cohort are needed to further corroborate this finding.

IO is a widely used therapy in NSCLC, but due to under-representation of the geriatric population in the pivotal trials, IO efficacy in this population needs to be further elucidated. Age-related decline of the immune system, also known as "immunosenescence," is believed to mitigate the benefit of IO in elderly patients and has been reported in cohorts of patients aged above or equal

to 75 years.[8,9,17] Nevertheless, recent data still suggest that IO benefits patients entering the geriatric age range. A retrospective study comparing chemotherapy to chemotherapy plus IO in patients aged 75 years and older found a survival benefit in the combination arm, but to a lesser degree in older patients.[9] A retrospective Japanese study found that patients aged above or equal to 75 years who received chemotherapy plus IO had poorer OS and progression-free survival compared with younger patients, particularly in the arm that received pemetrexed.[10] Although our study observed poorer outcomes in elderly patients who received IO alone compared with those who received chemotherapy alone or chemotherapy plus IO, it is important to note that other key trials in NSCLC are contradicting. In the KEYNOTE-024 study and its updated analysis, IO was found to improve survival over single-agent chemotherapy even at prolonged follow-up for patients with advanced NSCLC with PD-L1 score of 50% or greater and without EGFR/ALK mutations.[3,18] Of note, these patients had a minimum PD-L1 of 50% and a median age of 64.5 years. In a pooled analysis of patients older than 75 years from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies, IO alone in patients with PD-L1 more than or equal to 1% compared with chemotherapy had improved survival outcomes.[19] Although our analysis did reveal that IO utilization improves outcomes in patients 80 years and older, our data also revealed that patients who received IO alone had poorer OS compared with chemotherapy and chemotherapy plus IO. Our study did not have individual PD-L1 activity for the patients, so it is not known how this finding would have affected the results. Moreover, the poorer outcomes in IO alone may have been based off patient selection. Although CDCC score proportions were similar across the treatment groups, it is possible that patients who received IO alone had poorer performance status than those who had more aggressive therapies and thus more likely to have poorer outcomes.

Our data reveals that multiagent chemotherapy and chemotherapy plus IO have the best outcomes, with no differences found between single-agent chemotherapy plus IO versus multiagent chemotherapy plus IO. Chemotherapy plus IO is known to improve survival outcomes, but with more frequent potentially treatment-limiting toxicities, as reported in the KEYNOTE-021 and KEYNOTE-407 trials.[2,20] In a recent International Experts Panel Meeting by the Italian Association of Thoracic Oncology to review the available literature of IO in elderly patients with NSCLC, it was advised that single-agent IO be considered for patients 80 years and older with a PD-L1 greater than or equal to 50% in the first line. In addition, chemotherapy plus IO can be considered in select cases.[21] Nevertheless, as with many

studies, patients 80 years and older are underrepresented in clinical trials, and so, these recommendations are driven by limited data. Although our findings suggest that IO plus single-agent chemotherapy confers similar survival benefit compared with IO plus multiagent chemotherapy studies assessing toxicities, treatment adherence, and outcomes with this type of regimen, a prospective setting is needed in older patients. Ongoing trials (NCT04396457, NCT03293680, NCT03977194) assessing various IO alone or in combination with chemotherapy are awaited with anticipation.

Non-systemic therapies including radiation and surgery conferred further survival benefits in this study, which has also been found in other studies of older individuals. In a Surveillance, Epidemiology, and End Results (SEER)–based retrospective study that compared patients aged 65 to 74 years with patients age greater than 75 years with locally advanced NSCLC from 2004 to 2014, patients who underwent surgical intervention with or without adjuvant therapy had better survival compared with those who underwent chemoradiation, chemotherapy alone, radiation therapy alone, and best supportive care.[22] Chemoradiation therapy was found to improve survival compared with chemotherapy or radiation therapy alone. The survival benefit from chemoradiation was also revealed by a randomized, controlled, phase 3 trial by the Japanese Clinical Oncology Group (JCOG0301).[7,23] Our study illustrates the added benefit of primary site surgery, non-primary site surgery, and radiation therapy in the geriatric population with advanced/metastatic NSCLC. Given that this patient group represents a diverse population with varying comorbidities and performance statuses, careful selection of patients who would benefit from primary/non-primary site surgeries or radiation along with risk/benefit discussions is crucial. Furthermore, whether the recent pivotal results of the CheckMate 816 study assessing neoadjuvant chemo-IO can be extrapolated to the geriatric stage III population needs to be further elucidated, as the median age in the study arm was 64 (41–82) years.[24]

Our analysis revealed significant demographic disparities in older adults, which negatively influenced treatment provision and outcomes. Patients who were treated at an academic hospital, females, insured patients, and patients with adenocarcinoma or SCC all had improved outcomes. Patients who live in the Midwest, non-Hispanic whites, and patients with increasing age or CDCC score all had poorer outcomes. Furthermore, patients with increasing age or CDCC score, females, blacks, and Hispanics were more likely to not receive systemic treatment. Insured patients, Asians, and patients who were treated at an academic institution, comprehensive community network, or if residing within the

Northeastern region United States were less likely to not receive systemic treatment. The demographic disparities found here are consistent with younger age cohorts, suggesting these disparities exist irrespective of age. In a NCDB study looking at patients with stage III NSCLC from 2004 to 2013, black patients were found to have better survival than white patients.[25] Another NCDB study assessing octogenarians with stage III NSCLC from 2004 to 2013 found that advancing age, male sex, non-adenocarcinoma subtype, and stage IIIB NSCLC had poorer survival, whereas a CDCC of 0 and treatment at academic institution had better outcomes.[26] Other studies across age cohorts have also highlighted the benefit of receiving treatment at an academic program.[27,28] Demographic disparities persisting into older age are not unique to our study; a SEER-Medicare of patients older than 66 years with stage IV NSCLC from 2012 to 2015 found that patients with increasing age, black race, and greater than two comorbidities were less likely to receive systemic therapy.[29] Our study suggests that similar selection disparities persist through the advanced decades of life and into geriatric aged cohorts. Strategies are needed to ameliorate these disparities and augment systemic therapy provisions.

Although the large number of older patients included in this analysis allowed for a robust analysis and multiple subgroup analyses, limitations should be recognized. First, discrepancies in the data provided may exist given this is a hospital-based database only including CoC-accredited centers, a distinct difference between SEER-based studies that are population based. CoC-accredited centers comprise 30% of U.S. hospitals, and the proportion of these vary state by state and may lead to patient over- or under-representation. For instance, 89% of patients in Delaware versus 27% of patients in Arizona are represented.[30,31] Moreover, this may also affect representation of different ethnicities of varying socioeconomic statuses. Because NCDB is a hospital-based rather than population-based database, these results should be validated in additional studies. Other limitations inherent to databases should be recognized, including absence of data on specific chemotherapy and IO regimens used, errors in reporting, cause of death-limiting cancer-specific survival data, extent of metastatic disease, PD-L1 status, and whether driver gene mutations were present. For example, in this analysis, 57.4% of the patients had a CDCC score of 0. Although this may have been because patients had comorbidities not included in the CDCC scoring system, it is also possible that comorbidities were underreported to the database. The CDCC score is based on reported International Classification of Diseases, Ninth Revision, and International Classification of Diseases, Tenth Revision, scores, and so it is possible that underreporting led to

this high proportion of patients without a listed comorbidity. Furthermore, there are no data on additional lines of therapy, cause of death, cycles of therapy, treatment toxicities, or information that would allow calculation of progression-free survival. These data would be best derived from prospective studies or real-world institutional studies. Finally, this database does not include data on formal geriatric assessments. Since 2018, the American Society of Clinical Oncology has recommended that adults 65 years and older to receive systemic therapy for their cancer and receive a formal geriatric assessment to identify vulnerabilities not routinely identified with routine oncology assessments.[32] This is not reported in the data set and should be used in line with future studies in older patients to identify appropriate systemic therapies.

In conclusion, adults 80 years of age and older derive benefit from systemic therapy, with greater benefit derived from either multiagent chemotherapy or chemotherapy plus IO. Although multiagent confers better OS compared with single-agent chemotherapy, single-agent chemotherapy plus IO had similar outcomes to multiagent chemotherapy plus IO. The addition of surgery and radiation adds additional survival benefits and should be considered in select patients. Geographic-, racial-, and sex-based disparities continue to exist even into the octogenarian age range.

CRediT Authorship Contribution Statement

Ethan A. Burns: Conceptualization and design, data curation, investigation, formal analysis and interpretation, methodology, drafting of the original article, critical review and editing.

Winnie Chen: Conceptualization and design, methodology, drafting of original article, critical review and editing.

Sunil Mathur: Conceptualization and design, methodology, formal analysis and interpretation, software, critical review and editing.

Ryan B. Kieser: Conceptualization and design, investigation, visualization, review and editing.

Jun Zhang: Conceptualization and design, methodology, formal analysis, critical review and editing.

Eric H. Bernicker: Conceptualization and design, methodology, data curation, formal analysis and interpretation, supervision, critical review and editing.

Supplementary Data

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