Upfront surgery as first-line therapy in selected patients with stage IIIA non–small cell lung cancer

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ABSTRACT

Objective: Surgery plays an important role in the multidisciplinary treatment strategy for patients with stage IIIA non–small cell lung cancer (NSCLC). Besides induction therapy, patients could benefit from surgery followed by adjuvant chemotherapy and radiotherapy. This study analyzed a subset of patients with pIIIA NSCLC who underwent upfront surgery as first-line therapy.

Methods: Selected patients with pIIIA NSCLC who received upfront surgery were retrospectively analyzed. Clinicopathologic characteristics and survival outcomes including progression-free survival (PFS) and overall survival (OS) were evaluated.

Results: A total of 668 patients were identified. Five hundred sixty-five patients received adjuvant chemotherapy, and 157 patients received adjuvant radiotherapy after surgery. The median PFS and OS were 17.0 and 44.0 months, respectively. The 3-year and 5-year PFS rates were 31.6% and 21.0%, and the 3-year and 5-year OS rates were 54.7% and 43.0%. Patients with adenocarcinoma (AD) had better OS than those with squamous cell carcinoma (5-year OS: $P = .026$). Patients with low-grade AD (acinar and papillar) had a similar PFS and OS compared with patients with high-grade AD (solid, micropapillary, and mucinous) (5-year PFS: $P = .894$; 5-year OS: $P = .439$). Patients with mutated epidermal growth factor receptor had a similar OS to patients with wild-type epidermal growth factor receptor (5-year OS: $P = .121$). Patients with clinical N0 status ($P = .004$) and patients with single-station of pathologic N2 ($P < .001$) had better OS.

Conclusions: Upfront surgery followed by adjuvant therapy may provide favorable survival outcomes for selected patients with pIIIA NSCLC, especially for patients with AD or patients with clinical N0 and pathologic single-station N2 diseases. (J Thorac Cardiovasc Surg 2018;155:1814-22)

Survival curve of overall survival of patients with IIIA non–small cell lung cancer.

Central Message

Upfront surgery could provide favorable survival outcomes for selected patients with pIIIA non–small cell lung cancer, especially for patients with adenocarcinoma, or patients with cN0 and single-station pN2 diseases.

Perspective

Patients with stage IIIA non–small cell lung cancer have various survival outcomes depending on different subgroups. Treatment should be considered individualized. Surgery plays an important role in the multidisciplinary treatment strategy. Besides induction therapy, a subset of selected patients could benefit from upfront surgery followed by adjuvant chemotherapy and radiotherapy.

See Editorial Commentary page 1823.

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Treatment for patients with stage IIIA lung cancer remains one of the most challenging domains in thoracic oncology, in view of the intrinsic heterogeneity of this population. Multidisciplinary therapy based on chemotherapy, radiotherapy, or chemoradiotherapy combined with surgery was regarded as the standard option during the last 2 decades.¹⁻³ However, the optimal combination and sequence of these 3 options pose an ongoing challenge in

Scanning this QR code will take you to supplemental figures, tables, and video for this article.

Abbreviations and Acronyms

AD	= adenocarcinoma
CI	= confidence interval
CT	= computed tomography
EGFR	= epidermal growth factor receptor
HR	= hazard ratio
NSCLC	= non–small cell lung cancer
OS	= overall survival
PFS	= progression-free survival
PRS	= postrecurrent-free survival
SCC	= squamous cell carcinoma

clinical practice. First, most guidelines recommended induction treatment followed by surgical resection, but that the data supporting this approach compared with surgery followed by adjuvant treatment were mixed. In addition, the addition of radiotherapy to induction chemotherapy failed to improve survival compared with induction chemotherapy alone.^{4,5} Moreover, 2 randomized clinical trials showed that induction chemoradiotherapy plus surgery failed to present a survival benefit compared with definitive chemoradiotherapy. Although preoperative treatment did not increase the complexity of surgery or surgical-related adverse events, there were still some clinical trials that reported a greater perioperative mortality and morbidity.^{6,7} Furthermore, patients with incidentally discovered microscopic IIIA tumor could greatly benefit from initial surgical resection even without induction treatment.⁸

This dilemma was primarily caused by the heterogeneous subgroups of this disease. Therefore, the identification of certain patients with stage IIIA non–small cell lung cancer (NSCLC) who have decent outcomes with appropriate multimodality regimens and who have the best chance of long-term survival with surgery is necessary. In this study, we analyzed the characteristics and prognosis of a subset of patients with pIIIA NSCLC who underwent upfront surgery as first-line therapy. The aim of this study was to explore the role of upfront surgery in treating selected patients with pIIIA NSCLC.

PATIENTS AND METHODS

Patients

We prospectively collected data and retrospectively identified consecutive patients with pIIIA (including T₁₋₃N₂, T₃₋₄N₁, T₄N₀) NSCLC between August 2006 and December 2013 from the medical records at Fudan University Shanghai Cancer Center. All patients were initially treated with surgery. Those patients who received induction therapy were excluded from this study. Most of the patients received adjuvant chemotherapy or selective radiotherapy after surgery. Of these patients, survival data and clinicopathologic material were collected and evaluated.

Patients were preoperatively staged and evaluated according to routine protocol, which included enhanced chest computed tomography (CT) scan, enhanced brain magnetic resonance imaging or CT scan, bone scanning,

abdominal CT or ultrasonography, fiberoptic bronchoscopy, and cardiopulmonary tests. Positron emission tomography–CT was performed on highly suspicious patients with bulky mediastinal mass (tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured). A patient’s clinical stage was mainly assessed by chest CT scan. Patients whose tumors were considered initially unresectable received invasive mediastinal staging operations to receive pathology confirmation followed by induction therapy. These patients were excluded from this study.

A group of experienced thoracic surgeons performed surgeries. Video-assisted thoracic surgery or subaxillary muscle-sparing minithoracotomy was performed, and intraoperative frozen section was routinely performed.⁹ Once lung cancer was confirmed during the surgery, lobectomy with systematic mediastinal lymph node dissection was considered the standard operation (Video 1) and extension of anatomical pulmonary resection (bilobectomy or pneumonectomy) was performed if necessary (see flowchart in Figure 1). The systematic mediastinal and hilar lymphadenectomy (station 2, 3a, 4, 7, 8, 9, 10, and 11 on the right; station 5, 6, 7, 8, 9, 10, and 11 on the left) was strictly operated. Classification of lymph node station was based on the International Association for the Study of Lung Cancer lymph node map.¹⁰ All patients’ pathologic tumor, node, and metastasis stages were restaged according to the seventh edition of The Lung Cancer Staging Classification System. Lung adenocarcinoma (AD) specimens before 2011 were reviewed according to the 2011 classification of AD.¹¹

This study was conducted in line with the Declaration of Helsinki and was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center (Fudan University Shanghai Cancer Center IRB# 090977-1). Written informed consent was obtained from each patient to allow their biological samples to be genetically analyzed.

Follow-up

Patients were regularly followed every 3 ± 1 months during the first 3 years postoperatively. Enhanced chest CT scan and abdominal

VIDEO 1. Subaxillary muscle-sparing minithoracotomy and right upper lobectomy with upper mediastinal lymph node (group 2-4) dissection. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)32409-1/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)32409-1/fulltext).

FIGURE 1. Flowchart of clinical treatment strategy. *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *PET-CT*, positron emission tomography-computed tomography; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma.

ultrasonography were performed every 3 ± 1 months, whereas brain magnetic resonance imaging and bone scanning were required every 6 ± 1 months. From the third year after surgery, the follow-up period extended to every 6 ± 1 months, and every 12 ± 3 months from the sixth year. If tumor recurrence was suspected, pathologic confirmation was usually obtained. Follow-up was performed via the outpatient clinic visit and telephone calls.

Statistical Analysis

All data were recorded in Excel 2010 (Microsoft, Redmond, Wash) and analyzed with SPSS 16.0 (SPSS Inc, Chicago, Ill). A descriptive analysis was carried out in which categorical variables were expressed as absolute and relative frequencies and continuous variables as means $\pm$ SD. The primary endpoints were progression-free survival (PFS) and overall survival (OS). PFS was measured from the date of operation until the date of first progression or recurrence or death from any cause. OS was measured from the date of operation until the date of death from any cause or the date last seen alive.

Survival curves of PFS and OS were estimated by the Kaplan–Meier method. Differences in survival were assessed by the log-rank test. Variables with a *P* value less than .05 were entered into the Cox proportional hazards regression model for the multivariate analysis for prognostic factors. We used forward stepwise selection that formed stepwise selection

procedures with the likelihood ratio test. Factors statistically significant at the .05 level remained in the final model. The statistical results were expressed by 95% confidence intervals (CIs).

RESULTS

A total of 668 patients who received surgical resection at Department of Thoracic Surgery, Fudan University Shanghai Cancer Center and were pathologically confirmed as IIIA NSCLC were identified and included in this study. Their detailed characteristics were summarized in Table 1. The majority of patients ($n = 613$; 91.8%) received R0 resection. The mean number of the resected lymph nodes were 20.4 ± 10.0 , with a mean of 5.7 ± 5.9 metastasized lymph nodes. AD ($n = 434$; 65.0%) and squamous cell carcinoma (SCC; $n = 181$; 27.1%) were the predominant pathologic subtypes. Three hundred two patients with clinical N2 (45.2%) and 366 patients with clinical N0 (54.8%) were identified preoperatively. Six hundred twenty-eight patients with pathologic N2 diseases (94.0%) were postoperatively confirmed. Five hundred sixty-five patients

TABLE 1. Clinicopathologic characteristics of subjects in this study

Parameter	n (%)
Number	668
Age, y	
Median	59
Mean ± SD	59 ± 9.7
Range	22-86
Sex	
Male	415 (62.1)
Female	253 (37.9)
Smoking status	
Smoker	341 (51.0)
Never-smoker	327 (49.0)
Tumor location	
Peripheral	510 (76.3)
Central	158 (23.7)
Surgical approach	
VATS	49 (7.3)
Muscle-sparing minithoractomy	619 (92.7)
Resection extent	
Lobectomy	512 (76.6)
Bilobectomy	86 (12.9)
Pneumonectomy	70 (10.5)
Margin	
Positive	55 (8.2)
Negative	613 (91.8)
Pathologic subtype	
Adenocarcinoma	434 (65.0)
Squamous cell carcinoma	181 (27.1)
Adenosquamous carcinoma	27 (4.0)
Large cell lung cancer	18 (2.7)
Other subtypes	8 (1.2)
Clinical N2 status	
N0	366 (54.8)
N2	302 (45.2)
TNM stage (seventh)	
T1-3N2	628 (94.0)
T3-4N1	37 (5.5)
T4N0	3 (0.4)
Pathologic N2 status	
Single-station	337 (50.4)
Multistation	291 (43.6)
Adjuvant chemotherapy	
Yes	565 (84.6)
No (including unknown)	103 (15.4)
Adjuvant radiotherapy	
Yes	157 (23.5)
No	511 (76.5)

SD, Standard deviation; VATS, video-assisted thoracoscopy; TNM, tumor, node, and metastasis.

(84.6%) received adjuvant chemotherapy, and 157 patients (23.5%) received adjuvant radiotherapy after surgery. Six patients (0.9%) died within 1 month after surgery. Of these 6, 3 patients died due to surgery and another 3 patients died

due to tumor progression. The latter 3 did not receive radical resection, and their tumors progressed rapidly after surgery.

Progression-Free Survival

Six hundred fifty-three patients (97.8%) were regularly followed at the outpatient clinic and by telephone contact. Fifteen patients (2.2%) were lost during the follow-up period or because the follow-up time was less than 12 months. Four hundred thirty-two (cumulative incidence of recurrence at year 5: 69.7%) patients experienced tumor recurrence within 5 years after radical resection. More than 40% of these patients primarily had tumor recurrence in lung or superficial lymph node, all with pathologic confirmation. Patients whose tumor recurred in brain, bone, or abdominal organs were confirmed by the multidisciplinary tumor board, mainly based on the dynamic changes in imaging, tumor functional imaging, or liquid biopsy. The median PFS was 17.00 months (95% CI, 14.80-19.20). The 3-year and 5-year PFS rate was 31.6% and 21.0%, respectively (Figure 2, A). On univariable analysis, large tumor size ($P = .010$), clinical N2 status ($P = .002$), multistation of pathologic N2 ($P < .001$), muscle-sparing minithoractomy ($P = .029$), and without adjuvant chemotherapy ($P = .010$) were correlated with a greater risk of progression. On multivariable analysis, large tumor size (hazard ratio [HR], 1.232; 95% CI, 1.018-1.492; $P = .032$), clinical N2 status (HR, 1.220; 95% CI, 1.006-1.479; $P = .043$), multistation of pathologic N2 (HR, 1.456; 95% CI, 1.204-1.760; $P < .001$), and without adjuvant chemotherapy (HR, 1.311; 95% CI, 1.002-1.715; $P = .049$) were independently associated with worse PFS (Tables E1 and E2).

Overall Survival

Three hundred eighteen patients were alive or censored during the follow-up period. Three hundred forty-three (51.3%) patients died as the result of tumor progression. Seven (1.0%) patients died due to other causes, including gastric bleeding, bowel obstruction, fever, heart disease, and accident. The median OS was 44.0 months (95% CI, 37.78-50.22). The 3-year and 5-year OS rates were 54.7% and 43.0%, respectively (Figure 2, B). On univariable analysis, age older than 65 years ($P = .001$), smoker ($P = .032$), clinical N2 status ($P = .004$), muscle-sparing minithoractomy ($P = .004$), pneumonectomy or bilobectomy ($P < .001$), tumor larger than 3 cm ($P = .010$), non-AD ($P = .008$), R1 or R2 resection ($P < .001$), multistation of pathologic N2 ($P < .001$), and without adjuvant chemotherapy ($P < .001$) were associated with worse OS. On multivariable analysis, older age (HR, 1.308; 95% CI, 1.006-1.702; $P = .045$), smoker (HR, 1.277; 95% CI, 1.018-1.601; $P = .035$), multistation of pathologic N2 (HR, 1.671; 95% CI, 1.338-2.088; $P < .001$), positive margin (HR, 1.425; 95% CI, 1.188-1.709; $P < .001$), and

FIGURE 2. A, Survival curve of progression-free survival of patients with IIIA NSCLC. B, Survival curve of overall survival of patients with IIIA NSCLC. The colored dotted lines represent the 95% confidence interval for each curve.

without adjuvant chemotherapy (HR, 1.976; 95% CI, 1.468-2.660; $P < .001$) were independently associated with worse OS (Tables E1 and E2).

AD and SCC

Four hundred thirty-four patients with lung AD and 181 patients with lung SCC were pathologically confirmed. Their characteristics were listed in Table 2. Compared with lung SCC, lung AD was more commonly seen in female patients ($P < .001$) and never-smokers ($P < .001$). In addition, the tumor always showed peripheral location (located in or more peripheral to the subsegmental bronchus) ($P < .001$), small size ($P < .001$), but more N2 involvement ($P < .001$). Patients with AD had inferior 5-year PFS to patients with SCC (18.0% vs 29.4%), although there was no statistical significance ($P = .162$) (Figure 3, A). However, patients with AD had better 5-year OS than those with SCC (45.2% vs 40.6%; $P = .026$) (Figure 3, B). Moreover, we evaluated the postrecurrent-free survival (PRS) in these patients and found that patients with AD had a much better PRS than those with SCC (median PRS: 19 ± 1.5 vs

7.4 ± 1.3 months; $P < .001$) (Figure 4). According to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification,¹¹ there were no lepidic predominant, 194 acinar predominant, 73 papillar predominant, 132 solid predominant, 17 micropapillar predominant, and 18 mucinous subtypes in all ADs. In this study, acinar predominant and papillar predominant subtypes were classified as the low-grade AD ($n = 267$), whereas solid predominant, micropapillar predominant, and mucinous subtypes were classified as the high-grade AD ($n = 167$).¹² Compared with the high-grade AD, the low-grade AD had more small-sized lesions ($P < .001$), peripheral-located tumors ($P = .047$), and epidermal growth factor receptor (EGFR) mutations ($P < .001$). When analyzing PFS and OS by the architectural grade, we found that patients with low-grade tumors had a similar PFS compared with those with high-grade tumors (5-year PFS rate: 16.4% vs 20.7%, $P = .894$). Patients with low-grade tumors had a superior OS compared with those with high-grade tumors (5-year OS rate: 48.0% vs 39.2%, $P = .439$), although there was no statistical significance (Table E3 and Figure E1). When we analyzed OS by EGFR mutation, patients with mutated EGFR also had a similar OS to patients with wild-type EGFR (5-year OS rate: 47.7% vs 42.1%; $P = .121$) (Figure E2).

Clinical N2 and Pathologic N2 Diseases

Three hundred forty patients with preoperative N0 status were postoperatively confirmed N2 diseases in this study. These patients had a better PFS and OS than those with preoperative N2 diseases (5-year PFS rate: 22.6% vs 17.8%, $P = .003$; 5-year OS rate: 49.8% vs 35.5%, $P = .004$) (Figure E3). Moreover, for patients with pathologic N2 diseases, patients with single-station N2 had the significantly better PFS and OS than those with multistation N2 (5-year PFS rate: 25.6% vs 13.1%, $P < .001$; 5-year OS rate: 55.7% vs 28.5%, $P < .001$) (Figure E4).

DISCUSSION

Given the excellent results from the National Lung Screening Trial, detection and treatment of early-stage lung cancer have been improved, and the mortality of lung cancer has been reduced in recent years.^{13,14} However, advanced-stage lung cancer, especially those tumors with mediastinal lymph node involvement, is still commonly seen in real-world clinical practice. Treatment strategy for stage IIIA NSCLC is controversial, considering the intrinsic heterogeneity of this disease. These debates remain even in stage IIIA-N2 NSCLC.

In the early 1990s, 2 small randomized control trials conducted by Roth and colleagues¹⁵ and Rosell and colleagues¹⁶ reported the excellent results of induction chemotherapy followed by resection for patients with stage

TABLE 2. Comparison of characteristics of patients with lung AD and SCC

Parameter	AD (n = 434), n (%)	SCC (n = 181), n (%)	P value
Age, mean ± SD	58.5 ± 10.1	60.2 ± 8.5	.034*
Sex			<.001†
Male	216 (49.8)	162 (89.5)	
Female	218 (50.2)	19 (10.5)	
Smoking status			<.001†
Smoker	162 (37.3)	144 (79.6)	
Never-smoker	272 (62.7)	37 (20.4)	
Tumor location			<.001†
Peripheral	381 (87.8)	87 (48.1)	
Central	53 (12.2)	94 (51.9)	
Surgical approach			<.001†
Muscle-sparing	389 (89.6)	179 (98.9)	
VATS	45 (10.4)	2 (1.1)	
Resection extent			<.001†
Lobectomy	369 (85.0)	105 (58.0)	
Bilobectomy	44 (10.1)	35 (19.3)	
Pneumonectomy	21 (4.8)	41 (22.7)	
Margin			<.001†
Positive	23 (5.3)	30 (16.6)	
Negative	411 (94.7)	151 (83.4)	
Tumor size, cm			<.001*
≤3	238 (54.8)	38 (21.0)	
>3	196 (45.2)	143 (79.0)	
T			<.001†
T1a	67 (15.4)	5 (2.8)	
T1b	78 (18.0)	20 (11.0)	
T2a	208 (47.9)	62 (34.3)	
T2b	30 (6.9)	35 (19.3)	
T3	47 (10.8)	55 (30.4)	
T4	4 (0.9)	4 (2.2)	
Clinical N2 status			.001†
N0	264 (60.8)	84 (46.4)	
N2	170 (39.2)	97 (53.6)	
TNM stage			<.001†
T1-3N2	420 (96.8)	159 (87.8)	
T3-4N1	13 (3.0)	20 (11.1)	
T4N0	1 (0.2)	2 (1.1)	
Pathologic N2 status			.002†
Single-station	213 (49.1)	104 (57.5)	
Multistation	208 (47.9)	56 (30.9)	
Adjuvant chemotherapy			.934†
Yes	368 (84.8)	153 (84.5)	
No	66 (15.2)	28 (15.5)	
Adjuvant radiotherapy			.026†
Yes	113 (26.0)	32 (17.7)	
No	321 (74.0)	149 (82.3)	

(Continued)

TABLE 2. Continued

Parameter	AD (n = 434), n (%)	SCC (n = 181), n (%)	P value
Survival			
5-y PFS rate	18.0%	29.4%	.162‡
5-y OS rate	45.2%	40.6%	.026‡
Median PRS, mo	19 ± 1.5	7.4 ± 1.3	<.001‡
Median PFS, mo	18.8 ± 1.5	18.0 ± 2.8	.162‡
Median OS, mo	50.0 ± 4.7	33.8 ± 5.0	.026‡

AD, Adenocarcinoma; SCC, squamous cell cancer; SD, standard deviation; VATS, video-assisted thoracoscopy; TNM, tumor, node, and metastasis; PFS, progression-free survival; OS, overall survival; PRS, postrecurrent-free survival. *Analyzed by *t* test. †Analyzed by χ^2 test. ‡Analyzed by log-rank test.

IIIA-pN2 diseases compared with surgery alone, respectively. There were 60 patients in Roth and colleague's cohort and in Rosell and colleague's cohort. In the study of Roth and colleagues, the 3-year survival rate was 56% in perioperative chemotherapy group and 15% in surgery alone group. However, in the study by Rosell and colleagues, the 3-year survival rate was 27% and zero in each group. Surgical mortality in these 2 studies was 5% and 6.7%, respectively. Both trials stopped early and although they came to the same conclusions, the survival rates presented in these studies were quite different, making the benefit of induction chemotherapy appear unconvincing.

In addition, in 2002 Nagai and colleagues¹⁷ reported that in patients with stage IIIA N2 NSCLC, induction chemotherapy followed by surgery did not demonstrate a survival benefit compared with surgery alone. In the study of Nagai and colleagues, the 5-year survival rate was 10% in induction chemotherapy group and 22% in surgery alone group. The 5-year survival rate in surgery alone group seemed greater than that in induction chemotherapy group, although no statistical significance was reached. The authors attributed the negative result to the poor response to induction chemotherapy. Induction treatment including chemotherapy and/or radiotherapy combined with surgery could be beneficial and feasible for patients with resectable NSCLC.^{18,19} However, different meta-analyses showed opposite results comparing induction chemotherapy followed by surgery with surgery alone.²⁰⁻²² Subgroup analyses of stage IIIA patients were unavailable in the aforementioned literature. Controversies concerning induction chemotherapy in patients with stage IIIA NSCLC remain. Unfortunately, well-powered individual randomized controlled trials that show a clear survival advantage for induction chemotherapy or chemoradiotherapy are still unavailable.

According to previous reports, patients with stage IIIA-pN2 NSCLC who received preoperative chemotherapy or

FIGURE 3. A, Comparison of progression-free survival of patients with AD and patients with SCC. B, Comparison of overall survival of patients with AD and patients with SCC. The colored dotted lines represent the 95% confidence interval for each curve. AD, Adenocarcinoma; SCC, squamous cell cancer.

chemoradiotherapy combined with surgical resection had a median OS of nearly 25 months^{6,7,23-26} (Table 3). Recently, a multicenter, phase 3 randomized trial revealed that patients with stage IIIA-pN2 NSCLC who received induction chemotherapy and surgery had a median OS of 26.2 months, whereas patients who received induction chemoradiotherapy had a median OS of 37.1 months. This survival difference was statistically insignificant.⁵ In 2012, Japanese colleagues reported a nationwide analysis for patients with stage IIIA-cN2/pN2 NSCLC. Their results showed that patients receiving induction treatment had a 5-year survival rate of 28.1%, patients receiving adjuvant chemotherapy had a 5-year survival rate of 27.8%, and patients who underwent surgery alone had a 5-year survival rate of 33.7%. Therefore, regarding patients with IIIA-cN2/pN2

FIGURE 4. Comparisons of postrecurrent-free survival of patients with AD and patients with SCC. The colored dotted lines represent the 95% confidence interval for each curve. AD, Adenocarcinoma; SCC, squamous cell cancer.

NSCLC, surgery alone could provide favorable survival in comparison with those previously reported. However, in that study, only 34.6% patients received adjuvant chemotherapy, in whom 38 patients received oral chemotherapy.²⁷ Sophisticated selection of surgical candidate is important for patients with stage IIIA NSCLC, but postoperative adjuvant therapy is essential.²⁸

In the present study, we retrospectively analyzed 668 patients with stage IIIA NSCLC. These patients were either in cN0-1/pN2 or minimal N2 status by imaging evaluation preoperatively, and their tumors were considered initially resectable. Based on our treatment strategy, patients who were diagnosed with invasive lung cancer during surgery were subject to systematic lymph node dissection. Therefore, preoperative lymph node condition in these patients had little impact on our surgical procedure selection. Invasive mediastinal staging of lung cancer through mediastinoscopy endobronchial ultrasound-guided transbronchial needle aspiration or endoscopic ultrasound-guided needle aspiration not included in our treatment strategy, although most physicians believed that it was an important part of modern thoracic surgical oncology.^{29,30} Only initially unresectable patients received invasive mediastinal staging operations, whereas those patients with positive pathologic confirmations were initially given chemotherapy or induction chemotherapy.

Our strategy was slightly different from the current guidelines.³¹⁻³³ It was based on these strict criteria that patients included in this study could achieve favorable surgical outcomes. Ninety-four percent of the patients were IIIA-pN2 diseases. This subgroup of patients had a median PFS of 17.0 months and median OS of 44.0 months. Compared with previous reports (Table E2), this high OS rate might attribute to a high rate of cN0-1 patients in our study cohort. Moreover, for patients with clinical N2 diseases, the median PFS was 14.0 months and median OS was 34.9 months, respectively. Even for patients with multistation N2 involvement, the median PFS and OS were 13.8 months and 32.0 months, respectively. These results were unexpected but encouraging. Because of the postoperative adjuvant therapy and administration of EGFR-TKI for EGFR mutant lung AD, patients with stage IIIA-pN2 NSCLC received upfront surgery could achieve comparable or superior survival outcomes. Tumor size and lymph node status were the 2 most important prognostic factors for this disease, since with the surgical approach, extent and margin were determined by T and N status. Our data showed that even for T1a tumors, multistation mediastinal lymph node metastasis may occur anyway. Hence, tumor size was not an effective determinant for the final stage. Meticulous surgery including thorough mediastinal lymph nodes dissection was the “cornerstone.” In this study, each included patient received “aggressive” mediastinal lymphadenectomy, with an average of 20 lymph nodes resected. The

TABLE 3. World literature comparing the outcomes of surgery for stage IIIA-pN2 NSCLC

Author	Year	Study type	Number of patients	Induction therapy	Outcome, median	Result, mo (95% CI)	5-y survival rate (95% CI)	Study groups
Johnstone and colleagues ²⁴	2002	RCT	43	Chemo	OS	19.4 (–)	– (–)	CT + S vs CT + RT
Casali and colleagues ²⁵	2005	Retrospective	183	None	OS	24.0 (–)	20% (–)	S + CT
Van Meerbeeck and colleagues ⁷	2007	RCT	167	Chemo	OS	16.4 (13.3-19.0)	16% (10-20)	CT + S vs CT + RT
Albain and colleagues ⁶	2009	RCT	202	Chemo and RT	OS PFS	23.6 (–) 12.8 (–)	27% (–) 22% (–)	CT and RT + S vs CT + RT
Ratto and colleagues ²⁶	2009	Prospective	85	Chemo	OS	27.1 (–)	– (–)	S vs CT + S
Pless and colleagues ⁵	2015	RCT	117	Chemo&RT	PFS OS	12.8 (9.7-22.9) 37.1 (22.6-50.0)	– (–) – (–)	CT + S vs CT and RT + S
			115	Chemo	PFS OS	11.6 (8.4-15.2) 26.2 (19.9-52.1)	– (–) – (–)	
Current study	2016	Retrospective	668	None	PFS OS	17.1 (14.8-19.2) 44.5 (37.8-50.2)	21% (17-25) 43% (39-47)	

CI, Confidence interval; RCT, randomized controlled trial; Chemo, chemotherapy; OS, overall survival; –, data not reported; S, surgery; RT, radiotherapy; PFS, progression-free survival.

radical resection and precise N2 staging potentially contributed to the surprising survival outcomes.

Moreover, postoperative adjuvant chemotherapy and radiotherapy were absolutely necessary for these patients. Therefore, R0 resection and individualized postoperative adjuvant therapy were indispensable for patients with stage IIIA NSCLC. Furthermore, both systemic adjuvant chemotherapy and selective radiotherapy after surgery were necessary for achieving better outcomes.³⁴ All patients included in this study were recommended to receive adjuvant chemotherapy. Patients with positive margins or patients with multistation N2 involvement and high positive lymph node ratio (>50%) were required to receive adjuvant radiotherapy. As a result, 84.6% of the patients received chemotherapy; the rest of the patients refused the treatment due to personal reasons. Only 15 patients were lost to follow-up as well as their treatment information. As expected, adjuvant chemotherapy could effectively prolong overall survival. The role of radiotherapy in this study was more like a supplement to surgery rather than a mean to promote prognosis.

In addition, tyrosine kinase inhibitor therapy including gefitinib and erlotinib could greatly prolong the survival of patients with EGFR mutation.³⁵ In this study, most patients (80.4%) received 4 to 6 full cycles of platinum-based chemotherapy. When the recurrence was confirmed, patients with AD with a mutated EGFR were also recommended to receive maintenance therapy of EGFR-tyrosine kinase inhibitor. Remarkably, patients with AD had significantly better overall survival and postrecurrent survival than patients with SCC. Patients with EGFR mutation had a median OS of 57 months and a 5-year OS of 47.7%. EGFR mutation was more commonly seen in low-grade tumors. However, subtype analysis for AD showed that

low-grade AD promised a similar survival to high-grade ones. Accordingly, improvement of surgical techniques and increase prevalence of lung AD with EGFR mutation may be the reason for the good prognosis of patients with stage IIIA NSCLC.

There were several limitations of our study. First, this was a retrospective, single-institution study. Conclusions made from this study were not as solid as those from prospective and multicenter studies. A randomized controlled trial on this topic is still required. Second, there were no control groups in our study. Although our data were comparable with or even superior to other published data, the results should be treated with caution because of differences in baselines as well as selection bias. Third, our strategy did not include induction chemotherapy and excluded patients who received induction chemotherapy. Therefore, some of them should have been sensitive to induction chemotherapy, thereby improving the rate of radical resection and predicting the efficacy of adjuvant therapy and extending survival. Unfortunately, such important information could not be obtained from our study. Moreover, the survival condition of these patients could also affect the prognosis of overall patients with stage IIIA NSCLC. Fourth, comparisons between surgery versus nonsurgery and surgery alone versus induction therapy were not made or analyzed in this study, although they were important topics.

Primary surgery played a central role in this study. We selected qualified patients based on our treatment algorithm to receive upfront surgery as the first-line therapy. Surgery followed by chemotherapy or chemoradiotherapy could provide a favorable prognosis compared with other reports. Hopefully, this “single-arm” retrospective study will bring new insights to thoracic surgeons.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: non-small cell lung cancer, stage IIIA, upfront surgery, progression free survival, overall survival

FIGURE E1. A, Comparison of progression-free survival between high-grade and low-grade adenocarcinoma. B, Comparison of overall survival between high-grade and low-grade adenocarcinoma. The *colored dotted lines* represent the 95% confidence interval for each curve.

FIGURE E2. Comparison of overall survival between patients with mutated EGFR and wild-type EGFR. The *colored dotted lines* represent the 95% confidence interval for each curve.

FIGURE E3. A, Comparison of progression-free survival between patients with clinical N0 and patients with clinical N2. B, Comparison of overall survival between patients with clinical N0 and patients with clinical N2. The *colored dotted lines* represent the 95% confidence interval for each curve.

FIGURE E4. A, Comparison of progression-free survival between patients with single-station N2 and patients with multistation N2. B, Comparison of overall survival between patients with single-station N2 and patients with multistation N2. The *colored dotted lines* represent the 95% confidence interval for each curve.

TABLE E1. Univariate analysis of PFS and OS

Parameter	PFS			OS		
	HR	95% CI for HR	P value	HR	95% CI for HR	P value
Age, y						
>65	1.093	0.888-1.346	.402	1.491	1.185-1.876	.001
≤65	1.0			1.0		
Sex						
Male	1.095	0.909-1.319	.342	1.209	0.973-1.502	.087
Female	1.0			1.0		
Surgical approach						
Muscle-sparing	1.234	1.022-1.489	.029	1.440	1.121-1.852	.004
VATS	1.0			1.0		
Resection extent						
Pneumonectomy and bilobectomy	1.141	0.918-1.418	.236	1.528	1.204-1.940	<.001
Lobectomy	1.0			1.0		
Margin						
Positive	1.096	0.773-1.554	.607	1.370	1.157-1.621	<.001
Negative	1.0			1.0		
Tumor location						
Central	0.976	0.785-1.215	.831	1.201	0.937-1.538	.148
Peripheral	1.0			1.0		
Pathologic subtype						
AD	1.0			1.0		
Non-AD	0.934	0.769-1.135	.492	1.344	1.081-1.672	.008
Tumor size, cm						
≤3	1.0			1.0		
>3	1.271	1.058-1.527	.010	1.323	1.068-1.637	.010
Clinical N2 status						
Positive	1.326	1.106-1.591	.002	1.360	1.102-1.679	.004
Negative	1.0			1.0		
Pathologic N2 status						
Multistation	1.507	1.249-1.818	<.001	1.715	1.376-2.137	<.001
Single-station	1.0			1.0		
Adjuvant chemotherapy						
Yes	1.0			1.0		
No	1.395	1.081-1.799	.010	2.410	1.866-3.106	<.001
Adjuvant radiotherapy						
Yes	1.062	0.862-1.308	.573	0.896	0.700-1.147	.384
No	1.0			1.0		
Smoking status						
Smoker	1.079	0.900-1.293	.413	1.259	1.021-1.554	.032
Never-smoker	1.0			1.0		

PFS, Progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracoscopy; AD, adenocarcinoma.

TABLE E2. Multivariate analysis of PFS and OS

Parameter	PFS			OS		
	HR	95% CI for HR	P value	HR	95% CI for HR	P value
Age, y						
>65				1.308	1.006-1.702	.045
≤65				1.0		
Surgical approach						
Muscle-sparing				1.273	0.977-1.659	.073
VATS				1.0		
Resection extent						
Pneumonectomy and bilobectomy				1.292	0.989-1.688	.060
Lobectomy				1.0		
Margin						
Positive				1.425	1.188-1.709	<.001
Negative				1.0		
Tumor size, cm						
≤3	1.0	1.018-1.492	.032			
>3	1.232					
Clinical N2 status						
Positive	1.220	1.006-1.479	.043			
Negative	1.0					
Pathologic N2 status						
Multistation	1.456	1.204-1.760	<.001	1.671	1.338-2.088	<.001
Single-station	1.0			1.0		
Adjuvant chemotherapy						
Yes	1.0			1.0		
No	1.311	1.002-1.715	.049	1.976	1.468-2.660	<.001
Smoking status						
Smoker				1.277	1.018-1.601	.035
Never-smoker				1.0		

PFS, Progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracoscopy.

TABLE E3. Comparison of characteristics of the low-grade and high-grade groups

Parameter	Low-grade group (n = 267), n (%)	High-grade group (n = 167), n (%)	P value
Age, mean $\pm$ SD	59.2 $\pm$ 10.3	57.3 $\pm$ 9.7	.053*
Sex			.174†
Male	126 (47.2)	90 (53.9)	
Female	141 (52.8)	77 (46.1)	
Smoking status			.455†
Smoker	96 (36.0)	66 (39.5)	
Never-smoker	171 (64.0)	101 (60.5)	
Tumor location			.047†
Peripheral	241 (90.3)	140 (83.8)	
Central	26 (9.7)	27 (16.2)	
Surgical approach			.163†
Muscle-sparing	235 (88.0)	154 (92.2)	
VATS	32 (12.0)	13 (7.8)	
Resection extent			.513†
Lobectomy	231 (86.5)	138 (82.6)	
Bilobectomy	25 (9.4)	19 (11.4)	
Pneumonectomy	11 (4.1)	10 (6.0)	
Margin			.090†
Positive	18 (6.7)	5 (3.0)	
Negative	249 (93.3)	162 (97.0)	
Tumor size, cm			<.001*
≤ 3	165 (61.8)	73 (43.7)	
> 3	102 (38.2)	94 (56.3)	
T			<.001†
T1a	51 (19.1)	16 (9.6)	
T1b	55 (20.6)	23 (13.8)	
T2a	129 (48.3)	79 (47.3)	
T2b	11 (4.1)	19 (11.4)	
T3	20 (7.5)	27 (16.2)	
T4	1 (0.4)	3 (1.8)	
Clinical N2 status			.183†
N0	169 (63.3)	95 (56.9)	
N2	98 (36.7)	72 (43.1)	
Pathologic N2 status			.428†
Single-station	137 (51.3)	76 (45.5)	
Multistation	126 (47.2)	82 (49.1)	
Adjuvant chemotherapy			.124†
Yes	232 (86.9)	136 (81.4)	
No	35 (13.1)	31 (18.6)	
Adjuvant radiotherapy			.033†
Yes	79 (29.6)	34 (20.4)	
No	188 (70.4)	133 (79.6)	
EGFR mutation			<.001†
Mutated	154 (57.7)	42 (25.1)	
Wild-type	113 (42.3)	125 (74.9)	
Survival			
5-y PFS rate	16.4%	20.7%	.894‡
5-y OS rate	48.0%	39.2%	.439‡
Median PFS, mo	19.8 $\pm$ 1.5	16.0 $\pm$ 2.6	.894‡
Median OS, mo	57.0 $\pm$ 5.8	45.0 $\pm$ 3.8	.439‡

ACI and PAP subtypes were classified as the low-grade adenocarcinoma; SOL, MIP predominant, and MUC subtypes were classified as the high-grade adenocarcinoma. *SD*, Standard deviation; *VATS*, video-assisted thoracoscopy; *EGFR*, epidermal growth factor receptor; *PFS*, progression-free survival; *OS*, overall survival. *Analyzed by *t* test. †Analyzed by χ^2 test. ‡Analyzed by log-rank test.