ORIGINAL ARTICLE

The Impact of Immunotherapy Use in Stage IIIA (T1-2N2) NSCLC: A Nationwide Analysis

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ABSTRACT

Introduction: Multiple clinical trials have revealed the benefit of immunotherapy (IO) for NSCLC, including unresectable stage III disease. Our aim was to investigate the impact of IO use on treatment and outcomes of potentially resectable stage IIIA NSCLC in a broader nationwide patient cohort.

Methods: We queried the National Cancer Database (2004–2019) for patients with stage IIIA (T1-2N2) NSCLC. Treatment and survival were evaluated with descriptive statistics, logistic regression, Kaplan-Meier analysis, and Cox proportional hazards modeling.

Results: Overall, 5.5% (3777 of 68,335) of patients received IO. IO use was uncommon until 2017, but by 2019, it was given to 40.1% (1544 of 2308) of stage IIIA patients. The increased use of IO after 2017 was associated with increased definitive chemoradiation treatment (54.2% [6800 of 12,535] from years 2017 to 2019 versus 46.9% [26,251 of 55,914] from 2004 to 2016, $p < 0.001$) and less use of surgery (18.1% [2266 of 12,535] from years 2017 to 2019 versus 22.0% [12,300 of 55,914] from 2004 to 2016, $p < 0.001$). IO treatment was associated with significantly better 5-year survival in the entire cohort (36.9% versus 23.4%, $p < 0.001$) and the subsets of patients treated with chemoradiation (37.2% versus 22.7%, $p < 0.001$) and surgery (48.6% versus 44.3%, $p < 0.001$). Pneumonectomy use decreased with increased IO treatment (5.1% of surgical patients [116 of 2266] from years 2017 to 2019 versus 9.2% [1127 of 12,300] from 2004 to 2016, $p < 0.001$).

Conclusions: Increased use of IO was associated with a change in treatment patterns and improved survival for patients with stage IIIA(N2) NSCLC.

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Introduction

Stage IIIA NSCLC accounts for approximately 15% of all diagnosed lung cancers and historically has poor outcomes with 5-year survival rates as low as 10% to 15%.[1,2] Although multimodality therapy is recognized as optimal, guidelines consider multiple treatment paradigms for this heterogeneous group of patients, and no single combination or permutation of therapies has been found to be obviously superior.[3,4] In particular, trials such as EORTC 08941 and Intergroup 0139 that were focused on the efficacy of surgery versus radiation after neoadjuvant chemotherapy found equivocal and lackluster results with low overall survival (OS) rates.[4–6] Nevertheless, immunotherapy (IO) use was recently found to have great promise for patients with NSCLC. For

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resectable or potentially resectable disease, trials such as CheckMate 816, Keynote 671, AEGEAN, and NEOTORCH revealed improved survival with neoadjuvant chemotherapy plus IO versus just chemotherapy alone followed by surgical resection.[7–11] For unresectable stage III disease, however, the PACIFIC trial paved the way for the use of definitive concurrent chemoradiation followed by one year of consolidated durvalumab.[12] Results from the PACIFIC trial boasted a 5-year OS rate of 42.9%, which was more than twice better than other landmark trials at the time.[12]

The use of IO in thoracic oncology, whether in the preoperative setting or as part of definitive nonsurgical treatment, holds undisputed potential for survival benefit. IO use had been generally limited to clinical trial patients and used only when patients met very specific criteria, but the revealed benefits across multiple trials have likely affected practice across a wider spectrum of patients. This study was undertaken to investigate and characterize the use of IO in stage IIIA(N2) NSCLC to assess overall treatment benefits in a broad nationwide patient cohort.

Materials and Methods

Data Source

The National Cancer Database (NCDB) is managed by the American Cancer Society and the Commission on Cancer of the American College of Surgeons and reports new cancer diagnoses in the United States from more than 1500 hospitals. Data from 2004 to 2019 were included in the study. Patients are deidentified in this database, so this study was considered exempt from Stanford Institutional Review Board review.

Patient Cohort

All patients above 18 years of age diagnosed with having clinical stage IIIA (T1-2N2) NSCLC based on the seventh and eighth editions of the American Joint Committee on Cancer staging manual were included. As staging definitions changed in the course of the study, clinical T status was recorded per the staging manual edition in use during the year the case was diagnosed. As the recording of clinical T stage in the NCDB was variable in terms of being classified as either T1 or T2, versus a more specific subset of either, all T1 and T2 subsets were grouped as either cT1 or cT2, respectively. Although stage IIIA encompasses a more heterogeneous group of patients, the cohort was restricted to cT1 to 2N2 patients for whom surgery is generally most accepted as potentially appropriate and beneficial. Patients for whom the use of chemotherapy, surgery, radiation, and IO were not definitely known were excluded. The NCDB defines IO as any biological or chemical agent that alters the immune system or host response to tumor cells, including programmed cell death protein 1/programmed death-ligand 1 and CTLA-4 inhibitors. Patients who were treated with chemoradiation or had surgery with or without other therapies were considered to have had definitive therapy, whereas patients who received only chemotherapy or only radiation therapy were not considered to have had definitive therapy.

Patterns of use of the treatments listed previously were stratified by an early era (2004–2016) when IO use was uncommon versus a later era (2017–2019) where IO was used much more frequently. Characteristics of the entire cohort stratified by IO use were evaluated. Two subgroup analyses were performed isolating patients who received (1) chemoradiation alone stratified by IO use and (2) surgery stratified by IO use. In patients who were treated with surgery, major postoperative morbidity was defined as a composite of 30-day mortality, unplanned readmission, or postoperative stay longer than 14 days.

IO Use and Survival Analyses

We estimated independent predictors of undergoing IO in the entire cohort using multivariable logistic regression that included age, sex, race, insurance status, comorbidity score, education level, income, era (later 2017–2019 versus early 2004–2016), histology, distance to facility, and facility type. Survival was evaluated using Kaplan-Meier curves and Cox proportional hazards methods with the primary end point being 5-year OS. Variables chosen a priori for inclusion in the Cox model were patient characteristics known to affect survival and were age, sex, comorbidities, and treatment.

Statistical Analysis

The data were analyzed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Baseline demographic and preoperative clinical characteristics between the two groups were compared with Wilcoxon ranked sum test for continuous variables and Pearson's chi-square test for discrete variables. The Fisher's exact test was used for discrete variables with fewer than five outcomes. A *p* value of less than 0.05 was considered statistically significant.

Results

Trend Analysis of IO Treatment

Overall, 5.5% (3777 of 68,335) of patients in the entire cohort received IO. Figure 1 reveals the use of IO over the time period of the study. IO use was uncommon in the earlier years of the study time frame and was less than 1% in all years up to and including 2013. IO use
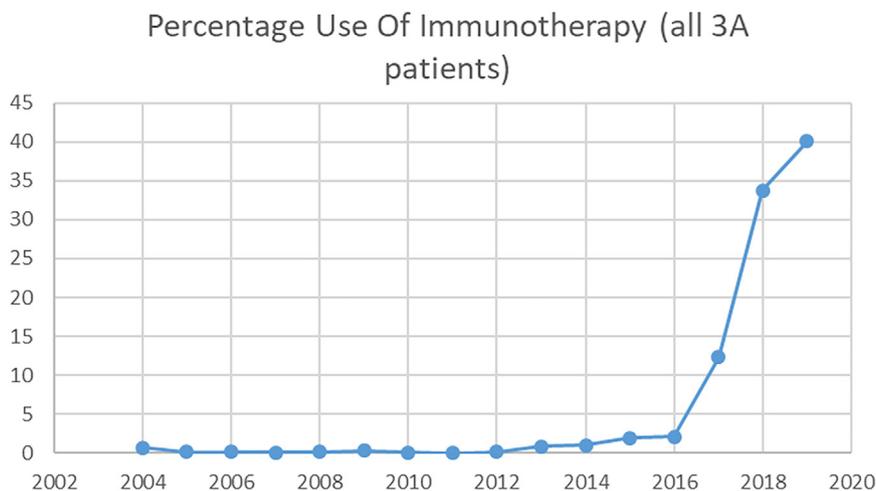
Percentage Use Of Immunotherapy (all 3A patients)

Figure 1. The use of immunotherapy from 2004 to 2019.

increased slowly in the next few years up to 2.1% (102 of 4677) in 2016. IO was subsequently given much more frequently starting in 2017 up to 40.1% (1544 of 2308) of N2 patients in 2019.

On the basis of the observed changes in the frequency of IO treatment, the study time frame was then stratified into an earlier era of 2004 to 2016 where IO was not often used (0.6% [359 of 55,914]) and a later era of 2017 to 2019 where IO was used much more often (27.5% [3418 of 12,535]) ($p < 0.001$). This increased use of IO in the later era was associated with a change in treatment patterns overall compared with the earlier era. Compared with the earlier time period, patients in the later era were more likely to receive radiation or chemotherapy (both $p < 0.001$) (Table 1). The use of chemoradiation treatment was also more common in the later era (54.2% [6800 of 12,535] versus 46.9% [26,251 of 55,914], $p < 0.001$), whereas surgery was used less frequently (18.1% [2266 of 12,535] versus 22.0% [12,300 of 55,914], $p < 0.001$) (Supplementary Fig. 1). Patients in the later period were overall more likely to receive some kind of definitive therapy (72.3% [9066 of 12,535] versus 68.9% [38,551 of 55,914], $p < 0.001$). The reason for no surgery was more often "not part of the treatment plan" in the later era compared with the earlier era (90.9% [6180 of 6800] versus 88.5% [23,234 of 26,251]), whereas the reason for no surgery being "contraindicated due to patient risk factors" was less common in the later era compared with the earlier era (7.8% [529 of 6800] versus 8.9% [2338 of 26,251], $p < 0.001$).

Among the patients who did get surgery, IO use also increased over time in a pattern similar to the use of overall IO (Supplementary Fig. 2). Of the 353 patients who had surgery and IO, the timing of IO was preoperative in 130 patients (36.8%), postoperative in 214

patients (60.6%), and unknown in nine patients (2.5%). Surgical patients in the later era were significantly more likely to receive IO (13.0% [295 of 2266] versus 0.5% [58 of 12,300], $p < 0.001$), in addition to also being more likely to receive chemotherapy (82.3% [1866 of 2266] versus 78.5% [9650 of 12,300], $p < 0.001$). The extent of surgical resection also differed between the two eras. Patients in the later era were more likely to undergo lobectomy and less likely to undergo pneumonectomy compared with those in the early era (80.5% versus 75.7% and 5.1% versus 9.2%, respectively, $p < 0.001$) (Supplementary Table 1).

Characteristics of the Entire Patient Cohort Stratified by IO Versus No IO Use

Table 2 illustrates the characteristics of the 3777 (5.5%) patients who received IO and the 64,558 (94.5%) patients who did not receive IO in the entire cohort. Patients in the IO group were younger (age 67 y versus 68 y, $p < 0.001$), more likely to be female (50% versus 47.2%, $p = 0.001$), more often insured (98.2% versus 97.6%, $p = 0.02$), lived farther from the treatment facility (11.1 miles versus 9.5 miles, $p < 0.001$), and more often treated at an academic or research program (40.6% versus 35.9%, $p < 0.001$). The IO group was significantly more likely to receive chemotherapy, radiation, and chemoradiation (all $p < 0.001$). They were more likely to receive definitive therapy (82.8% versus 68.8%, $p < 0.001$) and less likely to undergo surgery (9.3% versus 22%, $p < 0.001$).

On multivariable analysis, the strongest predictor of IO use was era of treatment, with the later era (years 2017–2019) having an OR of 56.9 (95% CI: 49.4–65.5, $p < 0.001$) (Table 3). Additional predictors of IO use

Table 1. Treatment Modalities Stratified by Early Versus Later Era

Treatment	Early Era (2004-2016) (n = 55,914)	Later Era (2017-2019) (n = 12,535)	p Value
Immunotherapy	359 (0.6)	3418 (27.5)	<0.001
Radiation	37,971 (67.9)	8964 (71.5)	<0.001
Chemotherapy	40,331 (72.1)	9404 (75)	<0.001
Treatment summary			<0.001
Chemotherapy only	4430 (7.9)	738 (5.9)	
Chemoradiation	26,251 (46.9)	6800 (54.2)	
None	8048 (14.4)	1849 (14.8)	
Radiation only	4885 (8.7)	882 (7)	
Surgery	12,300 (22)	2266 (18.1)	
Definitive therapy use	38,551 (68.9)	9066 (72.3)	<0.001

Note: All values are n (%).

Table 2. Characteristics of the Entire Cohort Stratified by Immunotherapy Use

Characteristics	Total (N = 68,335)	No Immunotherapy (n = 64,558)	Immunotherapy (n = 3777)	p Value
Age*	68 (61-76)	68 (61-76)	67 (61-74)	<0.001
Female sex	32,461 (47.4)	30,517 (47.3)	1889 (50)	0.001
Race				0.494
White	57,926 (85.2)	54,642 (85.2)	3190 (84.9)	
Black	8077 (11.9)	7619 (11.9)	445 (11.8)	
Other	2012 (3)	1883 (2.9)	123 (3.3)	
Education above median	32,087 (51.9)	30,344 (51.8)	1693 (53.6)	0.007
Income above median	32,823 (53.1)	31,066 (53.1)	1709 (54.1)	0.066
Charlson				0.655
0	39,340 (60.8)	37,154 (60.7)	2124 (61.3)	
1	18,240 (28.2)	17,260 (28.2)	952 (27.5)	
2+	7165 (11.1)	6764 (11.1)	387 (11.2)	
Distance*	9.5 (4.2-22.3)	9.5 (4.1-22.2)	11.1 (4.9-24.5)	<0.001
Insured	65,900 (97.7)	62,121 (97.6)	3671 (98.2)	0.02
Facility type				<0.001
Community program	6020 (11.1)	5697 (11.1)	316 (10.4)	
Comprehensive community program	28,708 (52.8)	27,163 (53)	1489 (49)	
Research/academic program	19,636 (36.1)	18,376 (35.9)	1232 (40.6)	
Tumor histology				<0.001
Adenocarcinoma	30,936 (45.3)	28,708 (44.5)	2228 (59.0)	
Adenosquamous	952 (1.4)	919 (1.4)	33 (0.9)	
Large cell neuroendocrine	1802 (2.6)	1765 (2.7)	37 (1.0)	
Squamous cell carcinoma	25,169 (36.8)	23,771 (36.8)	1398 (37.0)	
NSCLC NOS	9476 (13.9)	9395 (14.6)	81 (2.1)	
Tumor size (cm)*	3.6 (2.5-5.0)	3.6 (2.5-5.0)	3.2 (2.2-4.2)	<0.001
Clinical T stage				<0.001
Clinical T1	23,374 (34.2)	21,756 (33.7)	1618 (42.8)	
Clinical T2	44,961 (65.8)	42,802 (66.3)	2159 (57.2)	
Immunotherapy	3777 (5.5)	0 (0)	3777 (100)	<0.001
Radiation	46,935 (68.6)	43,734 (67.7)	3119 (82.6)	<0.001
Chemotherapy	49,735 (72.7)	46,262 (71.7)	3394 (89.9)	<0.001
Treatment summary				<0.001
Chemotherapy only	5168 (7.6)	4870 (7.5)	294 (7.8)	
Chemoradiation	33,051 (48.3)	30,206 (46.8)	2773 (73.4)	
None	9897 (14.5)	9639 (14.9)	233 (6.2)	
Radiation only	5767 (8.4)	5635 (8.7)	124 (3.3)	
Surgery	14,566 (21.3)	14,208 (22)	353 (9.3)	
Definitive therapy use	47,617 (69.6)	44,414 (68.8)	3126 (82.8)	<0.001

Note: All values are n (%) except for * which are mean (range).
NSCLC NOS, NSCLC not otherwise specified.

Table 3. Independent Predictors of Immunotherapy Use

Variables	OR (95% Confidence Interval)	*p* Value
Increasing age (per decade)	0.85 (0.80-0.89)	<0.001
Female sex (vs. male sex)	1.07 (0.97-1.17)	0.19
Race (vs. White)		
Black	0.97 (0.83-1.13)	0.67
Other	0.72 (0.56-0.93)	0.01
Insured (vs. uninsured)	1.03 (0.75-1.44)	0.83
Charlson comorbidity index (vs. 0)		
1	1.12 (1.00-1.24)	0.05
2+	1.04 (0.89-1.24)	0.66
Education above median (vs. below median)	1.14 (1.02-1.27)	0.03
Income above median (vs. below median)	0.99 (0.89-1.12)	0.98
Later era (vs. early era)	56.90 (49.43-65.50)	<0.001
Histology (vs. adenocarcinoma)		
Large cell neuroendocrine	0.45 (0.28-0.72)	0.001
Squamous cell	0.79 (0.72-0.89)	<0.001
Adenosquamous	0.76 (0.48-1.21)	0.246
NSCLC not otherwise specified	0.39 (0.29-0.53)	<0.001
Distance from treatment facility (per 50 miles)	0.70 (0.60-0.82)	<0.001
Academic/research program (vs. community)	1.18 (1.07-1.29)	0.001

were as follows: higher educational level (OR 1.14 [95% CI: 1.02–1.27], $p = 0.025$), Charlson comorbidity score 1 versus 0 (OR 1.12 [95% CI: 1.00–1.24], $p = 0.046$), and treatment at a research or academic hospital (OR 1.18 [95% CI: 1.07–1.30], $p = 0.001$). Independent predictors of not receiving IO were as follows: older age (OR 0.85 [95% CI: 0.81–0.89], $p < 0.001$), race other than White (OR 0.72 [95% CI: 0.56–0.93], $p = 0.011$), and histology other than adenocarcinoma ($p \leq 0.001$).

The Impact of IO Use on Survival

Figure 2 illustrates the Kaplan-Meier survival curve of the entire cohort stratified by IO use and reveals that the IO group had significantly better survival (5-y OS 36.9% versus 23.4%, median survival 69.9 versus 43.4 mo, $p < 0.001$). On Cox proportional hazards model, IO use was again associated with better survival with a hazards ratio of 0.48 (95% CI: 0.45–0.50, $p < 0.001$) (Table 4). Other independent predictors of improved survival included being female; receiving surgery, radiation, or chemotherapy; and having lower clinical T stage. Nevertheless, older age and higher comorbidity score independently predicted worse survival (all $p < 0.001$).

### The Impact of IO in Definitive Chemoradiation and Surgery Subsets

In the subgroup of patients who received chemoradiation (n = 32,979), those who underwent IO (n = 2773, 8.4%) were more likely to be younger, female, insured, live farther form the treatment facility, and be treated at an academic center, much like characteristics

of the overall cohort (Supplementary Table 2). In addition, the IO group had more comorbid conditions ($p = 0.011$) and a higher education level ($p = 0.048$). In this chemoradiation subgroup analysis, the IO group had better survival (5-y OS 37.2% versus 22.7%, median survival 63.1 mo versus 41.8 mo, $p < 0.001$) (Supplementary Fig. 3).

In the subgroup of patients who received surgery (n = 14,561), those who underwent IO (n = 353, 2.4%) were again more likely to be younger, female, live farther away, and be treated at an academic center, but they were also more likely to have received radiation (62.9% versus 55.6%, $p = 0.007$) and chemotherapy (92.6% versus 78.7%, $p < 0.001$) (Supplementary Table 3). IO use was also associated with improved survival in the patients treated with surgery (5-y OS 48.6% versus 44.3%, median survival 96.8 mo versus 73.8 mo, $p < 0.001$) (Supplementary Fig. 4).

Impact of IO Use on Perioperative Outcomes

In the subgroup of patients who underwent surgery, the IO group had a longer time to definitive surgery (105 d versus 81 d, $p < 0.001$) but better overall perioperative outcomes (Supplementary Table 4). The IO group had lower 30- and 90-day mortality rates (0.6% versus 2.8%, $p = 0.026$ and 1.5% versus 5.5%, $p = 0.002$), shorter length of hospital stay (4 versus 5, $p < 0.001$), and lower major morbidity (7.1% versus 10.6%, $p = 0.042$). They were less likely to receive lobectomy or pneumonectomy, but more likely to receive sublobar resection (15.3% versus 10.4%, $p < 0.001$). The IO group was also more likely to receive adjuvant radiation
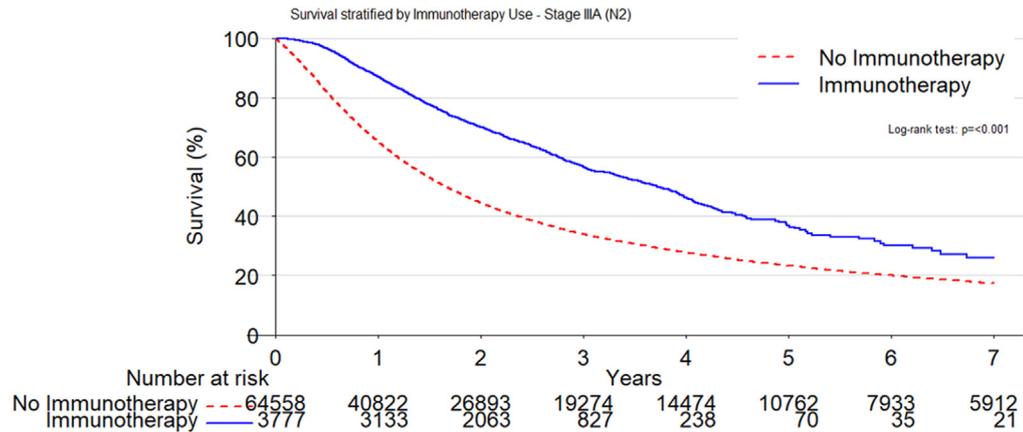
	No Immunotherapy	Immunotherapy
1 year survival	65.2% (64.8-65.6%)	87.1% (86-88.2%)
2 year survival	44.5% (44.2-44.9%)	70.1% (68.6-71.7%)
3 year survival	34% (33.6-34.4%)	56.7% (54.9-58.6%)
4 year survival	27.7% (27.4-28.1%)	46.1% (43.6-48.8%)
5 year survival	23.4% (23-23.7%)	36.9% (33.4-40.9%)
Median survival	43.4 months	69.9 months

Figure 2. Kaplan-Meier survival curves stratified by immunotherapy use.

(47.9% versus 29.7%, $p < 0.001$) and adjuvant chemotherapy (73.1% versus 41.7%, $p < 0.001$).

Discussion

Multiple treatment regimens can be used for potentially resectable stage IIIA(N2) NSCLC, and patient treatment can vary by physician and institution. In our nationwide analysis, we found that induction IO use for this NSCLC entity was rare until the year 2017, and subsequent increased IO use was associated with more patients receiving definitive treatment, though this

Table 4. Cox Proportional Hazards for Overall Survival in Patients With Stage IIIA(N2) NSCLC

Variables	OR	95% CI Lower	95% CI Higher	p Value
Age (per decade)	1.18	1.16	1.9	<0.001
Female (vs. male)	0.84	0.83	0.86	<0.001
Charlson comorbidity index (vs. 0)				
1	1.15	1.13	1.17	<0.001
2+	1.26	1.22	1.30	<0.001
cT1 (vs. cT2)	0.78	0.77	0.80	<0.001
Surgery	0.45	0.44	0.46	<0.001
Radiation	0.77	0.75	0.79	<0.001
Chemotherapy	0.62	0.61	0.64	<0.001
Immunotherapy	0.48	0.45	0.50	<0.001

CI, confidence interval; cT, clinical T.

occurred with an increase in definitive chemoradiation treatment and decrease in surgical treatment. The use of IO for surgical patients did not negatively affect short-term outcomes, and IO use was associated with improved perioperative outcomes such as lower short-term morbidity and mortality and shorter lengths of stay. The use of IO was associated with significantly improved survival both overall and in the subsets of patients treated with either chemoradiation or with surgery. The increased use of IO was associated with less use of pneumonectomy, and patients treated with surgery and IO had the highest OS, likely secondary to less postoperative complications and increased systemic response.

The improved survival observed with IO use in this nationwide cohort of patients is consistent with results from multiple NSCLC trials of IO in various settings.[7,8,12] Improved outcomes with IO use are likely also attributed to improved perioperative care and better patient selection for surgery overtime. The potential benefits of IO use for patients with N2 disease is very exciting, as advances in this area have been relatively limited because studies revealed benefit to both induction and adjuvant chemotherapy with surgery.[13–16] The PACIFIC trial has already revealed a somewhat remarkable survival benefit of IO for patients with unresectable stage III disease.[12] The results of our current study reveal that patients with potentially resectable stage III disease may also benefit from IO use.

The treatment trend with less use of surgery for stage IIIA(N2) NSCLC in this current study is also consistent with other recent observations in the real world.[17–19] Part of the decreased use in surgery may be from past trials failing to reveal a definite benefit over chemoradiation. Nevertheless, with numerous ongoing trials using neoadjuvant IO in NSCLC as summarized by Allaeys et al.,[20] we may find a reverse of this trend in the next decade as new randomized data are propagated. The current decrease in use of surgery may partially stem from the recognition that pneumonectomy in that setting can be associated with high perioperative mortality.[13–16] It is also possible that evidence from the randomized PACIFIC trial for patients with unresectable stage III NSCLC revealing improved survival with concurrent chemoradiation followed by one year of durvalumab may have shifted patients and providers further away from considering surgery as part of their multimodal treatment when a nonoperative option associated with relatively good outcomes was available.[12] Nevertheless, the trials that evaluated the impact of surgery in a multimodality regimen for stage III NSCLC were performed more than a decade ago, and we may start seeing the opposite trend with.[21,22] One reason why surgery may not have added a substantial survival benefit in past trials is that systemic agents were limited in preventing or treating distant disease, which dictates survival and usually occurs before or simultaneously with locoregional recurrence.[4,5,22] The use of IO in systemic therapy regimens in improving overall disease control may allow more patients with N2 disease to benefit from surgical resection, especially in light of our findings regarding outcomes of surgery combined with IO.

Recent advancements in the thoracic oncology world have led to advocating for IO in the preoperative setting as it has the potential to downstage unresectable tumors and increase patients' candidacy for surgical resection. Arguments against this strategy consider the risk of higher rates of positive margins and perioperative complications as a reason to stay the course with definitive chemoradiation and IO.[7,21,23] Although these hesitations are valid, cutting-edge research foci, such as the development of a consensus for the definition of resectability, and more sophisticated preoperative tumor and biomarker testing to identify patients who are more likely to respond well to IO will continue to answer these questions in the coming decade.[24–26] The CheckMate 816 trial recently revealed that patients who received neoadjuvant chemo-IO followed by definitive surgery maintained a disease-free survival regardless of surgical approach.[7] This bolsters further discussion about video-assisted and robotic-assisted resections being safe and efficacious for this group of heterogeneous patients. More randomized trials that specifically address the use of IO for potentially resectable patients with N2 disease would be ideal, but results are likely to take years to mature.[27,28] In the meantime, continuing to discuss these patients in a multidisciplinary tumor board will be key to individualizing optimal treatment with or without the use of IO.[29,30]

We acknowledge some limitations in our study due to the lack of detail such as the types of IO and chemotherapy drugs chosen, EGFR or other known genetic mutations, programmed death-ligand 1 levels, and the inability to ascertain whether patients completed their planned treatment courses. Our study also encompassed a relatively long time period during which staging definitions were revised and the overall cohort is therefore somewhat of a heterogeneous group where staging would have varied depending on the year of the study. Specifically, patients in the cohort in the earlier time period of the study with tumors more than 5 cm would have been classified as T3 by the eighth American Joint Committee on Cancer staging edition in 2018 onward and subsequently not have been included for analysis. In addition, we have limited information on patients' surgical candidacy at the time of diagnosis or treatment evaluation, such that those who did not undergo surgery may have had contraindications based on preoperative patient or tumor characteristics that we cannot delineate. We also recognize the potential for selection bias relative to the patients who received IO, such that patients given IO might have had other reasons to have better survival, including possibly IO being preferentially given to patients who were more fit or healthy overall and IO possibly being used in centers where overall surgical and nonsurgical care may have been somehow better than care at centers less likely to use IO. Although we attempted to control for selection bias with multivariable analysis, we recognize that we likely cannot control for some of these factors that are not measurable in the data set used. Nevertheless, we hope that studies such as ours that collate updated information on the dynamic treatment of stage IIIA(N2) NSCLC will help provide a broader overview of patterns of IO use and its impact on survival.

Treatment with IO has been found to have promise for patients with NSCLC in multiple trials. Our current study using a broad, real-world collection of patients with stage IIIA(N2) NSCLC suggests benefit in this realm as well, where progress has been relatively stagnant for a long time. The results from this study should be used to support further study of the use of IO for this challenging patient group. The results from this study can also be used when patients are evaluated in a multidisciplinary setting to help provide both patients and providers with realistic expectations of outcomes with available therapies.

CRediT Authorship Contribution Statement

Leah M. Backhus: Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.

Mark F. Berry: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.

Irmina A. Elliott: Investigation; Methodology; Project administration; Resources; Software; Writing—review and editing.

Douglas Z. Liou: Investigation; Methodology; Project administration; Resources; Software; Writing—review and editing.

Natalie S. Lui: Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.

Mohana Roy: Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.

Joseph B. Shrager: Funding acquisition; Validation; Visualization; Writing—review and editing.

Lye-Yeng Wong: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.

Disclosure

The authors delcare no conflict of interest.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100654.

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