ORIGINAL ARTICLE

Validation of the Proposed cN2 Subclassification in the Eighth Edition of the IASLC Staging System: A Prospective Phase II Multicenter Study

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ABSTRACT

Introduction: Surgery for N2 stage IIIA NSCLC is not recommended in major guidelines. Nevertheless, it has been noted that single-station N2 may have a better prognosis than multistation N2 and that surgery can be performed as the main therapeutic option.

Methods: We conducted a prospective phase II study for single-station clinical N2 (cN2) NSCLC to evaluate the efficacy and safety of surgical resection without induction therapy. Complete resection with lobectomy, bilobectomy, or pneumonectomy followed by ipsilateral mediastinal lymphadenectomy was performed in 32 of 34 enrolled patients, whereas the remaining two patients underwent incomplete resection. Three-quarters of the patients underwent subsequent adjuvant chemotherapy.

Results: The 5-year overall survival rate was 58.5% (95% confidence interval: 41.9–75.4) for all 34 patients, and eight patients (23.5%) with pN0 or pN1 seemed to have been enrolled. The 5-year overall survival rates for single-station cN2 without and with hilar node enlargement were 81.3% and 37.5%, respectively ($p = 0.025$). Surgical mortality was 0% for all, and no considerable perioperative complications were noted; however, two patients died of interstitial pneumonia and unknown cause within 3 months after surgical resection.

Conclusions: This is the very first prospective study on the surgical approach for cN2 NSCLC, and our result partially validated the proposed classification of the N descriptor in the new staging system. The treatment for single-station cN2 without hilar node enlargement would better if it were similar to that for cN1 disease. Induction chemotherapy or chemoradiotherapy may not be needed for such an entity.

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Introduction

According to the latest global data, lung cancer is the most often diagnosed cancer and the leading cause of cancer death worldwide.[1] Approximately 2.09 million new cases and 1.76 million deaths were reported in 2018.

NSCLC accounts for 85% to 90% of all lung cancers, and 11.7% of NSCLC is in stage IIIA in the United States.[2] In addition, in Japan,[3] stage IIIA accounts for 6.7% of all NSCLC cases. Clinical stage IIIA consists of a very wide spectrum of locally advanced NSCLC, such as cT4N0, cT3N1, cT1N2, cT2N2, and cT3N2, in accordance with the seventh edition of the TNM classification system coordinately proposed by the Union for International Cancer Control, the American Joint Committee on Cancer, and the International Association for the Study of Lung Cancer (IASLC). This has caused much confusion in managing stage IIIA NSCLC, especially for clinical N2 (cN2) disease, because cN2 also has a variety of characteristics from single-station cN2 to multistation cN2 or bulky cN2. Two major guidelines published by the National Comprehensive Cancer Network[4] and the European Society for Medical Oncology[5] have yet to include a definitive therapeutic algorithm for heterogeneous cN2.

Basically, for pathologically proven cN2, it is not recommended that patients undergo surgery first according to those guidelines; however, it has been pointed out that surgery might still be a possible option for potentially curative cN2, such as single-station cN2.[6] Thus, we, the Japan North-East Thoracic Surgical Study Group, started this study in 2008 to investigate whether NSCLC with single-station cN2 would reveal better prognosis after surgical resection without any induction therapy. To date, to our knowledge, there has not yet been a prospective study conducted like ours.

Recent improvements in targeted molecular therapy and immuno-oncology (IO) drugs have changed the approach for stage IIIA NSCLC, and the role of surgical resection for cN2 has seemed to decrease over time. Ever since our trial started, patient accrual remained low; it took 5 years to accumulate 34 patients for enrollment, and 5 more years had passed before reaching the ultimate end point. Here, we report the results of a phase II trial regarding the surgical approach for single-station cN2 NSCLC, and preferable options for such entities are discussed.

This study was registered with the University Hospital Medical Information Network Clinical Trials Registry in Japan with registration number UMIN-000013247.

Material and Methods

Organization, Ethics, and Participant Informed Consent

This study, the Japan North-East Thoracic Surgical Study Group 0801, was conducted with secure adherence to the Declaration of Helsinki. The study protocol was initially approved by the ethical board of the Miyagi Cancer Center on August 25, 2008, with approval number 08-19. After having been approved by six other facilities' ethical boards, the first patient was registered on October 28, 2008. All seven participating facilities were as follows: Tohoku University Hospital (responsible facility), Miyagi Cancer Center (core facility for study management and data collection), Yamagata Prefectural Central Hospital, Ohta-Nishinouchi Hospital, Iwate Prefectural Central Hospital, Kagoshima University Hospital, and Yamagata University Hospital. After having been thoroughly informed of the aim and details of the study, each patient from the respective facilities participated of their own will.

Inclusion Criteria

Patients who had resectable lung cancer (either definite or suspected) with single-station N2 node enlargement on computed tomography (CT) could be primarily enrolled. Histologic or cytologic definite diagnosis for primary lung nodules was not required to enter the study. The age limitation was set to 75 years or younger. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Currently, the Union for International Cancer Control, the American Joint Committee on Cancer, and the IASLC do not refer to the size of metastatic lymph nodes measured on CT in the lung cancer staging manual.[7] Therefore, the definition of both mediastinal (N2) and hilar (N1) enlargement was determined in accordance with the generally accepted size[8,9] as follows: 10 mm or more in the short-axis diameter measured on CT. Mediastinal lymph node enlargement with more than 20 mm in the short-axis diameter was regarded as bulky cN2 and was excluded. Those with two or more discrete enlarged N2 stations (cN2-multi) were also excluded. Patients with upper mediastinal lymph node enlargement (#2R, 2L, 4R) beyond #4L for left upper lobe lung cancer were also excluded.

Whether there was concomitant N1 node enlargement was not conditioned as an inclusion criterion in this study. Positron emission tomography (PET) was recommended but not mandatory. Endobronchial

ultrasonography, transbronchial needle aspiration cytology, and mediastinoscopy for the preoperative pathologic confirmation of N2 were not required in this study. Those who received any induction chemotherapy or chemoradiotherapy were excluded. Those with metastatic lung cancer, suspected extranodal invasion of the N2 node, or coincidental progressive cancer of other organs were also excluded.

Surgical Procedures

After enrollment, each patient underwent surgical resection immediately. The term "resectable" implied not only technical capability relating to tumor extent but also functional tolerance of the cardiopulmonary system in each participant who would undergo at least lobectomy. Complete ipsilateral mediastinal lymphadenectomy was required.[10,11] In cases for whom preoperative definite diagnosis was not obtained, an intraoperative pathologic examination was performed for the primary lesion. Nevertheless, no intraoperative pathologic examinations for mediastinal or hilar lymph nodes were performed.

Postoperative Pathologic Confirmation and Adjuvant Chemotherapy

After careful examination for existing pathologic conditions, patients with confirmed hilar node metastasis (pN1) and mediastinal node metastasis (pN2) were recommended to receive adjuvant chemotherapy in accordance with the major guidelines. Five-year follow-up from the date of surgical resection was carried out for each patient as far as possible.

End Points and Follow-Ups

Initially, 3-year and 5-year overall survival (OS) rates were set as the primary end points. Nevertheless, because of the low accrual, only the 5-year OS was calculated after every enrolled patient had completed their 5-year follow-up.

The recurrence-free survival (RFS) rate and sensitivity and accuracy of CT and PET for N1 and N2 nodes were evaluated as secondary end points.

Statistical Analysis

The required number of patients for this study was calculated by the openly available statistical tool, the "One Arm Survival Tool" of the SWOG (https://stattools.crab.org/Calculators/oneNonParametricSurvival.htm).

Reference values were derived from two previous reports.[12,13] Other statistical values, such as 5-year OS and RFS, were calculated with the use of SPSS software (IBM, Armonk, NY).

Results

Patient Enrollment

A total of 35 patients with single-station cN2 with lung tumors located in the parenchyma were primarily registered from the seven facilities between October 28, 2008, and February 20, 2014. Of them, 13 patients (37%) had no definitive diagnosis of NSCLC before surgical resection, whereas the remaining 22 patients (63%) had a definitive diagnosis of NSCLC by preoperative bronchofiberscope. Of the 13 yet diagnosed patients, 12 were confirmed as NSCLC by on-site examination for pathologic conditions during the surgical procedure, whereas the remaining patient was found not to have malignancy and was excluded from further analyses.

Preoperative Subclassification of cN2

Of the 34 patients finally enrolled in this study, 18 had one or more hilar node (N1) enlargements, and the remaining 16 had no N1 node enlargement, which would be called clinical skip metastasis. The study protocol did not limit the number of N2 nodes in a single station; nevertheless, all 34 patients had only one N2 node enlargement by chance. In summary, all 34 patients had single-station single-node cN2 without or with hilar enlargement.

Surgical Outcomes

All the patients' demographics are listed in Tables 1 and 2. A total of 30 patients underwent lobectomy; two, bilobectomy; one, pneumonectomy; and one, only wedge resection because of apparent pleural dissemination (R2 resection). One patient who underwent lobectomy seemed to have pathologically proven pleural dissemination (R1 resection). Both cases of incomplete resection (R1 and R2) had concomitant enlargement of the N1 node. Consequently, 32 patients (94% of the enrolled patients) had undergone complete curative resection with systematic ipsilateral lymphadenectomy.

The surgical mortality rate was 0%. No major perioperative complications were reported from the eight facilities. Nevertheless, two patients died of interstitial pneumonia and an unknown cause within 3 months after surgical resection.

Efficacy and Limitation of CT and PET for cN2 Evaluation

A total of 26 of the 34 cN2 cases seemed to have true positive pN2, so the accuracy of CT in cN2 evaluation was 76% (Table 3). The remaining eight cases of cN2 were five pN0, two pN1, and one undetermined case.

A total of 28 of the 34 patients with cN2 underwent PET scans, and regarding the N2 node, both the sensitivity and accuracy of PET were high at 100% and 89%,

Table 1. Demographics of the 34 Enrolled Patients

Variable	Value
Age (y)	67
Range	46–75
95% CI	62–72
Sex, n (%)	
Male	24 (71)
Female	10 (29)
Histology, n (%)	
Adenocarcinoma	20 (59)
Squamous cell carcinoma	11 (32)
Large cell carcinoma	2 (6)
Pleomorphic carcinoma	1 (3)
CT findings	
cN2 short-axis diameter (cm)	1.3
Range	1.0–2.0
95% CI	1.1–1.5
cN2 long-axis diameter (cm)	1.8
Range	1.0–2.4
95% CI	1.6–2.0
Primary tumor size (cm)	3.3
Range	1.0–8.0
95% CI	2.3–4.3
c-TNM (UICC 7), n (%)	
T1aN2M0	4 (12)
T1bN2M0	7 (20)
T2aN2M0	15 (44)
T2bN2M0	5 (15)
T3N2M0	3 (9)

CI, confidence interval; CT, computed tomography; UICC, Union for International Cancer Control; cN2, clinical N2.

Table 2. Demographics of the 34 Enrolled Patients (Sequel)

Clinical Character	n (%)
Definite diagnosis of primary lung tumor	
Yes	22 (65)
No	12 (35)
Location of primary tumor	cN2 location (number)
RUL	16 #4R (16)
RML	1 #7 (1)
RLL	7 #4R (5), #7 (2)
LUL	7 #4L (4), #5 (1), #6 (2)
LLL	3 #4L (1), #5 (1), #7 (1)
Enlarged single N2 station (CT)	
One node	34 (100)
Multiple nodes	0
Enlarged N1 station (CT)	
Yes	18 (53)
No	16 (47)
Extent of lung resection	
Lobectomy	30 (88)
Bilobectomy	2 (6)
Pneumonectomy	1 (3)
Wedge resection	1 (3)
Confirmed pN status	
pN0	5 (15)
pN1	2 (6)
pN2	26 (76)
(Single pN2)	24
(Multi-pN2)	2
pN undetermined	1 (3)

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; CT, computed tomography; cN2, clinical N2.

respectively. Nevertheless, the specificity of PET was considerably low. For the N1 node, both CT and PET revealed low sensitivity, specificity, and accuracy.

Regarding the 26 proven pN2 cases, there were 24 (92%) and two (8%) single- and multistation pN2 cases, respectively. Two multistation pN2 cases were accompanied by pathologic N1 node metastasis.

Adjuvant Chemotherapy and Follow-Ups

A total of 26 patients with cN2 (76%) underwent one or multiple cycles of platinum-based combined adjuvant chemotherapy (Table 4). Five patients (15%) underwent oral administration of tegafur and uracil in accordance with Japanese guidelines.[14] None of the patients underwent adjuvant radiotherapy or chemoradiotherapy.

The last patient was enrolled on February 20, 2014, and the 5-year follow-up period for that patient ended on March 31, 2019. The completion rates of the 3-year, 4-year, and 5-year follow-ups were 100%, 97%, and 91%, respectively. The median and mean follow-up times were 1817 days and 1525 days, respectively (range, 98–2505).

Cancer Recurrence

A total of 19 of the 34 patients (56%) with resected single-station cN2 experienced cancer recurrence, including two patients with incomplete resection. The major recurrence sites were as follows: mediastinal lymph node (seven [37%]); pleural dissemination (four); lung (three); brain (two); supraclavicular lymph node (two); kidney (one); liver (one); and bone (one). Mediastinal lymph node recurrence accounted for approximately one-third of all lesions.

Most cancer recurrences occurred within 2 years. When the RFS time of the two patients with incomplete resection was assumed to be 0 days, the median and the mean RFS times were 565 days and 965 days,

Table 3. Efficacy of CT and PET for the Evaluation of Node Status

Class of Node and Evaluation Mode	Sensitivity (%)	Specificity (%)	Accuracy (%)
N2 node			
CT			76
PET	100	40	89
N1 node			
CT	69	57	62
PET	42	75	61

CT, computed tomography; PET, positron emission tomography.

Table 4. Applied Regimens for Adjuvant Chemotherapy

Agent	n (%)
Cisplatin + Vinorelbine	8 (24)
Cisplatin + Pemetrexed	1 (3)
Cisplatin + S-1	1 (3)
Carboplatin + Paclitaxel	7 (20)
Carboplatin + Docetaxel	4 (12)
Carboplatin + S-1	3 (9)
Carboplatin + Gemcitabine	1 (3)
Carboplatin + Etoposide	1 (3)
Oral UFT	5 (15)
None	3 (9)

UFT, tegafur and uracil; S-1, tegafur, gimeracil, and oteracil potassium.

respectively (range, 0–2505). The 5-year RFS for all patients with cN2 was 40.8% (95% confidence interval [CI]: 23.8–57.9). The 5-year RFS rates of patients without and with N1 node enlargement were 53.6% and 29.6%, respectively, and there was no significant difference at $p = 0.129$ by the log-rank test (Fig. 1).

Use of EGFR Tyrosine Kinase Inhibitors After Recurrence

A total of 14 of 19 patients (74%) who experienced cancer recurrence underwent one or more modalities of treatment. Combination chemotherapy was used in four of those patients, and another four patients needed local control with radiotherapy or resection. EGFR tyrosine kinase inhibitors (EGFR TKIs) were administered to six of seven EGFR-positive patients with cancer recurrence. Four patients were administered gefitinib only, whereas two patients were administered gefitinib first and then erlotinib.

OS for Patients With Single-Station cN2

For all 34 patients with single-station cN2, the 5-year OS rate was 58.5% (95% CI: 41.9–75.4). The 5-year OS rate for patients without N1 node enlargement and with N1 node enlargement was 81.3% (95% CI: 62.1–100) and 37.5% (95% CI: 14.6–60.4), respectively, and there was a significant difference between those two groups by log-rank test at $p = 0.025$ (Fig. 2).

After omitting five patients with pN0, three patients with N1, and two patients with incomplete resection, the 5-year OS of patients with pN2 after complete resection was 61.1% (95% CI: 42.3–80.1) (figure not shown). When this cohort was divided into pN2 without and with definite N1 node metastasis, the 5-year OS was 68.8% and 46.7%, respectively, which was not statistically significant at $p = 0.369$; the 5-year RFS rates were 53.3% and 11.3%, respectively, at $p = 0.125$.

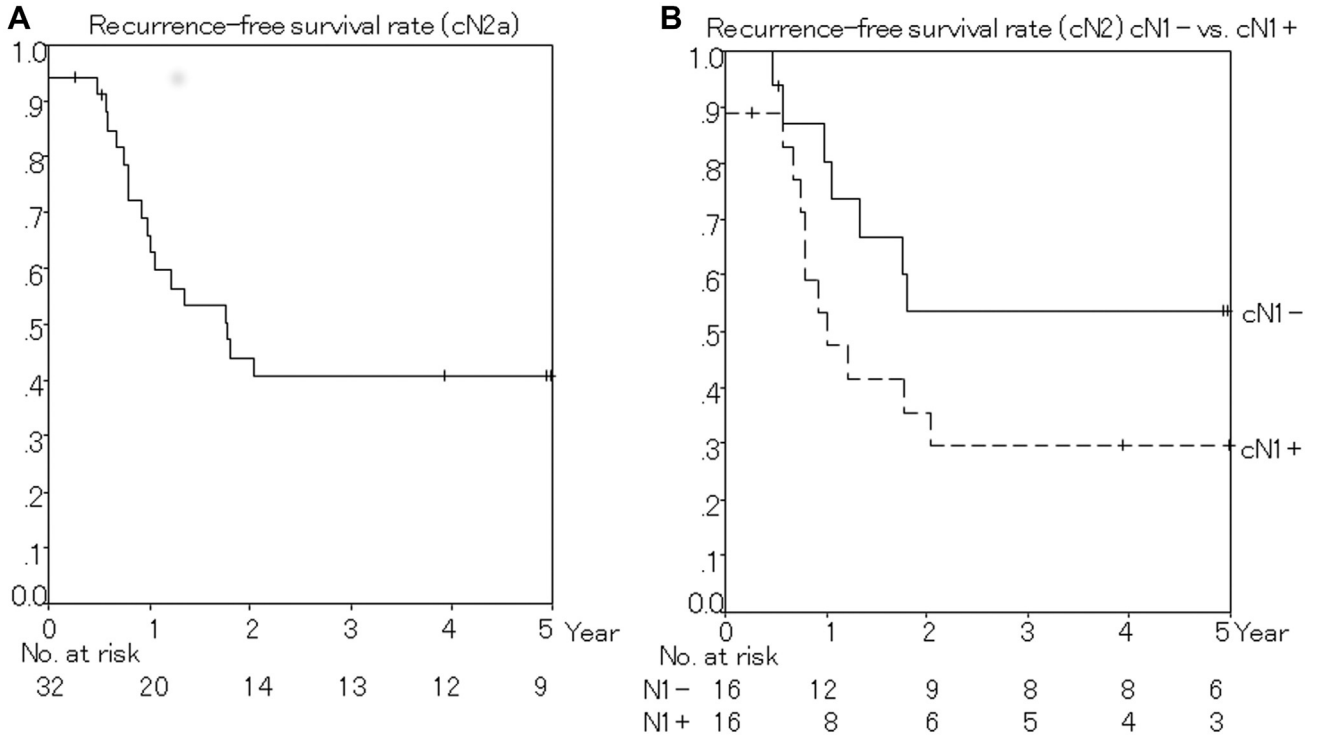

Figure 1. (*A*) Recurrence-free survival rate of all enrolled patients with clinical N2 stage IIIA NSCLC. Two patients with incomplete resection were included. (*B*) Recurrence-free survival rate regarding N1 status on computed tomography. Each curve represents clinical N2 without and with hilar enlargement as cN1− and cN1+, respectively.

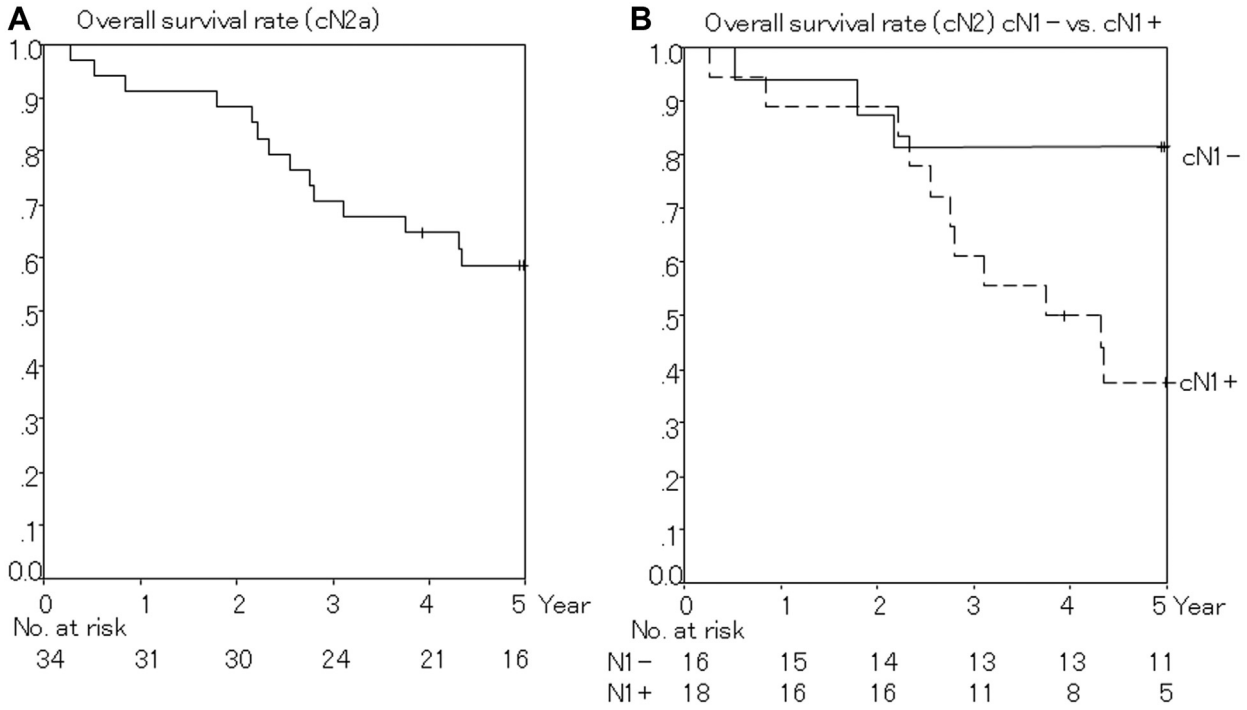

Figure 2. (*A*) Overall survival rate of all enrolled patients with clinical N2 (cN2) stage IIIA NSCLC. Median survival time has not been reached yet at 5 years after surgical resection. (*B*) Overall survival rate regarding N1 status on computed tomography. Each curve represents cN2 without and with hilar enlargement as cN1− and cN1+, respectively, which correspond to cN2a1 and cN2a2 in the appended proposal of the eighth edition of the International Association for the Study of Lung Cancer staging manual.

Discussion

According to the Lung Cancer Staging Project of the of IASLC,[15] the 5-year OS of patients with cN2 stage IIIA NSCLC who had been diagnosed between 1999 and 2010 was 23%. In the whole dataset of 94,708 patients analyzed, surgical resection was performed in 85%.[16]

Meanwhile, according to the Japanese Joint Committee of Lung Cancer Registry,[17,18] the 5-year OS of patients with cN2/pN2 stage IIIA who underwent surgical resection in 2004 was 30%. Because one-third of the patients with cN2 in that study had pN0 or pN1, the 5-year OS of undetermined patients with cN2 was supposed to be higher than 30%. In the latest Japanese Joint Committee of Lung Cancer Registry[3] with 18,973 patients, the 5-year OS of patients with resected cN2 was 45% in 2010. Thus, the 5-year OS of surgical resection for cN2 stage IIIA NSCLC has been improving over time. Moreover, compared with the survival rates of patients in those large-scale studies, the 5-year OS of patients with cN2 in our study (enrollment period from 2008 to 2013) was substantially high at 58.5%.

This general improvement in patients with resected cN2 may be attributed to the development of targeted therapy or the use of IO drugs after cancer recurrence instead of the innovation in surgery itself. Actually, in our study, the 5-year OS rates of patients with relapsed cancer with and without EGFR TKI treatment were 66.7% and 23.1%, respectively (log-rank test, $p = 0.057$).

In the early 1990s, the superiority of induction chemotherapy for clinical stage IIIA NSCLC was initially described.[19] Since then, many studies have been conducted, and induction chemotherapy or chemoradiotherapy followed by complete surgical resection has come to be recognized as the standard option for resectable cN2.[20] Currently, the National Comprehensive Cancer Network guidelines[4] clearly describe that cN2 with a single-station mediastinal node less than 3.0 cm in diameter can be administered induction chemoradiotherapy or chemotherapy and then surgically resected. Nevertheless, for bulky cN2, the surgical approach is considered inappropriate.

In contrast, for incidental postoperative pN2, cisplatin-based adjuvant chemotherapy has been regarded as the consensus for treatment.[21-23] In our study, 76% of all patients with cN2 received multiple cycles of adjuvant chemotherapy with platinum doublet in adherence with this principle.

It is still controversial whether postoperatively or preoperatively adding chemotherapy is more effective for patients with cN2. Some reports[24,25] described that there was no evidence of a difference in OS or disease-

free survival on the basis of the timing of the administration of chemotherapy.

For unresectable stage III NSCLC, a recent study[26,27] reported that definitive chemoradiotherapy followed by use of the IO drug durvalumab revealed an outstanding 3-year OS of 57%. For comparison, a large retrospective study[18] reported that the 3-year OS of patients with cN2 who underwent surgical resection was approximately 40%. Although those values could not be compared, it may be arguable that surgery is no longer the dominant option for cN2 stage III NSCLC. Meanwhile, in our study, the 3-year OS for single-station cN2/pN2 was 73%, which suggested that surgery can still be a possible option in a cautiously selected cohort of patients with cN2.

Thus, the surgical role in cN2 has been confusing partly because of the lack of adequate classification for cN2. Robinson's classification had been proposed to classify cN2 in the American College of Chest Physicians guidelines,[28] but it has not been widely used. Only a few studies[29,30] have referenced it to classify stage IIIA N2. Recently, the IASLC proposed a new subclassification for N2 in the latest eighth edition of the NSCLC staging system. According to that system, N2 would be divided into the following three subgroups: N2a1, N2a2, and N2b.[15] In their exploratory analyses in determining N descriptors, single-station pN2 without hilar metastasis (designated N2a1) revealed a significantly better 5-year OS of 54% than single-station pN2 with hilar metastasis (designated N2a2) or multistation pN2 (designated N2b) after R0 resection ($p = 0.0007$). Thus, it was suggested that patients with single-station cN2 with skip metastasis may be treated differently.[31]

Our results also revealed that single-station cN2 with skip metastasis (cN2a1 in the IASLC proposal) had an excellent 5-year OS of 81.3%, even though induction chemotherapy was not applied to all participants; instead, approximately three-quarters of the patients underwent adjuvant chemotherapy. Nevertheless, the 5-year RFS for the same cN2a1 group was 54%, which is unexpectedly low and was not significantly different from the 33% of cN2a2.

In our study, several parameters were compared between cN2a1 and cN2a2. For example, the cN2 and pN2 concordance rates were 86% and 75%, respectively; adjuvant platinum-doublet chemotherapy was applied in 86% and 83%; and the use of EGFR TKIs after cancer recurrence was 50% and 25%. The reason why cN2a1 had a preferable 5-year OS rate compared with that of cN2a2, despite having a relatively low 5-year RFS rate, might be that EGFR TKI usage after cancer recurrence was relatively high in patients with cN2a1. Nevertheless, in further analysis, after excluding patients who had been administered EGFR TKIs, the 5-year OS rates for cN2a1 and cN2a2 were 77% and 39%, respectively, which revealed that cN2a1 still had a relatively higher OS than cN2a2 ($p = 0.09$).

However, for pN2, the prognostic difference between pN2a1 and pN2a2 plus pN2b was not statistically demonstrated, which we consider resulted from the lack of statistical power.

In conclusion, our data regarding cN2 were almost consistent with the newly proposed IASLC subclassification of N2 stage IIIA. There are some similar studies that concluded that patients with single-station N2 with skip metastasis had a better prognosis.[32,33] In addition, a retrospective validation study[34] of the IASLC proposal for the N descriptor has been recently published.

This report is the first article of a prospective study that reported the prognostic superiority of single-station cN2 with skip metastasis in stage IIIA NSCLC. Ultimately, we deem that such entities can be treated similarly to N1 disease, which involves surgical resection first and then adjuvant chemotherapy. Nevertheless, as a study limitation, we will not know which option would be truly beneficial for single-station cN2 without hilar enlargement—surgical resection followed by adjuvant chemotherapy or definitive chemoradiotherapy followed by durvalumab—until we perform a randomized double-blind phase III trial.

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