Original Article

Adjuvant therapy in stage IIIA-N2 non-small cell lung cancer after neoadjuvant concurrent chemoradiotherapy followed by surgery

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Background: This study aimed to determine whether adjuvant therapy improves survival in patients with stage IIIA-N2 non-small cell lung cancer (NSCLC) after neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgery.

Methods: We retrospectively reviewed 467 consecutive patients with stage IIIA-N2 NSCLC who received neoadjuvant CCRT followed by surgery between 2004 and 2013. From these, we identified 398 eligible patients and their clinical outcomes were compared according to whether adjuvant therapy was provided.

Results: In total, 296 patients (74%) received adjuvant therapy consisting of chemotherapy alone (n=71) radiotherapy alone (n=118) and both chemotherapy and radiotherapy (n=107). Adjuvant therapy was not given to remaining 102 patients. Patients who receiving adjuvant therapy were significantly younger (P=0.001), and predominantly male (P=0.014) compared to patients who did not receive adjuvant therapy. Regarding to the pathologic response, the adjuvant therapy group had a significantly poor pathologic response. However, the 5-year overall survival (OS) rate did not significantly differ between the groups (adjuvant therapy group, 52.9%; no adjuvant therapy group, 54.9%; P=0.369). After adjusting for age, sex, type of operation, cell type and yp stage, adjuvant therapy was significantly associated with better OS (hazard ratio =0.59; 95% CI, 0.38–0.92; P=0.019) and disease free survival (hazard ratio =0.62; 95% CI, 0.44–0.87; P=0.006).

Conclusions: Our data indicate that adjuvant therapy is more often given to patients with poor pathologic findings. Adjuvant treatment after trimodal therapy is a significant predictor of survival after adjustment of clinical variables.

Keywords: Chemotherapy; radiotherapy; non-small cell lung cancer (NSCLC); surgery; outcomes

Submitted Jun 20, 2019. Accepted for publication Dec 05, 2019.
doi: 10.21037/jtd.2020.03.23
View this article at: http://dx.doi.org/10.21037/jtd.2020.03.23

Introduction

Approximately 20% of all non-small cell lung cancer (NSCLC) is stage IIIA-N2 (1). Those patients are heterogeneous in terms of disease extent and survival. Treatment options included induction chemotherapy or concurrent chemoradiotherapy (CCRT) followed by

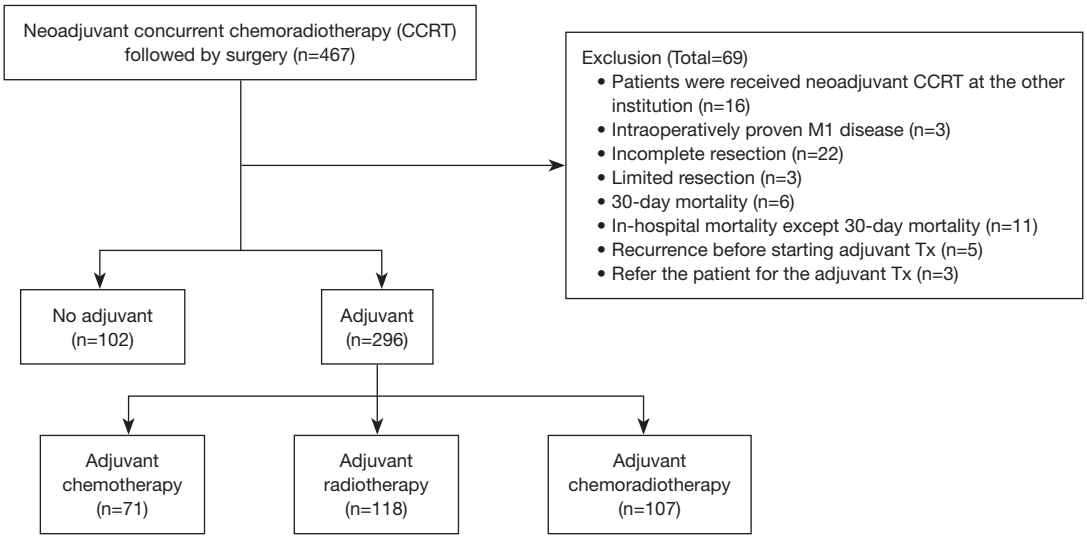

Figure 1 Diagram summarizing the study population.

surgery, or definitive CCRT (2-7). The optimal strategy for IIIA-N2 NSCLC remains controversial and no treatment is clearly recommended (8,9).

The overall prognosis of IIIA NSCLC is still poor, with a median survival time of 14–25 months despite multimodal therapy. Many patients develop local or distant recurrence eventually many patients develop local and distant recurrence (8-11). Additional adjuvant therapy may be needed to control the disease, although the benefit of adjuvant treatment after multimodal therapy is doubtful owing to the considerable toxicity of each therapy (12).

There are limited data on adjuvant therapy for patients who have undergone neoadjuvant CCRT and surgical treatment. Therefore, we examined the effects of the adjuvant therapy in patients with stage IIIA-N2 NSCLC after neoadjuvant CCRT followed by surgery.

Methods

Study population

We retrospectively reviewed the medical records of all patients who underwent surgery for NSCLC with curative intent surgery at the Samsung Medical Center a 1,961-bed referral hospital in Seoul, South Korea, between January 2004 and December 2013. During this period, 467 patients underwent neoadjuvant CCRT followed by surgical resection for stage IIIA-N2 NSCLC. Of these, patients who received CCRT at our institution and followed by complete resection with systematic lymph node (LN) dissection were included in this study population. Exclusion criteria were summarized in *Figure 1*. Ultimately, 398 patients were included: 102 patients did not receive the adjuvant therapy after surgery (no-therapy group) and 296 patients received adjuvant treatment including chemotherapy (n=71), radiotherapy (n=118) or chemoradiotherapy (CRT) (n=107) (therapy group). To review and publish the information obtained from patient records, the study was given approval by the Institutional Review Board of Samsung Medical Center (IRB No. 2015-05-143).

Preoperative staging work-up

The routine preoperative workup included pulmonary function tests, computed tomography (CT) scans of the chest and upper abdomen, positron emission tomography (PET)/CT scans, flexible bronchoscopy, and magnetic resonance imaging (MRI) of the brain. Preoperatively, 360 patients were pathologically confirmed to have mediastinal LN metastasis. Mediastinoscopy (n=213) and endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) (n=124), were performed most frequently to prove LN metastasis, although video-assisted thoracic surgery (VATS) LN biopsy (n=13), combined VATS and mediastinoscopy (n=4), anterior mediastinotomy (n=3), combined mediastinoscopy and mediastinotomy (n=3) were also performed. For the remaining patients, mediastinal staging was based on CT and PET/CT findings without

pathologic confirmation.

Neoadjuvant CCRT

Neoadjuvant CCRT included chemotherapy and concurrent thoracic radiotherapy. The therapeutic regimens of were different according to year of administration. Before October 2009, radiation therapy was delivered to patients with a total dose of 45 Gy (1.8 Gy/fraction/day) over 5 weeks. From October 2009 and thereafter, radiation dose was 44Gy (2.0 Gy/fraction/day) over 4.5 weeks using 10-MV X-rays. The chemotherapy regimen mostly consisted of weekly paclitaxel (50 mg/m^2 per week, iv) or docetaxel (20 mg/m^2 per week, iv) plus cisplatin (25 mg/m^2 per week, iv) or carboplatin (AUC 1.5/week, iv) for 5 weeks.

Surgery

Surgical resection was scheduled at 4–6 weeks following the completion of neoadjuvant CCRT. Operative procedures included lobectomies, bilobectomies, or pneumonectomies as indicated. Mediastinal LN dissection consisted of en bloc resections of all nodes at stations 2R, 4R, 7, 8, and 9 and 10R for a right-sided tumor and 4L, 5, 6, 7, 8, and 9 and 10L for a left-sided tumor.

Postoperative treatment and follow-up

Postoperative treatment was decided using multidisciplinary team approach after considering the extent of disease and general condition of each patient. Postoperative treatment included chemotherapy (taxane or vinorelbine, combined with platinum), radiotherapy (18 Gy in 10 fraction), CRT or no treatment. Patients were regularly evaluated by chest CT scans every 3 to 4 months for the first 2 years following surgery and every 6 months thereafter. Patients were annually evaluated by PET/CT scans for detection of recurrence.

Statistical analysis

The baseline characteristics assessing were compared using student *t*-test or ANOVA for continuous variables and chi-square or Fisher's exact test for categorical variables. Overall survival (OS) was defined as the time from the date of surgery until the last date of follow-up for patients who remained alive or until death. Disease-free survival (DFS) was defined as the time from the date of surgery to recurrence or death. The Kaplan-Meier method with the log-rank test and Cox proportional hazards model were conducted to determine the prognostic impact of adjuvant therapy. All statistical tests were two-sided with a significance level set at 0.05 and were performed using PASW Statistic 21 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Table 1 summarized the baseline characteristics according to whether adjuvant therapy was provided. The mean age was 59 years (range, 32–76 years) and the majority of patients were males. Patients in the adjuvant therapy group were significantly younger (61.2 *vs.* 57.9, P=0.001) and had a greater percentage of female (P=0.014) compared to those in the no adjuvant therapy group. Adenocarcinoma was the predominant cell type regardless of postoperative treatment; the incidence of adenocarcinoma and squamous cell carcinoma was significantly different between the two groups. In terms of type of surgery, lobectomy was the most common. More lobectomies tended to be performed in the adjuvant therapy group (P=0.075), while significantly more bilobectomies were performed in the no adjuvant therapy group (P=0.004).

Pathologic response according to adjuvant therapy

The postoperative pathologic findings are showed in *Table 1*. Mediastinal clearance was achieved in 213 patients (53.6%), whereas residual N2 disease was present in 185 patients (46.5%). More than half of patients (n=161) in the adjuvant therapy group had residual mediastinal metastasis, while only 25 patients had ypN2 disease in the no adjuvant therapy group. There was a significant difference in the mediastinal clearance between the two groups (P<0.0001). A complete pathologic response was observed in 52 patients (13.1%). Patients in the no adjuvant therapy group had significantly more pathologic response compare to the adjuvant therapy group (P<0.0001).

Patient characteristic and pathologic findings across adjuvant treatment types

As shown in *Table 2*, age, sex and histologic type were similar across the type of adjuvant therapy, whereas ypN stage (for N0, P=0.037; for N2, P=0.003) and overall yp

Table 1 Patient characteristics and pathologic findings according to whether adjuvant therapy was provided

Variables	Total (n=398)	No adjuvant (n=102)	Adjuvant therapy (n=296)	P value
Sex				0.014
Male	304 (76.4)	87 (85.3)	217 (73.3)	
Female	94 (23.6)	15 (14.7)	79 (26.7)	
Age, mean ± SD	58.8±8.60	61.2±8.28	57.9±8.56	0.001
Cell type				
Adenocarcinoma	236 (59.3)	49 (48.0)	187 (63.2)	0.007
Squamous cell	130 (32.7)	42 (41.2)	88 (29.7)	0.034
Others	32 (8.0)	11 (10.8)	21 (7.1)	0.237
Type of operation				
Lobectomy	324 (81.4)	77 (75.5)	247 (83.4)	0.075
Bilobectomy	35 (8.8)	16 (15.7)	19 (6.4)	0.004
Pneumonectomy	39 (9.8)	9 (8.8)	30 (10.1)	0.701
ypT stage				
No residual tumor	63 (15.8)	29 (28.4)	34 (11.5)	<0.0001
T1/2	295 (74.1)	66 (64.7)	229 (77.4)	0.012
T3/4	40 (10.1)	7 (6.9)	33 (11.1)	0.214
ypN stage				
N0	161 (40.5)	70 (68.6)	91 (30.7)	<0.0001
N1	52 (13.1)	7 (6.9)	45 (15.2)	0.031
N2	185 (46.5)	25 (24.5)	160 (54.1)	<0.0001
yp stage				<0.0001
CR	52 (13.1)	27 (26.5)	25 (8.4)	
I	94 (23.6)	37 (36.3)	57 (19.3)	
II	59 (14.8)	13 (12.7)	46 (15.5)	
III	193 (48.5)	25 (24.5)	168 (56.8)	

Continuous variables were expressed mean and standard deviation. SD, standard deviation; CR, pathologic complete response.

stage (P=0.009) were significantly higher in the radiotherapy or CRT groups compare to the chemotherapy group.

OS/DFS with adjuvant therapy

Kaplan-Meier curves and the log-rank test showed no significant differences in OS (*Figure 2A*, P=0.369) and DFS (*Figure 2B*, P=0.736) between patients with or without adjuvant therapy. The 5-year OS was 54.9% in the adjuvant therapy group and 52.9% in the no adjuvant therapy group; the values for 5-year DFS were 30.7% and 45.1%, respectively.

In regards to yp stage, 5-year OS was significantly different by yp stage (pathologic complete response,72.3%; stage I,66.2%; stage II, 54.8% and stage III, 41.4%; P=0.029) (*Figure 3A*). Adjuvant therapy was associated with significantly better OS in patient with yp stage II (*Figure 3B*,*C*,*D*,*E*, 19.7% *vs.* 61.8%, P=0.008). Also, DFS differed according to yp stage (CR, 64.6%; stage I, 50.8%; stage II, 28.5% and stage III, 17.8%, P<0.0001) (*Figure 4A*). Patients with yp stage III is likely to have survival benefit with adjuvant treatment (DFS, 16.7% *vs.* 18.7%,

Table 2 Patient characteristic and pathologic findings across adjuvant therapy types

Variables	Chemotherapy (n=71)	Radiotherapy (n=118)	CRT (n=107)	P value
Sex				0.356
Male	48 (67.6)	91 (77.1)	78 (72.9)	
Female	23 (32.4)	27 (22.9)	29 (27.1)	
Age, mean ± SD	58.8±8.11	57.8±8.66	57.5±8.77	0.606
Cell type				
Adenocarcinoma	46 (64.8)	69 (58.5)	72 (67.3)	0.372
Squamous cell	19 (26.8)	42 (35.6)	27 (25.2)	0.194
Others	6 (8.5)	7 (5.9)	8 (7.5)	0.793
Type of operation				
Lobectomy	64 (90.1)	94 (79.7)	89 (83.2)	0.171
Bilobectomy	2 (2.8)	11 (9.3)	6 (5.6)	0.214
Pneumonectomy	5 (7.0)	13 (11.0)	12 (11.2)	0.612
ypT stage				
No residual tumor	10 (14.1)	14 (11.9)	10 (9.3)	0.616
T1/2	57 (80.3)	86 (72.9)	86 (80.4)	0.324
T3/4	4 (5.6)	18 (15.3)	11 (10.3)	0.118
ypN stage				
N0	30 (42.3)	35 (29.7)*	26 (24.3)*	0.037
N1	15 (21.1)	13 (11.0)	17 (15.9)	0.167
N2	26 (36.6)	70 (59.3)*	64 (59.8)*	0.003
yp stage				0.009†
CR	8 (11.3)	8 (6.8)	9 (8.4)	
I	20 (28.2)	23 (19.5)	14 (13.1)	
II	16 (22.5)	12 (10.2)	18 (16.8)	
III	27 (38.0)	75 (63.6)	66 (61.7)	

Continuous variables were expressed mean and standard deviation. *, P value <0.05, versus chemotherapy; †, P value for trend. CRT, chemoradiotherapy; SD, standard deviation; CR, pathologic complete response.

P=0.036), otherwise statistical significance was not found (*Figure 4B,C,D,E)*.

Prognostic impact of adjuvant therapy/type of adjuvant therapy for OS and DFS

After adjusting for age, sex, type of operation, cell type and yp stage, adjuvant therapy was associated with a significantly better OS [hazard ratio (HR) =0.593; 95% CI, 0.383–0.918; P=0.019] (*Table 3*) and DFS (HR =0.616; 95% CI, 0.435–0.872; P=0.006) compared to patients in the no adjuvant therapy group (*Table 4*).

In terms of type of adjuvant treatment, adjuvant chemotherapy and CRT were associated with a significantly better OS (adjuvant chemotherapy; HR =0.416; 95% CI, 0.22–0.79; P=0.003, adjuvant CRT; HR =0.587; 95% CI, 0.349–0.987; P=0.044) in the multivariable analysis (*Table 3*), while adjuvant radiotherapy and CRT were associated with

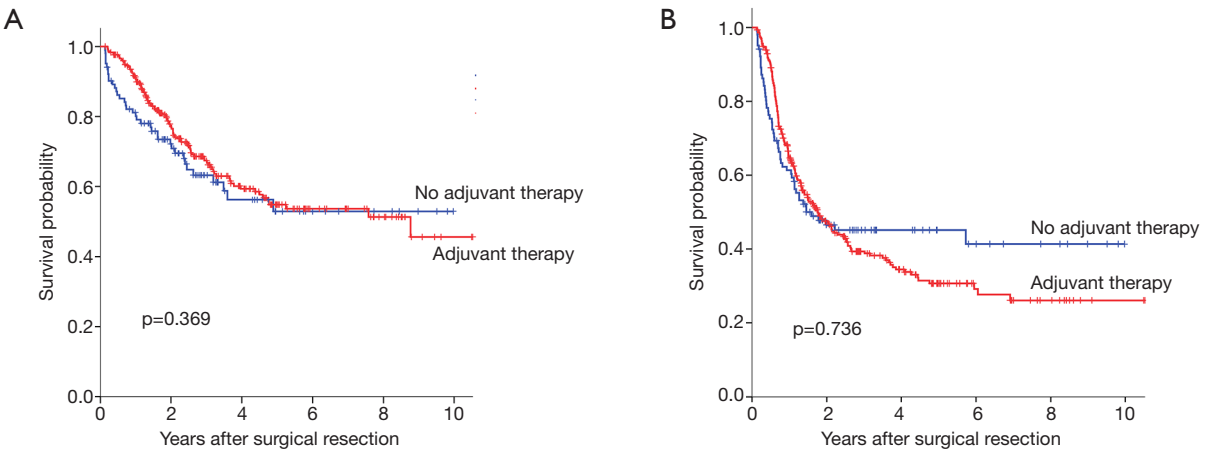

Figure 2 Overall survival (OS) and disease free survival (DFS) between patients in the no-adjuvant therapy group and adjuvant therapy group. (A) There was no a statistically significant difference in the OS between the two groups (P=0.369); (B) there was no a statistically significant difference in the DFS (P=0.736).

a better DFS after adjusting for clinical variables (*Table 4*).

Discussion

The OS rate and DFS rate were similar whether adjuvant therapy was given to patients who received neoadjuvant CCRT with subsequent complete surgical resection for stage IIIA-N2 NSCLC, although patients in the no adjuvant therapy group had better pathologic response to neoadjuvant treatment compare to patients in the adjuvant therapy group. Remarkably, a Cox-regression model showed that adjuvant therapy was independent prognostic factors related to better OS and DFS even after adjustment of sex, age, histology, surgical procedure and pathologic stage.

Several factors have been described to predict survival after neoadjuvant treatment followed by surgery. Mediastinal downstaging and regression of the primary tumor is associated with improved survival compared with patients with residual N2 disease (8,9,13-18). Previously, we obtained a similar result; the ypN stage was significant prognostic factor of OS ad DFS (19). Single node station, minimal N2 disease and decrease in intensity of uptake on PET scan are also considered favorable prognostic factors (8,9,20,21).

Cisplatin-based adjuvant chemotherapy has become the standard for patients with completely resected stage II or III NSCLC (22-24). Postoperative radiotherapy is controversial and not recommended routinely for patients with completely resected N2 NSCLC. A study based on the Surveillance, Epidemiology, and End Results (SEER) database and Adjuvant Navelbine International Trialist Association (ANITA) trial demonstrated the benefit of postoperative radiotherapy for N2 disease after surgical resection (25,26). However, for patients who underwent neoadjuvant CCRT, the role of adjuvant chemotherapy or radiotherapy was not known.

To the best of our knowledge, this is the first investigation to document the impact of adjuvant therapy for patients who underwent trimodal therapy for stage IIIA-N2 NSCLC. The overall 5-year OS was 54%, and according to ypN stage, the OS in patients with N0, N1 and N2 disease was 65.8%, 58.5% and 40.8%, respectively. These outcomes are quite favorable compared to the reported survival rate of patients with ypN2 disease of 9–29% (4,6,9,27-29).

At our institution, selected patients were given adjuvant treatment after trimodal therapy. The extent of disease was the critical factor when deciding whether to give adjuvant therapy. Using a multidisciplinary team approach, each patient was evaluated to determine the risks and benefits of adjuvant treatment. If the patient was deemed able to tolerate further treatment, we recommended adjuvant therapy, especially for patients with persistent mediastinal disease, which is a known prognostic factor. Typically, patients who was expected favorable outcomes (less extent of disease) and relatively healthy patients might undergo surgical resection. Therefore, our survival results are not applicable to all patients with N2 disease. In the subgroup analysis according to yp stage, adjuvant therapy resulted in significantly better survival in patients with yp stage II and better DFS in patients with yp stage III. This suggests that

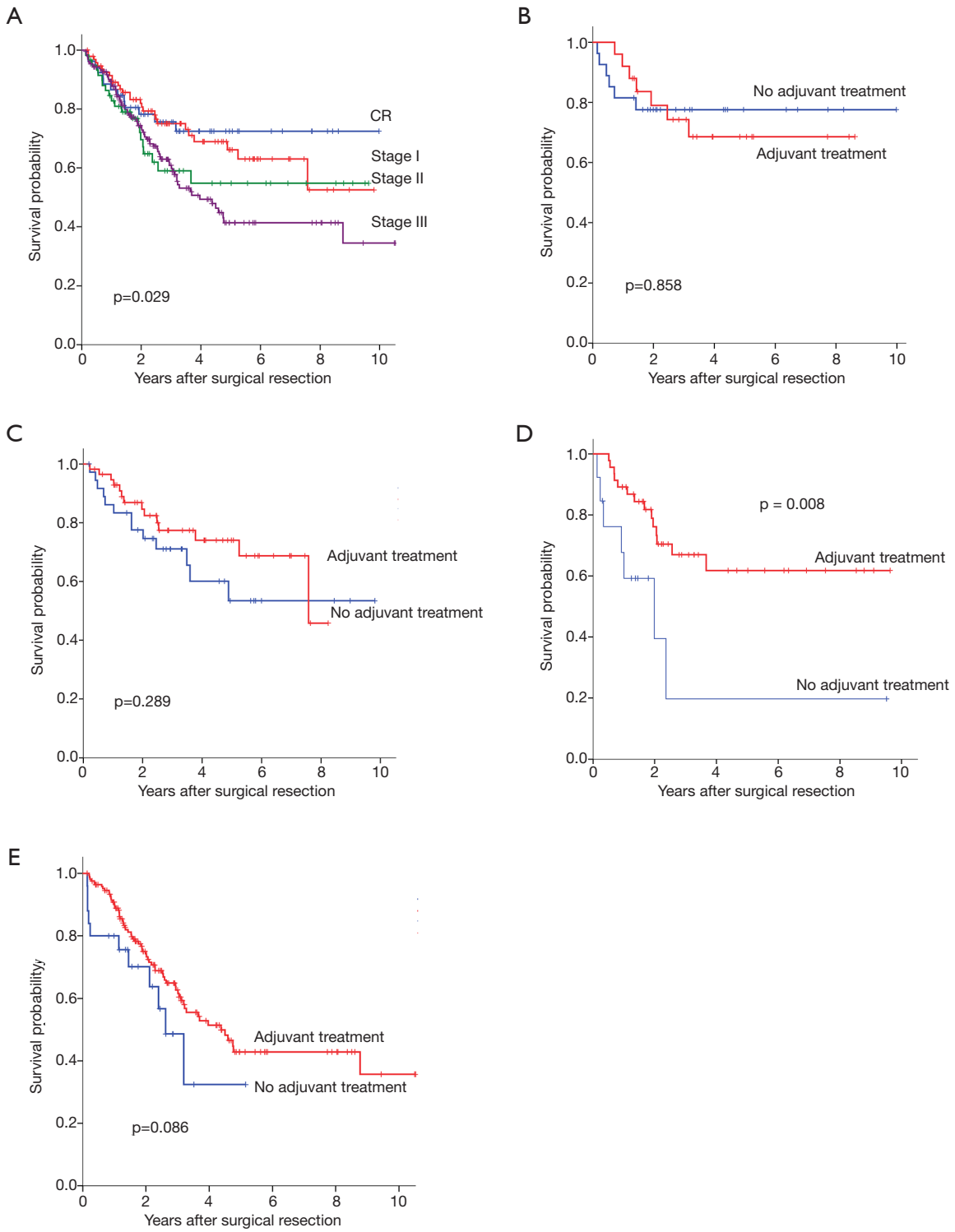

Figure 3 Subgroup analysis of overall survival (OS) between patients in the no-adjuvant therapy group and adjuvant therapy group. OS was statistically different according to yp stage (A) (P=0.029). OS according to whether adjuvant therapy was provided in patients with pathologic complete response (B), yp stage I (C), yp stage II (D) and yp stage III (E). Adjuvant therapy was associated with better OS in patient with yp stage II (P=0.008).

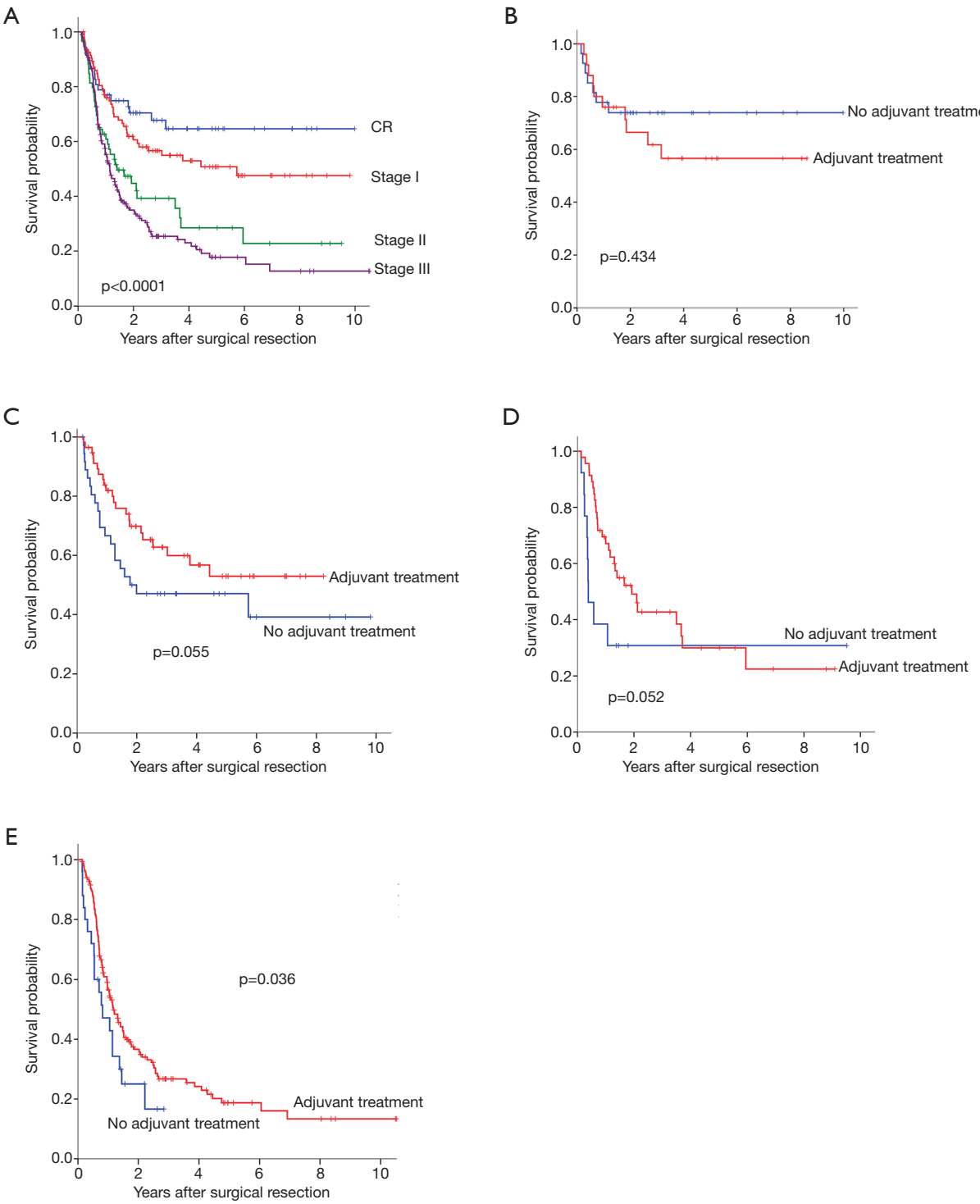

Figure 4 Subgroup analysis of disease free survival (DFS) between patients in the no-adjuvant therapy group and adjuvant therapy group. DFS was statistically different according to yp stage (P<0.0001) (A). DFS according to whether adjuvant therapy was provided in patients with pathologic complete response (B), yp stage I (C), yp stage II (D) and yp stage III (E). Adjuvant therapy was associated with better DFS in patients with yp stage III (P=0.036).

Table 3 Multivariate Cox-regression analysis of prognostic factor for overall survival

Variable	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.023 (1.002–1.044)	0.030	1.024 (1.003–1.045)	0.024
Male	1.351 (0.865–2.111)	0.186	1.316 (0.842–2.057)	0.228
Type of operation				
Lobectomy *vs.* bilobectomy	0.921 (0.489–1.732)	0.798	0.898 (0.478–1.689)	0.740
Lobectomy *vs.* pneumonectomy	3.257 (2.003–5.296)	<0.0001	3.274 (2.015–5.319)	<0.0001
Cell type				
Adenocarcinoma	1.077 (0.712–1.628)	0.726	1.057 (0.698–1.599)	0.794
yp stage				
CR *vs.* stage I	1.267 (0.650–2.469)	0.488	1.274 (0.653–2.485)	0.477
CR *vs.* stage II	2.219 (1.075–4.581)	0.031	2.390 (1.151–4.965)	0.019
CR *vs.* stage III	2.760 (1.434–5.314)	0.002	2.708 (1.402–5.232)	0.003
Type of adjuvant treatment				
No adjuvant	1 (reference)		1 (reference)	
Adjuvant	0.593 (0.383–0.918)	0.019		
Chemotherapy			0.416 (0.218–0.792)	0.003
Radiotherapy			0.684 (0.424–1.103)	0.120
CRT			0.587 (0.349–0.987)	0.044

Model 1: this model represents the HR for any adjuvant treatment compared to those of no adjuvant treatment. Model 2: this model represents the HR for adjuvant treatment including chemotherapy, radiotherapy and chemoradiotherapy compared to those of no adjuvant treatment. HR, hazard ratio; CI, confidence interval; CR, pathologic complete response; CRT, chemotherapy and radiotherapy.

the impact of adjuvant treatment differs according to yp or ypN stage. Overall, our findings suggest that adjuvant therapy is beneficial in selected patients who have a poor pathologic response. They might also explain the good survival outcomes in patients with ypN1 or N2 disease.

There are several limitations to our study. First, this retrospective study was conducted at a single referral center. Second, the administration of adjuvant therapy was decided case-by- case using multidisciplinary team approach, and was not based on the consistent guideline. Patients who expected to have relatively better outcomes were selected at the discretion of the treating physicians and surgeons, possibly biasing the outcome. Therefore, the adjuvant therapy group might have consisted of patients with relatively better performance status, which can influence OS. Therefore, our results should be interpreted carefully. We tried our best to improve internal validity, limiting the study to patient who completed the treatment in the same institution and only including cases who had undergone complete resection. However, surgical candidates with N2 disease are relatively rare and considering heterogeneity of N2 disease, it is difficult to conduct a well-designed randomized controlled trial. Our real-world practice provides some evidence for further investigations.

In conclusion, administration of adjuvant therapy following trimodal therapy was a significant prognostic indicator of OS and DFS. To confirm our results, better-designed prospective study is required.

Table 4 Multivariate Cox-regression analysis of prognostic factor for disease free survival

Variable	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.001 (0.986–1.017)	0.856	1.001 (0.986–1.017)	0.875
Male	1.134 (0.829–1.551)	0.431	1.145 (0.836–1.569)	0.400
Type of operation				
Lobectomy *vs.* bilobectomy	0.723 (0.430–1.214)	0.220	0.726 (0.432–1.221)	0.227
Lobectomy *vs.* pneumonectomy	2.205 (1.427–3.406)	<0.0001	2.227 (1.441–3.442)	<0.0001
Cell type				
Adenocarcinoma	1.541 (1.115–2.129)	0.009	1.556 (1.125–2.151)	0.008
p stage				
CR *vs.* stage I	1.481 (0.834–2.620)	0.177	1.475 (0.834–2.610)	0.182
CR *vs.* stage II	2.963 (1.618–5.427)	<0.0001	2.975 (1.622–5.456)	<0.0001
CR *vs.* stage III	3.575 (2.053–6.227)	<0.0001	3.579 (2.054–6.237)	<0.0001
Type of adjuvant treatment		0.006		0.040
No adjuvant	1 (reference)		1 (reference)	
Adjuvant therapy	0.616 (0.435–0.872)			
Chemotherapy			0.644 (0.412–1.006)	0.053
Radiotherapy			0.652 (0.443–0.959)	0.030
CRT			0.556 (0.370–0.837)	0.005

Model 1: this model represent the HR for any adjuvant treatment compared to those of no adjuvant treatment. Model 2: this model represent the HR for adjuvant treatment including chemotherapy, radiotherapy and chemoradiotherapy compared to those of no adjuvant treatment. HR, hazard ratio; CI, confidence interval; CR, pathologic complete response; CRT, chemotherapy and radiotherapy.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.03.23). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was given approval by the Institutional Review Board of Samsung Medical Center (IRB No. 2015-05-143).

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Cite this article as: Shin S, Kim HK, Cho JH, Choi YS, Kim K, Kim J, Zo JI, Sun JM, Ahn MJ, Park K, Pyo H, Ahn YC, Shim YM. Adjuvant therapy in stage IIIA-N2 non-small cell lung cancer after neoadjuvant concurrent chemoradiotherapy followed by surgery. J Thorac Dis 2020;12(5):2602-2613. doi: 10.21037/jtd.2020.03.23

