Select octogenarians with stage IIIa non–small cell lung cancer can benefit from trimodality therapy

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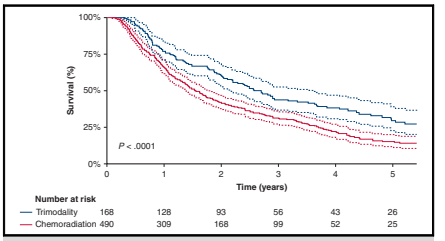
ABSTRACT

Objectives: Currently, more than 36% of patients diagnosed with lung cancer are 75 years of age or older. Management of stage IIIA cancer is variable, especially for octogenarians who might not be offered surgery because of questionable benefit. In this study we investigated the outcomes of definitive chemoradiotherapy (CR) and trimodality therapy (TM) management (CR and surgery) for clinical stage IIIA non–small cell lung cancer (NSCLC) in patients 80 years of age or older.

Methods: The National Cancer Data Base was queried for stage IIIA NSCLC in patients 80 years of age or older between 2004 and 2015. Patients were divided according to treatment type: definitive CR and TM. Patient demographic characteristics, facility type, Charlson–Deyo score, final tumor pathology, and survival data were extracted. Univariate analysis was performed, followed by 3:1 propensity matching to analyze overall survival differences. Unadjusted and adjusted Kaplan–Meier survival analyses were performed.

Results: From the database, 6048 CR and 190 TM octogenarians were identified. Patients in the TM group were younger (82 years old [TM] vs 83 years old [CR]; $P < .0001$), more likely to be treated at an academic/research institution (36% [TM] vs 26% [CR]; $P = .003$), had greater proportion of adenocarcinoma (52% [TM] vs 34% [CR]; $P < .001$), and a smaller tumor size (38 mm [TM] vs 33 mm [CR]; $P = .025$). After 3:1 matching, the 5-year overall survival for the TM group was 29% (95% CI, 22%-38%) versus 15% (95% CI, 11%-20%) for the CR group.

Conclusions: Selected elderly patients with stage IIIa NSCLC can benefit from an aggressive TM approach. (JTCVS Open 2022;10:395-403)



Propensity matched 5-year survival in octogenarians undergoing treatment for stage IIIa NSCLC.

CENTRAL MESSAGE

Octogenarians with stage IIIa NSCLC undergoing trimodality therapy have improved survival compared with a propensity matched cohort undergoing definitive chemoradiotherapy.

PERSPECTIVE

Octogenarians diagnosed with stage IIIa NSCLC might not be considered for trimodality therapy on the basis of chronological age and there are minimal outcomes data for this population. Overall survival for octogenarians with stage IIIa NSCLC was shown to be superior to a matched cohort undergoing definitive chemoradiotherapy. Aggressive treatment of stage IIIa NSCLC might benefit select octogenarians.

The management of stage IIIa (T4N0-N1, T3N1, T1-2N2) non–small cell lung cancer (NSCLC) remains a challenging issue with substantial practice variability regarding the use of chemoradiotherapy (CR) and surgery documented in the literature.[1,2] There is evidence that the use of trimodality therapy (TM) (induction CR followed by surgery) provides a survival benefit in appropriately selected stage IIIa patients.[3-5] This aggressive approach to locally advanced disease, however, is balanced against the risks of an aggressive oncologic regimen followed by anatomic lung resection. Appropriately staging and selecting patients able to fully tolerate this tripartite approach is difficult at the time of diagnosis with the choice driven by provider and institutional practice patterns.[5-7]

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Abbreviations and Acronyms
CR = chemoradiotherapy
NCDB = National Cancer Database
NSCLC = non–small cell lung cancer
TM = trimodality therapy

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Chronologic age is often used as a selection criterion in research and clinical practice as a surrogate for frailty and comorbidities, creating a barrier to certain types of care on the basis of this predefined threshold or because minimal data exist to justify a particular management strategy in an elderly patient population.[2,8,9] NSCLC is more common in the elderly, with >36% of new cancers identified in those 75 years or older and with 80-year-old Americans forecasted to live another 9.3 years.[10,11] For these older patients, variability in the treatment of stage IIIa cancer is particularly significant because comorbidities, frailty, and remaining life span are considered in a multidisciplinary, but somewhat ad hoc manner, which might bias against robust and relatively healthy elderly patients.[2,8,12,13] Older patients are more likely to receive definitive CR for stage IIIa NSCLC, and there has been little study about the potential benefit of surgery in appropriately selected older patients as part of TM.[2,4,8]

To study this issue, we queried the National Cancer Database (NCDB) for stage IIIa NSCLC patients 80 years of age and older and compared outcomes for those who underwent definitive CR with those who underwent TM. We hypothesized that within this selected cohort, those who received full TM would show improved overall survival compared with octogenarians who underwent CR.

METHODS

Data Source

The NCDB is a database that captures approximately 70% of all new cancers occurring in the United States. This is a joint effort of the American College of Surgeons and the Commission on Cancer to capture and maintain demographic, facility, survival, and cancer-related variables. Only deidentified data from accredited hospitals are collected.[14] Patient informed consent was not obtained and institutional review board approval was not required for this minimal risk database analysis. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigators.

Patient Selection

The NCDB was queried for octogenarians diagnosed with clinical stage IIIA NSCLC from 2004 through 2014. All 6238 patients were 80 years or older, treated in the United States, and had known survival and treatment information. Patients were divided into 2 treatment groups: those who received definitive CR and those who underwent TM (Figure 1).

Variables Collected

Clinical and pathologic data obtained from the NCDB included age, sex, race, modified Charlson–Deyo score, insurance status, education level, income, facility type, facility location, histology, tumor location, and clinical and pathologic stage (including T and N data). These variables are further described in the NCDB Participant User File data dictionary (for details, see https://www.facs.org/-/media/files/quality-programs/cancer/ncdb/puf_data_dictionary.ashx).

Data Analysis

Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing). Continuous variables are summarized as mean ± standard deviation or equivalent 25th, 50th (median), and 75th percentiles if the distribution was skewed; comparisons were made using the Wilcoxon rank sum (nonparametric) test. Categorical data are summarized as frequencies and percentages; comparisons were made using the χ^2 test, or Fisher exact test when frequencies were <5.

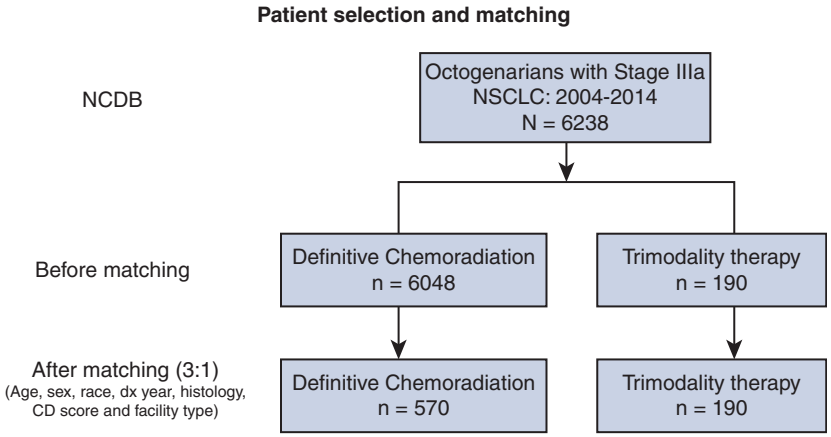

FIGURE 1. Patient selection and matching: the National Cancer Database (*NCDB*) was queried for octogenarians who underwent treatment for stage IIIa non–small call lung cancer (*NSCLC*) between 2004 and 2014. The population was divided into groups on the basis of treatment type (CR vs TM) and then underwent propensity score-matching on the basis of included variables resulting in matched CR and TM groups. *dx*, Diagnosis; *CD*, Charlson–Deyo.

Propensity Score-Matching

Using clinically significant variables age, sex, race, year of diagnosis, histology, comorbidity score and facility type, a parsimonious model was created (C-statistic = 0.68). From this, a propensity score was generated for each patient and greedy matching was used to match 3 CR patients for every 1 TM patient (Figure E1). The final propensity score-matched cohort consisted of 570 CR and 190 TM patients (100% of possible matches; Figure 1 and Table E1).

Survival Analysis

Unmatched and matched overall survival were assessed nonparametrically using the Kaplan–Meier method and stratified according to CR versus TM. Survival data were unavailable for patients who underwent treatment in 2015, and therefore were not included in survival analysis. Differences in survival were tested between the groups using the log rank test.

TABLE 1. Patient demographic and cancer characteristics

	Trimodality	Chemoradiotherapy	*P* value
n	190	6048	
Age, y	82 (80-83)	82 (81-84)	<.001
Female sex	81 (43)	2531 (42)	.888
Facility type			.003
Community cancer program	12 (6.3)	759 (13)	
Comprehensive community cancer program	88 (46)	3059 (51)	
Academic research program	70 (36)	1588 (26)	
Integrated network cancer program	20 (11)	642 (11)	
Charlson–Deyo Score			.628
0	121 (64)	3961 (66)	
1	49 (26)	1399 (23)	
2	17 (8.9)	516 (8.5)	
>2	3 (1.6)	172 (2.8)	
Time to first treatment, d	29 (15-46)	34 (21-50)	.001
Radiation dose, cGy	5000 (4500-5450)	5800 (4140-6300)	.001
Distance to facility, miles	10 (4.4-24)	7.4 (3.5-17)	.001
Histology			<.001
Adenocarcinoma	99 (52)	2061 (34)	
Squamous cell carcinoma	18 (9.5)	1042 (17)	
NOS	69 (36)	2761 (46)	
Other	4 (2.1)	184 (3.0)	
Grade			<.001
Well differentiated	12 (6.3)	198 (3.3)	
Moderately differentiated	53 (28)	917 (15)	
Poorly differentiated	68 (36)	1867 (31)	
Undifferentiated	1 (0.5)	76 (1.3)	
Unknown	56 (30)	2990 (49)	
Tumor size, mm	38 (29-57)	44 (30-60)	.025
Clinical T			.014
c0	0 (0.0)	22 (0.4)	
c1	45 (24)	1035 (17)	
c2	74 (39)	2618 (43)	
c3	51 (27)	1588 (26)	
c4	15 (7.9)	591 (9.8)	
cX	5 (2.6)	183 (3.0)	
Clinical N			.083
c0	16 (8.4)	461 (7.6)	
c1	24 (13)	517 (8.6)	
c2	143 (75)	4937 (82)	
c3	1 (0.5)	33 (0.5)	
cX	6 (3.2)	87 (1.4)	

Data are presented as n (%) or median (25th-75th percentile), except where otherwise noted. *NOS*, Not otherwise specified.

RESULTS

Baseline Characteristics

Of the 6048 CR and 190 TM patients, TM patients were more likely to receive treatment at academic research centers (70 [36%] vs 1588 [26%]; $P = .003$), lower median radiation dose (5000 vs 5800 cGy; $P = .001$), more adenocarcinoma (99 [52%] vs 2061 [34%]; $P < .001$), and smaller median tumor size (38 vs 44 mm; $P = .025$; Table 1). Patients had similar breakdown according to sex, race, Charlson–Deyo scores, and clinical node staging. The pathway for allocation into groups is shown in Figure 1.

Operative Outcomes in the TM Cohort

Most of the resections were performed via an open approach 84 (79%) with a median 6-day length of stay and 2.4% 30-day mortality and a 4.1% 90-day mortality (Table 2). Positive margins were found in 29 cases (16%), with 11 patients (6.0%) who had pathologic nodal upstaging. Although most of the patients remained stage III on pathologic staging, 25 (17%) were pathologic stage I and 11 (7.6%) were pathologic stage II.

Overall Survival

Patients who underwent TM had superior overall survival compared with those who underwent CR (log rank $P < .001$; Figure 2). Five-year unmatched survival was 29% (95% CI, 22%-38%) versus 11% (95% CI, 10%-12%) for the TM and CR cohorts respectively.

In the propensity matched group, the TM cohort still had superior overall survival compared with the matched CR patients (log rank $P < .001$; Figure 3). Five-year matched survival was 29% (95% CI, 22%-38%) versus 15% (95% CI, 11%-20.0%) for the TM and CR cohorts, respectively.

TABLE 2. Operative outcomes for trimodality patients

	Available n	Trimodality, n (%) or median (25th-75th percentile)
Overall	190	
Approach	107	
Open		84 (79)
Video-assisted thoracoscopic surgery		17 (16)
Robotic		6 (5.6)
Positive margins	183	29 (16)
Nodes examined	158	10 (5-16)
Positive nodes	165	1 (0-3)
Pathologic upstaging	145	2 (1.4)
Nodal upstaging	183	11 (6.0)
Pathologic stage		
I		25 (17)
II		11 (7.6)
III		107 (74)
IV		2 (1.4)
Pathologic T		
p0		19 (10)
p1		48 (25)
p2		57 (30)
p3		33 (18)
p4		12 (6.6)
pX		14 (7.7)
Pathologic N		
p0		57 (31)
p1		23 (13)
p2		91 (50)
p3		1 (0.5)
pX		11 (6.0)
Length of stay, d	166	6.0 (4.0-8.0)
30-Day mortality	169	4 (2.4)
90-Day mortality	169	7 (4.1)
30-Day hospital readmission	190	15 (7.9)

DISCUSSION

In this study of octogenarians with stage IIIa NSCLC in the NCDB, those who underwent induction CR followed by surgery showed a superior overall survival compared with a propensity matched cohort who received definitive CR (Figure 3). These patients had an acceptable length of stay and a 90-day mortality similar to that reported in other studies.[3,4] Patients who underwent TM were more likely to undergo treatment at an academic research center, and over the 12 years studied (2004-2015), open thoracotomy remained the predominant approach.

The management of stage IIIa disease remains challenging, but these findings add clarity in 2 important ways. First, using long-term data from a representative database, an overall survival benefit was again shown for patients who underwent TM compared with definitive CR.[1,15] This lends to the existing body of knowledge supporting an aggressive approach in locoregionally advanced NSCLC for patients who can tolerate multimodality therapy.[1,4] Although TM was associated with a survival benefit, overall survival in this study of octogenarians was lower than in other studies of stage IIIa patients after induction and surgery, in which 5-year OS ranging from 35% to 45% was reported.[3,4,9] Only Yang and colleagues[9] specifically examined a cohort of patients 75 years and older (for whom there was a trend toward worse survival compared with younger cohorts) and a difference in overall survival between younger and older patients was anticipated.[6,8]

Determining which patients will tolerate surgery after TM is a highly selective, but naturally imprecise process and advanced age is often used as nonspecific surrogate for frailty and comorbidities in evaluation of individuals. The preference to manage older patients with definitive

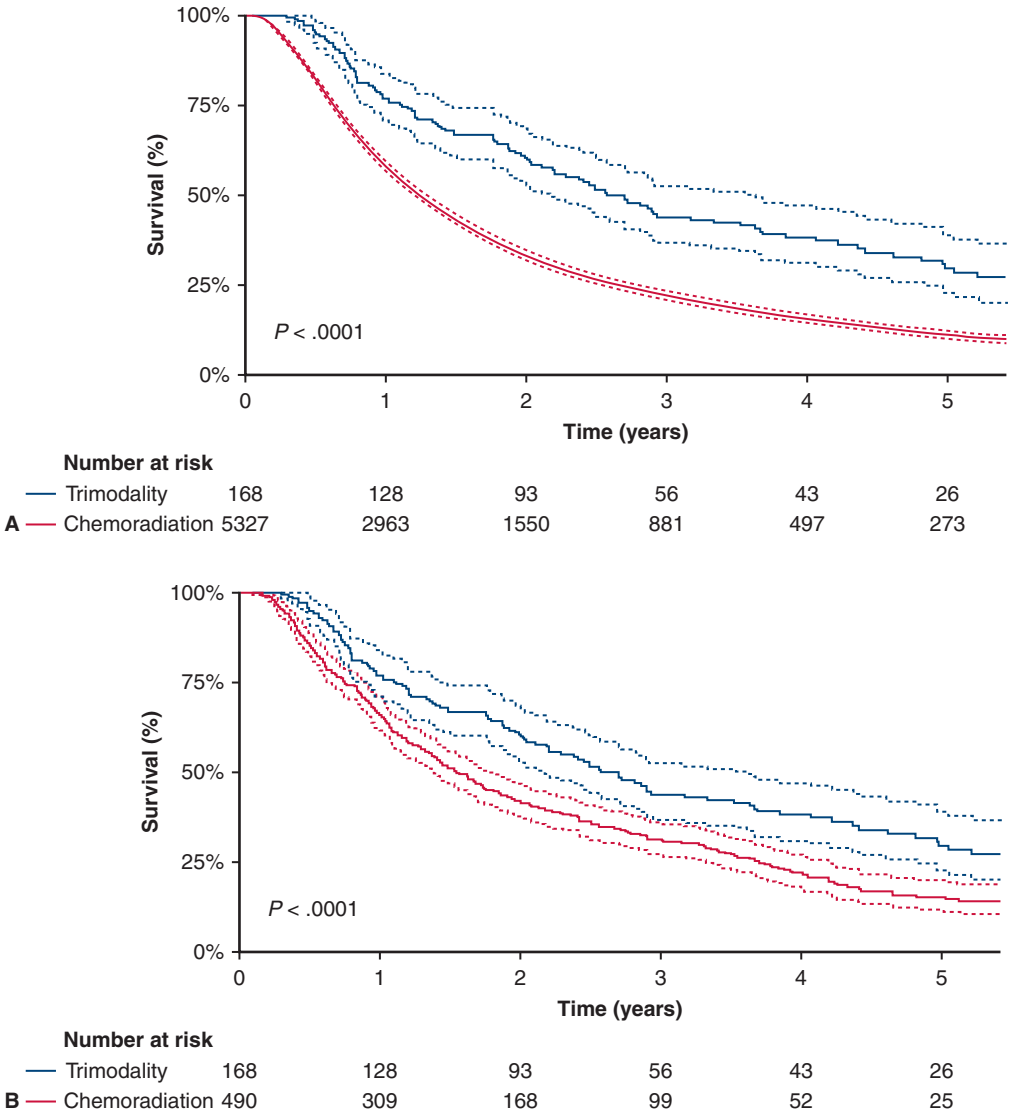

FIGURE 2. Kaplan–Meier overall 5-year survival stratified according to treatment modality. A, Unmatched Kaplan–Meier overall survival in a comparison of trimodality therapy (TM) and definitive chemoradiotherapy (CR), 29% TM (95% CI, 4%-22%) versus 11% CR (95% CI, 10%-12%); log rank $P < .001$. B, Matched Kaplan–Meier overall survival in a comparison of TM and definitive CR, 29% (95% CI, 22.2%-38.6%) versus 15% (95% CI, 11.3%-20.0%); log rank $P < .001$.

CR has been shown in multiple publications, in which the use of advanced age as an exclusion criterion crystalizes the intuitive belief that younger patients will better tolerate the rigors of induction therapy and resection. This bias is self-reinforcing, limiting the information available to shift practice in an evidence-based fashion.[1,2,5,8] But like stage IIIa NSCLC, patients of a given chronologic age are heterogenous and our findings specifically contradict the concept that age alone should be used as a surrogate marker to contraindicate TM.[2,9] Appropriately selected octogenarians maintained a survival benefit with TM and the 90-day mortality for these patients was lower at 4.1% than that reported in similar studies ranging from 4.5% to 6.5%.[3,4,16] This is not to suggest that all octogenarians with stage IIIa disease are appropriate surgical candidates. Efforts to quantify who passes the "eyeball test," and why they do, is a work in progress.[17,18] In one study of octogenarians who underwent lobectomy, up to half experienced some complication (15% thought to be significantly morbid), adding hospital days and an increased rate of discharge to a nursing facility.[13] Many of these complications were pulmonary (atelectasis, pneumonia), suggesting the need for particular evaluation of functional and respiratory capacity in this age group. It should also be considered that, like in this study, stage IIIa patients are heterogenous. Factors, such as multistation N2 disease or central tumors potentially requiring pneumonectomy, that portend worse overall outcomes in ideal patients, are likely best avoided in octogenarians.[19] Finally,

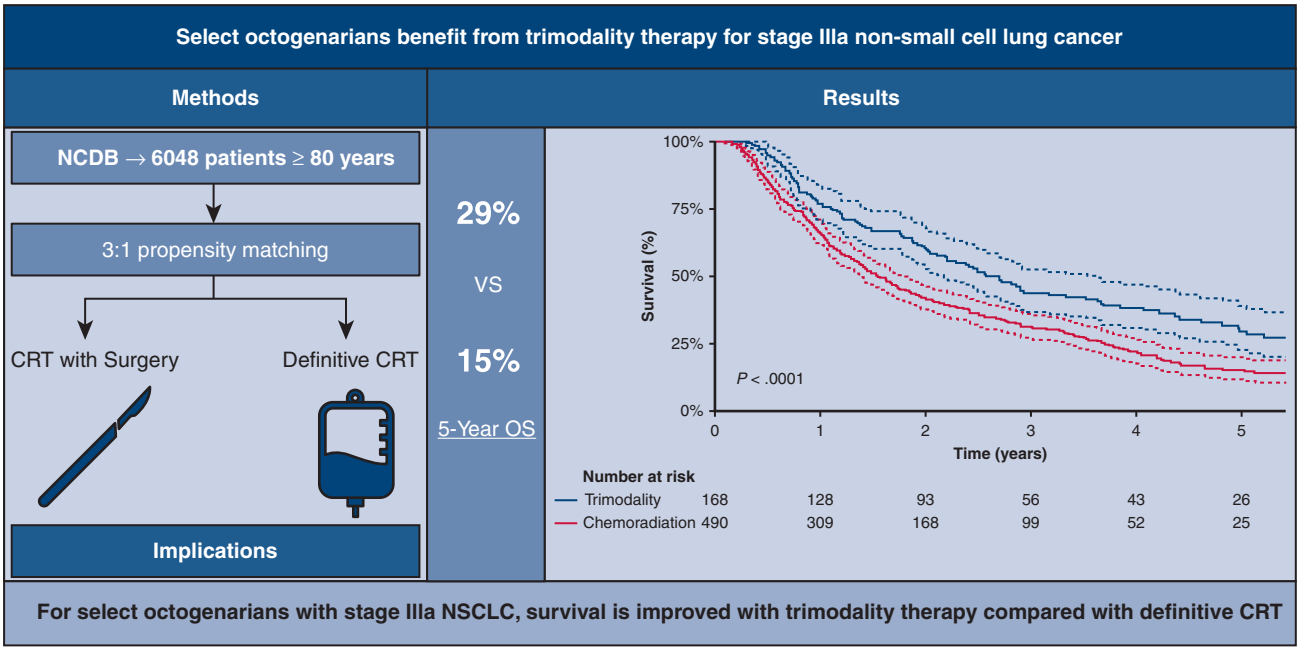

FIGURE 3. In a propensity-matched study of octogenarians with stage IIIa non–small cell lung cancer (*NSCLC*) from the National Cancer Database (*NCDB*), those who underwent trimodality therapy were shown to have improved survival compared with those who underwent definitive chemoradiotherapy (*CRT*). This suggests that age alone does not preclude aggressive management of these patients, and that careful patient selection is a key factor in this population. *OS*, Overall survival.

when considering major interventions at the extremes of age, this very substantial risk of complications should be factored into the risk to benefit ratio to quality, not just quantity of life, when counseling patients and their families. The success of immunotherapy in advanced NSCLC further complicates this calculus. Promising results from multiple completed and ongoing trials in a diversity of patients have shown significant improvements in overall and progression-free survival with the additional use of immunotherapy with standard chemotherapy regimens in resectable and unresectable patients.[20] Recent 4-year outcomes from the PACIFIC trial specifically, compare favorably with our historical data, with improved survival (median OS, 47.5 months vs 29.1 months in the placebo arm) and a more palatable complication profile.[21] As experience with these agents grows, the need to consider surgery as a driver of survival might diminish, particularly in populations in which frailty is more common.

This study carries the limitations of a retrospective database review. As noted previously, the judicious choice of patients is critical for the successful completion of TM, a judgment which naturally creates a strong selection bias within these data.[22,23] The lack of granular comorbidity, laboratory, and frailty data limits our ability to understand the extent of this bias or which factors were most prominent in the choice between TM and CR for individual patients. Moreover, the limits of this database analysis preclude us from definitively identifying patients selected for surgery on the basis of a successful response to CR. Recognizing this bias, we emphasize that these findings suggest that appropriately selected octogenarians can benefit from TM regardless of their chronologic age, but certainly not all octogenarians should be considered. The risk of overextending these data considering the inherent bias should be understood, and multidisciplinary teams should determine which elderly stage IIIa NSCLCs are appropriate for aggressive management in their hands. Direct application of these findings in the context of immunotherapy is also limited, however, the concept of determining complex treatment plans for patients in a holistic manner, not on the basis of a single factor such as age, remains a poignant message.

CONCLUSIONS

Induction CR followed by surgical resection continues to show a survival benefit for appropriately selected octogenarians with stage IIIa NSCLC in the NCDB compared with definitive CR. This suggests that age alone is not a contraindication to TM management of this disease. Advances in the oncologic and surgical care of these patients should be matched by investigation to characterize factors that predict successful tolerance of a multimodality approach.

Webcast

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Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: NSCLC, stage IIIa, octogenarian, trimodality therapy

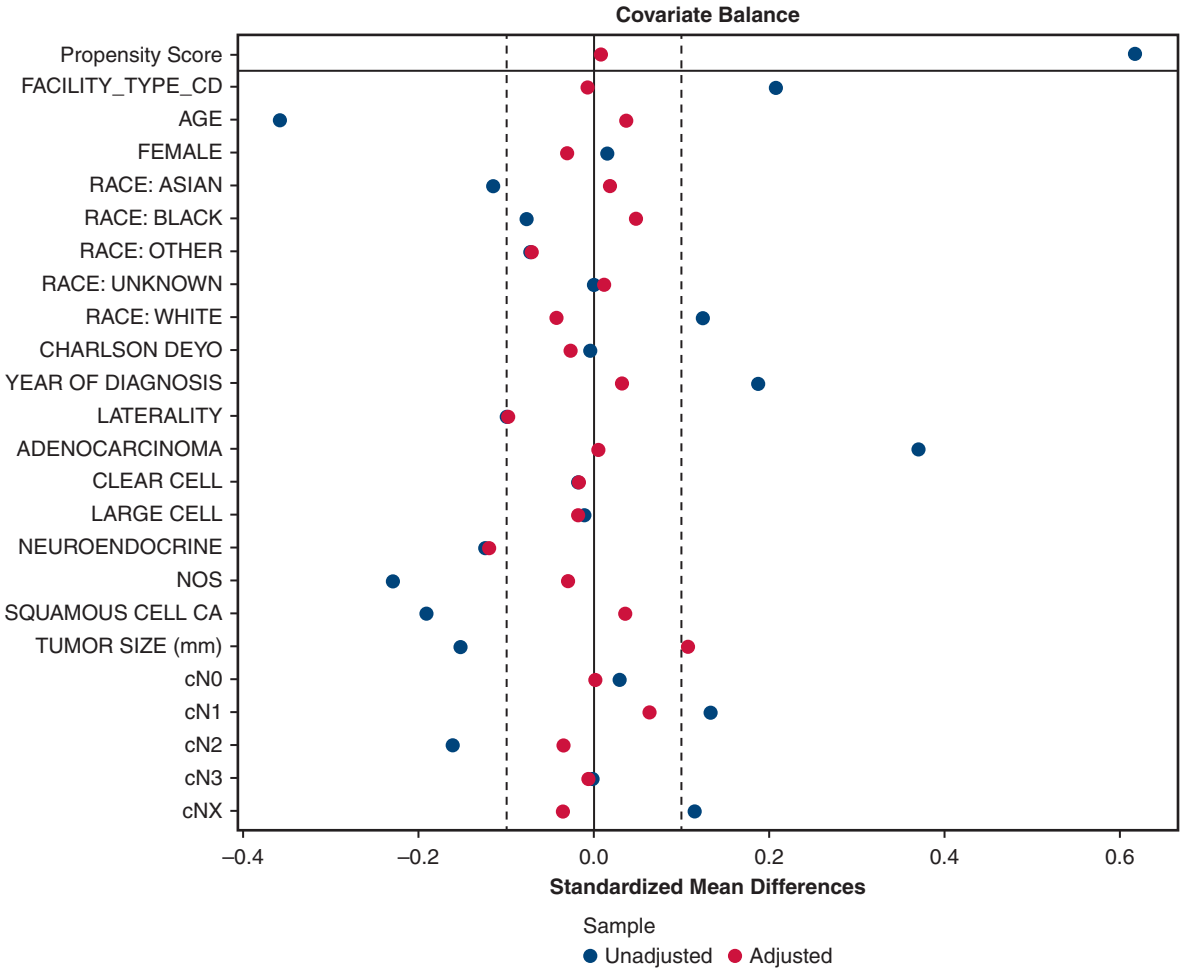

FIGURE E1. Display of covariate balance before and after propensity score-matching using a parsimonious model (C-statistic = 0.68). *CD*, Charlson–Deyo.

TABLE E1. Patient demographic characteristics before and after propensity score-matching

	Before propensity score-matching			After propensity score-matching		
	Chemoradiotherapy	Trimodality	SMD	Chemoradiotherapy	Trimodality	SMD
n	6048	190		570	190	
Age, y	82.7 ± 2.5	81.9 ± 2.02	0.358	82.0 ± 2.1	81.9 ± 2.0	0.053
Female sex	2531 (42)	81 (43)	0.016	252 (44)	81 (43)	0.032
Race, %			0.159			0.060
White	5501 (91)	179 (94)		533 (94)	179 (94)	
Asian	105 (1.7)	1 (0.5)		5 (0.9)	1 (0.5)	
Black	394 (6.5)	9 (4.7)		27 (4.7)	9 (4.7)	
Other	16 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)	
Unknown	32 (0.5)	1 (0.5)		5 (0.9)	1 (0.5)	
Facility type			0.287			0.119
Community cancer program	759 (13)	12 (6.3)		49 (8.6)	12 (6.3)	
Comprehensive community cancer program	3059 (51)	88 (46)		248 (44)	88 (46)	
Academic research program	1588 (26)	70 (37)		224 (39)	70 (37)	
Integrated network cancer program	642 (11)	20 (10)		49 (8.6)	20 (10)	
Charlson–Deyo score			0.104			0.060
0	3961 (66)	121 (64)		372 (65)	121 (64)	
1	1399 (23)	49 (26)		133 (23)	49 (26)	
2	516 (8.5)	17 (8.9)		55 (9.6)	17 (8.9)	
>2	172 (2.8)	3 (1.6)		10 (1.8)	3 (1.6)	
Time to first treatment, d	40 ± 31	32 ± 24	0.276	41 ± 34	32 ± 24	0.315
Distance to facility, miles	22 ± 102	36 ± 129	0.125	24 ± 110	36 ± 129	0.100
Histology			0.405			0.031
Adenocarcinoma	2061 (34)	99 (52)		305 (54)	99 (52)	
Clear cell	1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Large cell	137 (2.3)	4 (2.1)		11 (1.9)	4 (2.1)	
Neuroendocrine	46 (0.8)	0 (0.0)		0 (0.0)	0 (0.0)	
Squamous cell carcinoma	2761 (46)	69 (36)		203 (36)	69 (36)	
NOS	1042 (17.2)	18 (9.5)		51 (8.9)	18 (9.5)	
Grade			0.469			0.441
Well differentiated	198 (3.3)	12 (6.3)		25 (4.4)	12 (6.3)	
Moderately differentiated	917 (15)	53 (28)		93 (16)	53 (28)	
Poorly differentiated	1867 (31)	68 (36)		165 (29)	68 (36)	
Undifferentiated	76 (1.3)	1 (0.5)		5 (0.9)	1 (0.5)	
Unknown	2990 (49)	56 (30)		282 (50)	56 (30)	
Tumor size, mm	48 ± 35	44 ± 21	0.151	44 ± 22	44 ± 22	0.034
Clinical T			0.326			0.287
c0	22 (0.4)	0 (0.0)		1 (0.2)	0 (0.0)	
c1	514 (8.5)	19 (10)		36 (6.3)	19 (10)	
c1A	201 (3.3)	6 (3.2)		40 (7.0)	6 (3.2)	
c1B	320 (5.3)	20 (10)		52 (9.1)	20 (10)	
c2	1560 (26)	32 (17)		76 (13)	32 (17)	
c2A	668 (11)	30 (16)		81 (14)	30 (16)	
c2B	393 (6.5)	12 (6.3)		45 (7.9)	12 (6.3)	
c3	1596 (26)	51 (27)		160 (28)	51 (27)	
c4	591 (9.8)	15 (7.9)		66 (12)	15 (7.9)	
cX	183 (3.0)	5 (2.6)		12 (2.1)	5 (2.6)	
Clinical N			0.188			0.105
c0	461 (7.6)	16 (8.4)		51 (9.0)	16 (8.4)	
c1	517 (8.5)	24 (13)		72 (13)	24 (13)	
c2	4950 (82)	143 (76)		433 (76)	143 (76)	
c3	33 (0.5)	1 (0.5)		3 (0.5)	1 (0.5)	
cX	87 (1.4)	6 (3.2)		9 (1.6)	6 (3.2)	

Data are presented as n (%) or mean ± SD, except where otherwise noted. *SMD*, Standardized mean difference; *NOS*, not otherwise specified.