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)

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
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (Figure 1). Older patients with Stage IIIa NSCLC: 2004-2014

Patient selection and matching

Octogenarians with Stage IIIa NSCLC: 2004-2014
N = 6238

Before matching

Definitive Chemoradiation
n = 6048

Trimodality therapy
n = 190

After matching (3:1)
(Age, sex, race, dx year, histology, CD score and facility type)

Definitive Chemoradiation
n = 570

Trimodality therapy
n = 190

FIGURE 1. Patient selection and matching: the National Cancer Database (NCDB) was queried for octogenarians who underwent treatment for stage IIIa non–small cell 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. \textit{dx}, Diagnosis; \textit{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.

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. 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. This lends to the existing body of knowledge supporting an aggressive approach in locoregionally advanced NSCLC for patients who can tolerate multimodality therapy.

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. Only Yang and colleagues 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. 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

### Table 2. Operative outcomes for trimodality patients

| Available n | Trimodality, n (%) or median (25th-75th percentile) |
|-------------|--------------------------------------------------|
| Overall     | 190                                              |
| **Approach**|                                                  |
| Open        | 107 (79)                                         |
| Video-assisted thoracoscopic surgery | 17 (16) |
| Robotic     | 6 (5.6)                                          |
| Positive margins | 84 (16)  |
| Nodes examined | 158 (5-16) |
| Positive nodes | 165 (0-3) |
| Pathologic upstaging | 145 (2-14) |
| Nodal upstaging | 183 (11-60) |
| **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) |
| 90-Day mortality | 169 (4.1) |
| 30-Day hospital readmission | 190 (15.7) |
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 heterogeneous 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 heterogeneous. 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 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 \(P < .001\).
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. 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. 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. 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

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/21%20AM/AM21_M17/AM21_M17_05.mp4.

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 | 253 (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.