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ORIGINAL ARTICLE

Prognostic factors for recurrence-free survival in resected pathologic N2-stage III non-small cell lung cancer treated with upfront surgery

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Abstract

Background: The standard treatment for pathological N2 (pN2) non-small-cell lung cancer (NSCLC) patients is definitive chemoradiation. Surgery might be beneficial for resectable pN2 disease, so we investigated the recurrence-free interval of upfront surgery for selected patients with resectable pN2 disease.

Methods: The clinicopathologic characteristics of patients with pN2 NSCLC who underwent upfront anatomical resection at Taipei Veterans General Hospital from 2011 January to 2019 December were retrospectively reviewed. A Cox regression model was used to identify prognostic factors of recurrence-free survival (RFS).

Results: In total, 84 patients after curative lung anatomic resection were analyzed, with a 44-month median survival. The 1-, 3-, and 5-year RFS rates were 63.1%, 31.3%, and 19.9%, respectively, with a median RFS of 18.9 months. Multivariable cox regression analysis identified that the significant predictor for RFS was a tumor size of more than 3 cm (hazard ratio [HR] = 1.74, 95% CI, 1.07-2.83, $p = 0.027$). Visceral pleural invasion, LN harvest number, tumor stage, and N2 status including single zone (N2a) or multiple zones (N2b) were not prognostic factors in this study.

Conclusion: Upfront surgery for resectable N2 disease achieved favorable outcomes in selected patients, especially better recurrence control with limited tumor size. Therapeutic advances might encourage surgeons to aggressive intervention.

Keywords: Local advanced lung cancer; N2-stage III disease; Upfront surgery

1. INTRODUCTION

Patients with non-small-cell lung cancer (NSCLC), a disease involving the ipsilateral mediastinum (N2), are embodied by a spectrum of disease states. The presence of N2 metastasis indicates a dismal prognosis and high risk of relapse, with 5-year overall survival (OS) rates <35%.[1] Concurrent chemoradiotherapy is recommended for unresectable or bulky N2 disease[2] but potentially resectable N2 disease may be treated by neoadjuvant chemotherapy followed by surgery,[2] even without radiotherapy.[3] According to a Cardiothoracic Surgery Network survey,[4] an overwhelming number of respondents (84%) would choose neoadjuvant chemoradiation followed by surgical resection relative to adjuvant delivery for microscopic N2 disease. Indeed, most thoracic surgeons in North America would favor surgical treatment after induction therapy for clinical N2 disease.

However, the optimal treatment modality for N2 disease remains selected differences in clinical practice owing to clinical heterogeneity despite published guidelines. In general, thoracic surgeons in Europe may offer surgery as the initial treatment in selected N2 cases with more aggressive intraoperative nodal dissection.[5] Among the preoperatively and postoperatively treated for resectable N2 disease in the National Cancer Database, longitudinal outcomes associated with postoperative chemotherapy were not superior.[6] The choice of therapeutic approach for patients with N2 disease depends on the clinical status of nodal disease, the available institutional expertise, as well as patient factors and preferences. Favorable outcomes of upfront surgery followed by adjuvant therapy have been demonstrated in some studies[7,8] and are considered one of the multimodality options.

Nonetheless, the recurrence rates of NSCLC patients remain high despite curative resection.[9] As the most common cause of death, poor prognosis, and quality of life are common after postoperative recurrence. Therefore, this study focused on evaluating the recurrence-free survival period and identified clinical-pathologic factors for resected pathological N2 (pN2) patients by upfront surgery as the first-line treatment.

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2. METHOD

2.1. Study design and eligibility criteria

Patients with resected pathologic N2-stage III NSCL at the Veteran General Hospital, Taipei, Taiwan between January 2011 and December 2019 were retrospectively reviewed. Patients with small cell carcinoma, who were lost to follow-up in 2 years or with missing data, wedge resection or induction therapy before surgery, and distal metastasis or incidental pleural seeding were excluded (Fig. 1). In total, 142 patients were included in this study. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital and patient informed consent was waived (approval no. 2023-02-002CC).

The preoperative staging workup included a chest and upper abdomen CT scan. A whole-body bone scan and brain CT scan or MRI for distant metastasis were performed. Positron emission tomography/CT scans were also available as a staging modality. Mediastinal evaluation as mediastinoscopy, endobronchial ultrasound fine-needle aspiration, and intraoperative lymphadenectomy were applied. Thoracic oncology multidisciplinary team meetings were initiated in December 2006, with the specialists focused on discussing complicated cases or those with stage III tumors.

2.2. Surgery and pathological examination

Surgical resection was performed by thoracotomy or video-assisted thoracic surgery (VATs) with uni- or bi-portal technique. All patients underwent intraoperative mediastinal lymph node dissection with more or equal to three N2 stations harvested. The pathologic stage was determined using the eighth edition of the American Joint Committee on Cancer (AJCC) (primary tumor [T], regional lymph node [N], distant metastasis [M]) classification (TNM) system for lung cancer. According to the International Association for the Study of Lung Cancer (IASLC) recommendation,[10] pN2 was subdivided into pN2 single (pN2a) and pN2 multiple (pN2b) according to the involved N2 stations. The subcategory of pN2a was further subdivided into pN2a1 and pN2a2 according to the presence or absence of skip metastasis.

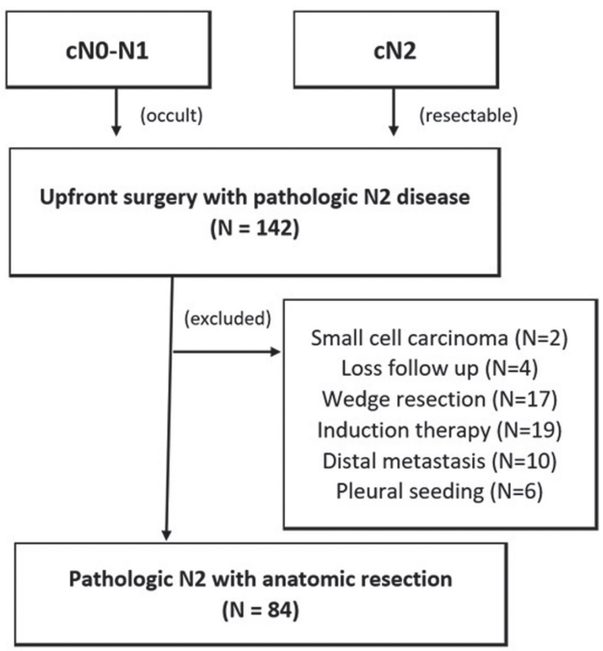

Fig. 1 Summary of patient flowchart.

2.3. Follow-up protocol

All patients were followed routinely every 3 months in the first 2 years and every 6 to 12 months thereafter at our outpatient department. The follow-up modalities and protocols included serum tumor markers, chest radiography, and computed tomography (CT) scans from the neck to the upper abdomen. Radionuclide bone scans were arranged every 6 months in the first 2 years and annually thereafter. When neurological symptoms or clinical suspicions occurred, a brain CT scan or magnetic resonance imaging (MRI) was performed accordingly. Locoregional recurrence was defined as tumor recurrence in a contiguous anatomic site after surgical resection, in ipsilateral hemithorax or mediastinum. All other sites of recurrence were classified as distant metastasis. Recurrences were confirmed by tissue biopsy or clinically determined by the multidisciplinary team meeting.

2.4. Statistical analyses

All categorical variables were analyzed by chi-square test and independent *t* test for the comparison of continuous variables. In the survival analysis, OS was defined as the period between surgical resection to death or the last follow-up. RFS was defined as the period between the date of surgical resection to the date of first recurrence or the last follow-up. Survival curves were plotted by the Kaplan-Meier method and compared by log-rank test. The Cox proportional hazards model was used for univariate and multivariate survival analysis with $p \leq 0.1$ in the univariate analysis included in the multivariate model. A $p < 0.05$ was indicative of statistical significance. All calculations were performed using IBM SPSS 25.0 software, and picture design was finished based on R version 4.1.1 (The R Foundation for Statistical Computing, Vanderbilt University, Nashville, TN) using the Survival, ggplot2, and survminer packages.

3. RESULTS

3.1. Patient characteristics

In total, 84 patients with pathologic N2-stage III NSCL who underwent upfront surgery were included in this study and their characteristics are summarized in Table 1. There were 45 (53.6%) females and 39 (46.4%) males with a median age of 64 years. Most patients (37; 44.1%) had clinical stage N0 disease, followed by resectable cN2 (30; 35.7%) and cN1 (17; 20.2%). Most patients (95.2%) underwent at least standard lobectomy, minimal invasive surgery (82.1%), and R0 resection (97.6%), with a median tumor length of 3.1 cm (interquartile range [IQR] = 2.5-4.2 cm). The median number of harvested LNs was 17 (IQR = 13.3-26). The final N stage distribution was 28.6 of patients with pN2a1, 44.1% of patients with pN2a2, and 27.3% of patients with pN2b. Pathological stage IIIA disease was observed in 64 (76.2%) patients and stage IIIB disease in 20 (23.8%) patients. The pathologic histology of the resected specimens confirmed adenocarcinoma in 66 (78.6%) patients, squamous cell carcinoma in 11 (13.1%) patients, and other histology in 7 (8.3%) patients. After surgery, 73 (86.9%) patients underwent adjuvant chemotherapy or chemoradiotherapy, mostly a cisplatin-based regimen.

3.2. Recurrence-free survival

During follow-up, 62 patients (73.8%) experienced tumor recurrence including 17 (20.2%) with locoregional recurrence only, 36 (42.9%) with distant recurrence only, and 9 (10.7%) with combined recurrence while encountering first episode of tumor relapse (Table 2). The median OS for all patients was 57.7 (95% CI, 12.7-82.5) months and the RFS was 18.9 (95% CI, 3.5-25.8) months (Fig. 2), with overall 1-, 3-, and 5-year RFS rates of 63.1%, 31.3%, and 19.9%, and 1-, 3-, and 5-year OS rates of 94.0%, 68.8%, and 49.5%.

Table 1

Characteristics of pN2 NSCL patients who underwent upfront surgery (N = 84)

Variables	Number (%)	Variables	Number (%)
Age, median (IQR)	64.0 (57.3-70.5)	Pathologic T stage (8th edition)	
>65	39 (46.4%)	pT1	13 (15.5%)
≤65	45 (53.6%)	pT2	51 (60.7%)
Sex		pT3	12 (14.3%)
Male	39 (46.4%)	pT4	8 (9.5%)
Female	45 (53.6%)	Pathologic tumor length, cm, median (IQR)	3.1 (2.5-4.2)
Smoking status		Pathological N stage (8th edition)	
Smoker	28 (33.3%)	pN2a1	24 (28.6%)
Nonsmoker	56 (66.7%)	pN2a2	37 (44.1%)
CCI		pN2b	23 (27.3%)
0	53 (63.1%)	LN harvest number, median (IQR)	17 (13.3-26)
≥1	31 (36.9%)	Visceral pleural invasion	
Clinical T stage (8th edition)		PL0	23 (27.3%)
cT1	36 (42.9%)	PL1	18 (21.4%)
cT2	31 (36.9%)	PL2	40 (47.7%)
cT3	12 (14.3%)	PL3	3 (3.6%)
cT4	5 (5.9%)	Tumor grading	
Clinical N stage (8th edition)		N/A	3 (3.6%)
cN0	37 (44.1%)	Moderate (G2)	25 (29.7%)
cN1	17 (20.2%)	Poorly (G3)	56 (66.7%)
cN2	30 (35.7%)	Lymphovascular invasion	
Operative method		Negative	4 (4.8%)
Segmentectomy	4 (4.8%)	Positive	80 (95.2%)
Lobectomy	75 (89.2%)	Resection margin	
Bi-lobectomy	3 (3.6%)	R0 resection	82 (97.6%)
Pneumonectomy	2 (2.4%)	R1 resection	2 (2.4%)
Surgical approach		Recurrence site	
VATs	69 (82.1%)	Locoregional recurrence	17 (20.2%)
Thoracotomy	15 (17.9%)	Distal metastasis	36 (42.9%)
Histological structure		Combined	9 (10.7%)
Adenocarcinoma	66 (78.6%)	No recurrence	22 (26.2%)
Squamous cell carcinoma	11 (13.1%)	Adjuvant therapy	
Other	7 (8.3%)	Chemotherapy	62 (73.8%)
Pathological stage (8th edition)		Chemoradiotherapy	11 (13.1%)
IIIA	64 (76.2%)	Target therapy	4 (4.8%)
IIIB	20 (23.8%)	No or delayed treatment	7 (8.3%)

Other histology indicates large cell carcinoma, adenosquamous carcinoma, mucoepidermoid carcinoma, and lymphoepithelioma-like carcinoma.
CCI = Charlson Comorbidity Index; IQR = interquartile range; N/A = not applicable; NSCLC = non-small-cell lung cancer; PN2 = pathological N2; VATs = video-assisted thoracic surgery.

Table 2

The pattern of recurrence in 62 resected pN2 patients

Recurrence pattern	Locoregional	Distal	Combined
Contiguous anatomical sites	7		6
Ipsilateral pleural	6		5
Ipsilateral mediastinum	7		0
Contralateral lung		12	2
Brain metastasis		18	3
Bone metastasis		7	4
Liver metastasis		3	2
Chest wall metastasis		2	0
Other		1	0

Other indicates small intestine.
PN2 = pathological N2.

3.3. Prognostic factors in the Cox regression model

Survival outcomes analyzed using univariable and multivariable Cox regression analysis are presented in Table 3, showing that a tumor size of more than 3 cm was a significant independent prognostic factor for RFS ($p = 0.027$). There were no significant differences in pathologic stage, N stage distribution, harvested LNs number, and surgical method. Furthermore, survival curves in the subgroup analyses for RFS showed no statistical significance in the pathologic stage (stage IIIA vs IIIB; median 21.5 vs 9.6 months, $p = 0.237$) and N stage distribution (N2a1 vs N2a2

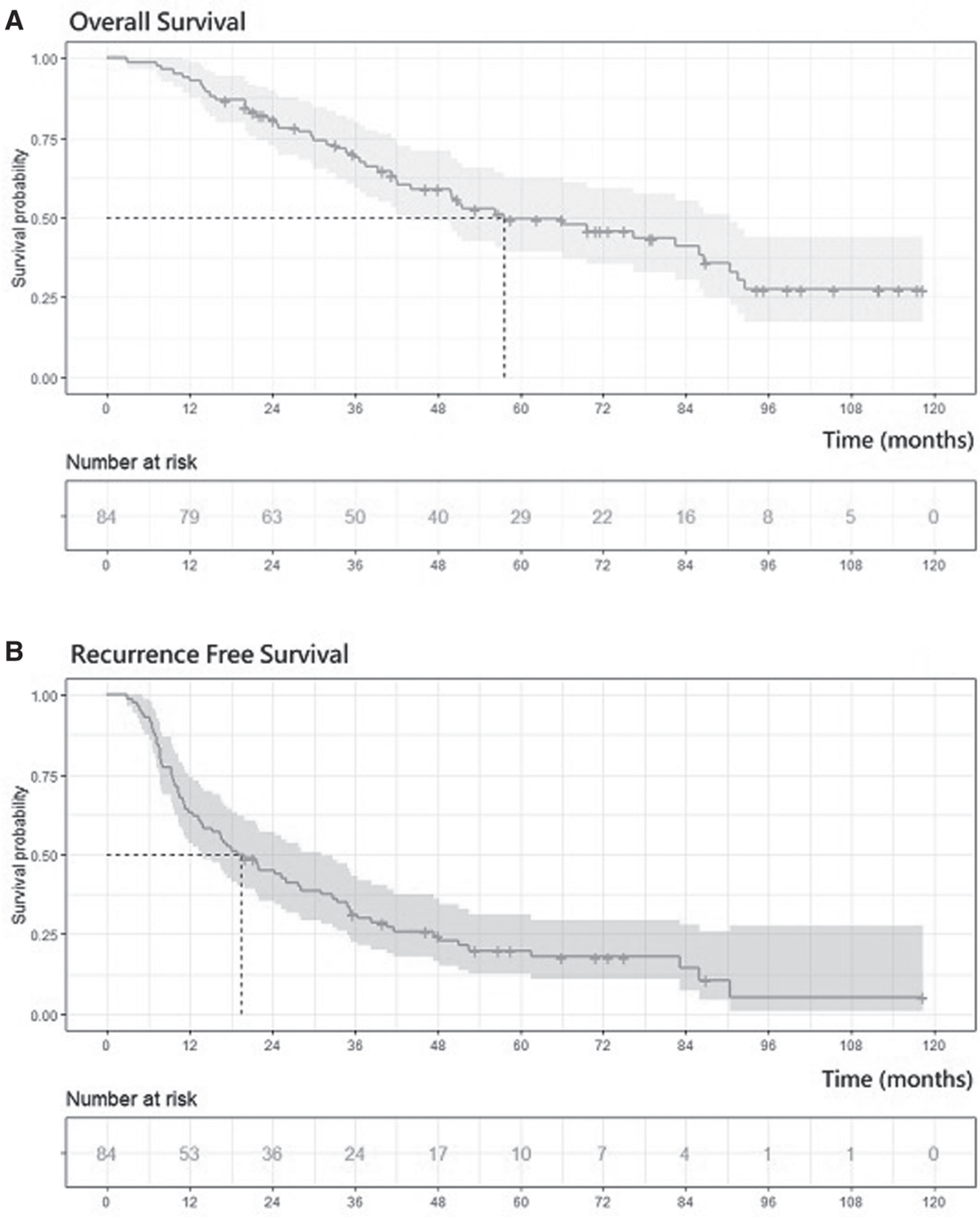

Fig. 2 Overall survival (A) and recurrence-free survival (B) based on overall patients with pathological N2 disease.

vs N2b; median 18.9 vs 21.8 vs 17.4 months, $p = 0.994$), except for tumor size (>3 vs ≤ 3cm; median 11.3 vs 32.7 months, $p = 0.024$) (Fig. 3).

4. DISCUSSION

Despite the heterogeneity of stage III disease, those with locally advanced NSCLC may benefit from surgery and survive longer.[11,12] Induction chemotherapy with or without radiotherapy followed by surgery or upfront surgery with adjuvant therapy has been under debate for the long term and there is no consensus regarding the optimal treatment strategies for those with potentially resectable tumors. The European Society for Medical Oncology (ESMO) guideline recommends surgical resection as a reasonable strategy option for single-station N2 disease.[13] In a few cases of clinical N2 disease diagnosed by PET/CT and chest CT, the final pathological report was N0 or N1. Despite improved mediastinal staging procedures, N2

Table 3

Predictors of RFS in resectable pathologic N2 lung cancer according to the Cox regression hazards model

	Univariable analysis		Multivariable analysis	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age				
>65	1.36 (0.85-2.20)	0.203		
≤65				
Sex				
Male	1.09 (0.68-1.76)	0.720		
Female				
Smoking status				
Smoker	1.27 (0.77-2.10)	0.349		
Nonsmoker				
Tumor size				
>3 cm	1.74 (1.07-2.84)	0.026	1.74 (1.07-2.83)	0.027
≤3 cm				
AJCC 8th stage				
IIIB	1.39 (0.80-2.42)	0.240		
IIIA				
Clinical N stage				
cN2	0.76 (0.46-1.26)	0.289		
cN0/N1				
N2 zone				
N2b (multiple)	1.03 (0.61-1.75)	0.912		
N2a (single)				
VPI				
PL2/PL3	1.58 (0.97-2.56)	0.066	1.57 (0.97-2.55)	0.068
PL0/PL1				
LN harvest number				
>15	1.06 (0.65-1.72)	0.821		
≤15				
Surgical method				
VATs	0.63 (0.35-1.15)	0.132		
Thoracotomy				

Stepwise selection in the multivariable model. Univariate factors with $p < 0.1$ were included in the multivariable model.

AJCC = American Joint Committee on Cancer; LN = lymph node; OR = odds ratio; RFS = recurrence-free survival; VPI = visceral pleural invasion; VATs = video-assisted thoracic surgery.

disease is only documented intraoperatively.[13] Regarding disease progression, immediate surgical resection for resectable cN2 disease may offer timely local control compared to invasive mediastinal staging for diagnosing. A meta-analysis from Europe suggested upfront surgery as a valid treatment option if the lung cancer community was not opposed, no further mediastinal staging was recommended even in patients with PET-CT-positive N2 disease.[14] For the patients who underwent upfront surgery in our study for resectable pN2 disease, the 5-year RFS rate was 19.9% and the 5-year OS rate was 49.5%. In previous studies of upfront surgery as first-line therapy, Zheng et al[8] demonstrated the 5-year RFS rate and 5-year OS rate of 21.0% and 43.0%, respectively, in selected patients with pIIIA NSCLC. Another study[7] reported a 5-year RFS rate of 33.8% and a 5-year OS rate of 44.7% in resectable pN2 disease. Similarly, the present study demonstrated acceptable outcomes with the upfront approach for pN2 disease. If the multidisciplinary team approach demonstrated the multimodality treatment of stage III NSCLC as suitable candidates for surgical resection, survival outcomes might be better than a traditional care model.[15]

For patients with preoperatively confirmed N2 disease, current guidelines[2,16] recommended possible strategies including induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy. However, the incidence of unsuspected pN2 has been reported from 2% to 18.5% who received preoperative staging procedures.[17] The presence of occult N2 (cN0/N1) disease in our subgroup was not significantly different in the Cox regression model for RFS. According to the National Cancer Data Base (NCDB),[17,18] unsuspected N2 disease is also associated with equivalent survival benefits vs known N2 disease treated by curative intent surgical resection. The population-based analysis reporting that unsuspected pN2 NSCLC treated with lobectomy without compromising outcomes when adjuvant therapy was used emphasizes the importance of adjuvant chemotherapy in improving survival for nodal disease. However, these cN2 patients could have been highly selected for upfront surgery with a favorable risk profile, therefore the need for further scrutiny is suggested.

Additional N2 descriptors were proposed by IASLC[10] for the combination of the location of metastatic nodes and the presence of skip metastasis, which may give a more accurate prognosis. The presence of multiple involved lymph node stations (pN2b) or skip metastasis (pN2a2) has a poorer prognostic impact than without (pN2a1). Besides, there was no statistically significant difference in survival between pN1b and pN2a1. Upfront resection could be performed as a reasonable treatment option for single-station, non-bulky N2 disease, as better prognostic factors to multiple-station in previous studies.[7,8] Based on the subclassification of pN2 disease, there was no statistical difference in RFS (N2a1 vs N2a2 vs N2b; median 18.9 vs 21.8 vs 17.4 months, $p = 0.994$) or the univariable Cox regression model (N2a vs N2b, $p = 0.912$). Chen et al[19] also

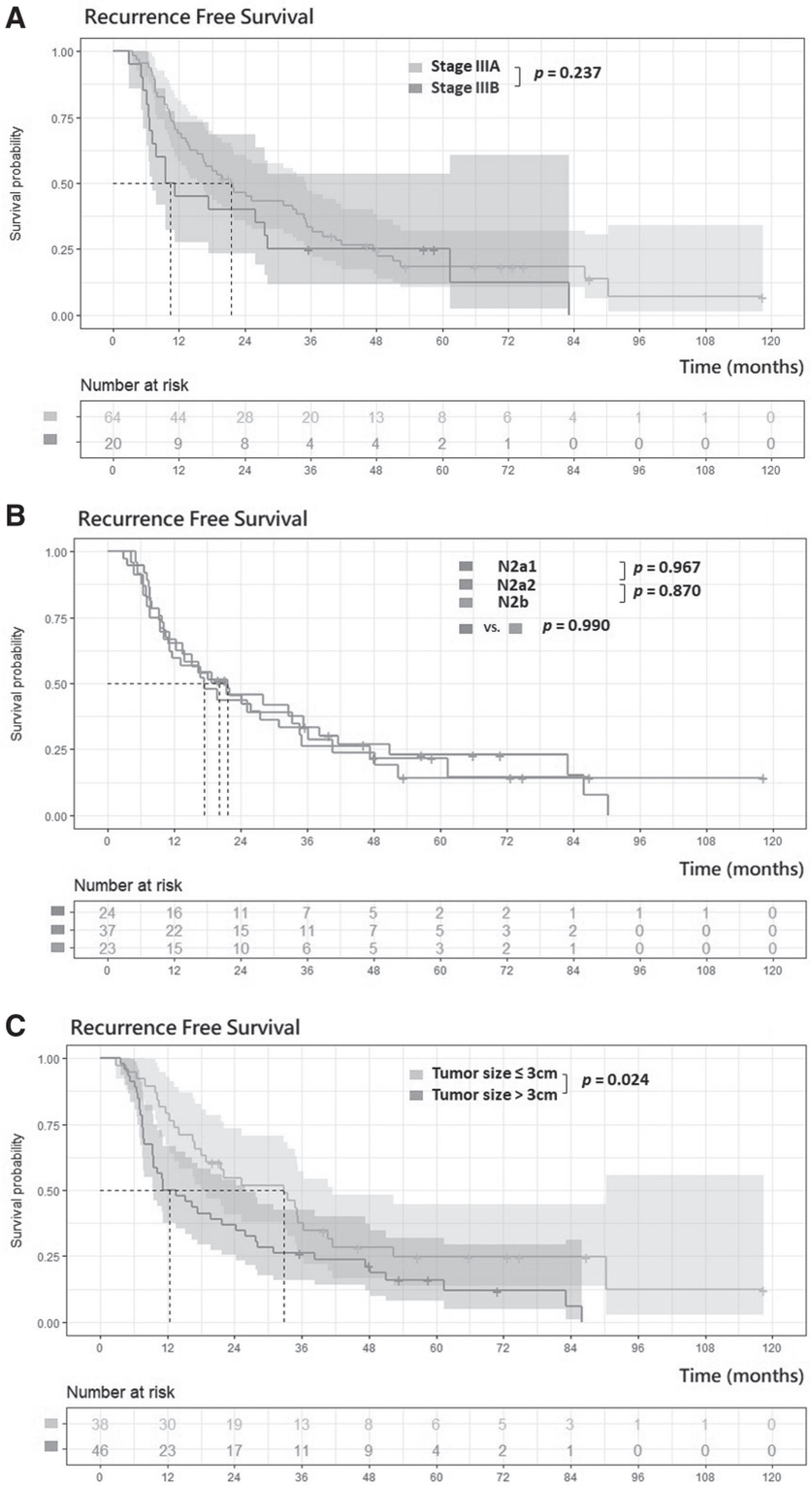

Fig. 3 Recurrence-free survival of patients according to stage III (A), pN2 level (B), and tumor size (C).

demonstrated multiple N2 stations (hazard ratio = 1.056, CI, 0.550-2.028, p = 0.870) were not a prognostic factor compared to single-station N2 disease. With the wide application of VAT and advancement in adjuvant therapy, the benefit of multimodality treatment cannot be confined to single-station N2 disease.

Initiation surgical intervention without further mediastinal staging is suggested for patients with a peripheral lung tumor <3 cm with normal mediastinal and hilar nodes at CT and/or positron emission tomography (PET).[20] Once the primary tumor measures more than 3 cm even without mediastinal involvement on CT or PET-CT, mediastinal involvement (N2 disease) increases the risk to 6% to 30%. Furthermore, a tumor exceeding 3 cm is an independent risk for developing unsuspected multiple-station N2 disease in Cho et al[21] study. Also, we investigated resected pN2 disease identifying a tumor size >3 cm as an independent prognostic factor for experienced postoperation recurrence (p = 0.024). According to a recent meta-analysis,[22] lymph node micro-metastases could contribute to the high recurrence rate which may be missed by conventional histopathological evaluation, even complete resection. Immunohistochemistry (IHC) or reverse transcriptase polymerase chain reaction (RT-PCR) with different target genes could support the decision-making for neoadjuvant therapy or upfront surgery when pN2 micro-metastases are present. The role of systemic therapy in personalized or precision medicine should be investigated to reduce the recurrence risk in these patients.

This study has several limitations. First, this is a retrospective single-institution study, so patient selection bias and choice of the surgical method were different based on clinicians' expertise, even for the multidisciplinary team approach. Second, we only investigated the recurrence survival of resected pN2 disease because of similar adjuvant therapy in our cohort. The selection bias of treatment modalities for recurrence was inevitable, we did not analyze the OS of these patients which might influence by different target genes or multiplex decision-making after recurrence. Third, N2 disease heterogeneity existed even with our highly selective study with diverse therapeutic approaches. Finally, limited cases following the selection criteria may limit the power of statistical significance. A multicenter or prospective randomized controlled study is needed.

In conclusion, we retrospectively reported the clinical outcomes for resected pN2 patients who underwent upfront surgery showing that tumor size >3 cm was the only independent predictor of an increased risk of recurrence. Further prospective studies are required of patients with resectable N2 disease to confirm these results.

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