Role of invasive mediastinal nodal staging in survival outcomes of patients with non-small cell lung cancer and without radiologic lymph node metastasis: a retrospective cohort study

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Summary

Background Lung cancer diagnostic guidelines advocate for invasive mediastinal nodal staging (IMNS), but the survival benefits of this approach in patients with non-small cell lung cancer (NSCLC) without radiologic evidence of lymph node metastasis (rN0) remain uncertain. We aimed to investigate the impact of IMNS in patients with rN0 NSCLC by comparing the long-term survival between patients who underwent IMNS and those who did not (non-IMNS).

Methods In this retrospective cohort study, we included patients with NSCLC but without radiologic evidence of lymph node metastasis from the Registry for Thoracic Cancer Surgery and the clinical data warehouse at the Samsung Medical Centre, Republic of Korea between January 2, 2008 and December 31, 2016. We compared the 5-year overall survival (OS) rate as the primary outcome after propensity score matching between the IMNS and non-IMNS groups. The age, sex, performance statue, tumor size, centrality, solidity, lung function, FDG uptake in PET-CT, and histological examination of the tumor before surgery were matched.

Findings A total of 4545 patients (887 in the IMNS group and 3658 in the non-IMNS group) who received curative treatment for NSCLC were included in this study. By the mediastinal node dissection, the overall incidence of unforeseen mediastinal node metastasis (N2) was 7.2% (317/4378 patients). Despite the IMNS, 67% of pathological N2 was missed (61/91 patients with unforeseen N2). Based on propensity score matching, 866 patients each for the IMNS and non-IMNS groups were assigned. There was no significant difference in 5-year OS and recurrence-free survival (RFS) between two groups: 5-year OS was 73.9% (95% confidence interval, CI: 71%–77%) for IMNS and 71.7% (95% CI: 68.6%–74.9%; p = 0.23), for non-IMNS (hazard ratio, HR 0.90, 95% CI: 0.77–1.07), while 5-year RFS was 64.7% (95% CI: 61.5%–68.2%) and 67.5% (95% CI: 64.3%–70.9%; p = 0.35 (HR 1.08, 95% CI: 0.92–1.27), respectively. Moreover, the timing and locations of recurrence were similar in both groups.

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Translation For the Korean translation of the abstract, see the Supplementary Materials section.

Interpretation IMNS might not be required before surgery for patients with NSCLC without LN suspicious of metastasis. Further randomised trials are required to validate the findings of the present study.

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Keywords: Non-small-cell lung cancer; Invasive mediastinal nodal staging

Research in context

Evidence before this study

According to international guidelines for non-small cell lung cancer (NSCLC), invasive mediastinal nodal staging (IMNS) is recommended for suspected mediastinal and/or hilar nodal involvement (over 1 cm in short axis in CT scan or maximal standardized uptake value over 2.5 in PET-CT scans), central tumors, and tumors greater than 3 cm. We searched PubMed up to February 28, 2023, for research articles containing the terms "(invasive mediastinal nodal staging or mediastinoscopy or endobronchial ultrasound)" AND "NSCLC", without date or language restrictions. In some studies, the frequency of unforeseen N1/N2 based on whether IMNS was performed in patients who underwent surgery has been reported, and there have also been reports on the impact of IMNS on survival rates in patients who received radiation therapy. To date, there have been no studies investigating whether IMNS affects survival rates in patients with radiographic N0 NSCLC.

Added value of this study

This study compared the long-term survival between patients who underwent IMNS and those who did not (non-IMNS) based on data from a large prospectively designed registry. Results showed that there were no differences in overall survival and recurrence-free survival of patients with radiographic N0 disease after adjusting for confounding factors. Hence, IMNS might not be required before surgery if there is no detectable FDG-avid lymph node enlargement on CT and PET-CT scans.

Implications of all the available evidence

Our findings implied that if there is no lymph node suspicious of metastasis on CT and PET-CT scans, patients might be able to have upfront surgery or receive definitive radiotherapy without worry of obsolete surgery. Further randomized controlled studies are required to validate the findings of the present study.

Introduction

Accurate nodal staging is the most important aspect of pretreatment assessment and therapeutic decision-making in patients with non-small cell lung cancer (NSCLC).[1] Performing imaging studies such as computed tomography (CT) scan and ^{18}F-Fluorodeoxyglucose positron emission tomography-CT (FDG PET-CT) scan is the first step to achieve accurate staging. However, these imaging studies have limited accuracy, calculated as (true negative + true positive)/total number of cases, which is equal to the number of correct assessments divided by the total number of assessments. CT scans for mediastinal staging of NSCLC show accuracy rates between 64% and 79%, while PET/CT accuracy is reported at about 78%.[2,3] Notably, approximately 10% of patients with radiographic N0 (rN0) disease present with unsuspected N2 disease, which is identified via surgical lymph node (LN) dissection.[4–6] Furthermore, a significant number of patients with clinical N0 NSCLC are discovered to have occult N1 disease (approximately 16.6%).[7] Given these limitations, lung cancer diagnostic guidelines now advocate for invasive mediastinal nodal staging (IMNS) methods such as mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration/endoscopic ultrasound fine-needle aspiration, to achieve more accurate staging.[1,8,9]

Nonetheless, IMNS is associated with a risk of false-negative findings in patients with rN0 disease. Unforeseen N2 diseases commonly have microscopical involvement (diameter: <3 mm) of a single nodal station.[10] Therefore, they are extremely challenging to identify on endosonography. We previously investigated the use of endosonography in patients with rN0 NSCLC. Results showed that the prevalence of occult mediastinal metastases in rN0 NSCLC was low at 11.3%. Therefore, in patients with rN0, the sensitivity of EBUS was extremely low even in patients with tumors measuring >4 cm or those with centrally located tumors.[6,11] Meanwhile, the specificity, PPV, NPV, and accuracy were reported as 100%, 100%, 92.6%, and 93.1%, respectively. Moreover, this method is intrinsically invasive and carries a risk of procedure-related complications, even though the risk is very low at 3.21% for patients who underwent the transbronchial biopsy and 1.15% for those who did not.[12] Importantly, the survival benefit after treatment based on IMNS is uncertain.[4] Considering the widespread use of lung cancer screening

methods and the increasing incidence of rN0 disease, it should not be deferred further to make conclusions.[5]

To address this concern, randomised controlled trial (RCT) should be conducted to compare the survival outcomes between patients with rN0 NSCLC who underwent IMNS and those who did not. However, this type of study is practically challenging to perform, and conclusions can be obtained after a 5-year follow-up. Propensity score matching can be an alternative method. IMNS has been performed for several decades, and the number of cases with or without IMNS is already sufficient. Thus, propensity score-matched survival analyses can be performed to better evaluate the clinical benefit of IMNS.

Therefore, the current study aimed to examine the importance of invasive mediastinal staging workup in patients with rN0 NSCLC by comparing the long-term survival between patients who underwent invasive mediastinal staging and those who did not, based on a large, prospectively designed registry with data on long-term follow-up outcomes and recurrence.

Methods

Study design and patients

In this retrospective cohort study a total of 9016 patients who received curative treatment for NSCLC between January 2, 2008 and December 31, 2016 were selected from the Registry for Thoracic Cancer Surgery (RTCS) and the electronic medical records of the clinical data warehouse. The RTCS was established in 1994 at Samsung Medical Centre, Seoul, Repubilic of Korea, to comprehensively register patients undergoing thoracic surgery, encompassing an array of clinical, perioperative, pathological, and survival data.[13] This universal database has been prospectively utilised to meticulously record information for each surgical patient. The variables within the registry were defined through a consensus among thoracic surgery experts and are consistently collected irrespective of specific study objectives. Consequently, the RTCS provides an unbiased repository of extensive data, including preoperative clinical details (such as smoking history, cardiopulmonary function, imaging findings, implementation and outcomes of IMNS, diagnosis, staging, comorbidities, and preoperative treatment strategies), intraoperative parameters (encompassing the extent of resection and nodal dissection), detailed pathologic examination results, postoperative complication profiles, and the modalities of adjuvant treatments administered. Moreover, information on survival and recurrence is updated quarterly by trained data managers using electronic medical records until December 2021. Details on patients who underwent curative treatment rather than surgery were collected from the clinical data warehouse (CDW). The CDW is a real-time database of Samsung Medical Centre that aggregates data from various clinical sources to provide the entirety of clinical data for each patient from a unified view. The CDW's functional user interface provides clinicians with access to non-identified and anonymous high-quality data sets.[14]

The present study was approved by the Institutional Review Board of Samsung Medical Centre (IRB no. 2021-07-070) and the need for informed consent was waived as de-identified data were used in the study analysis. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

The inclusion criteria were as follows: age of 18 years and older and a curative treatment of NSCLC between January 1, 2008 and December 31, 2016. Patients with multiple primary lung cancer (n = 607), primary cancer at other organs within 5 years (n = 1133), and radiologic N1-3 disease (n = 2119) as well as those who received preoperative chemoradiotherapy (n = 612) were excluded from the analysis. In total, 4545 patients were included in the final analysis (Fig. 1).

Procedures

rN0 disease was defined as the presence of mediastinal and hilar LNs with the following parameters: 1) a short-axis diameter of ≤1 cm on CT scan, and 2) less FDG uptake than the mediastinal blood pool activity or definite high attenuation/calcification irrespective of FDG uptake on PET-CT scan.[15–20] In cases where the clinical N stage is equivocal during the preoperative diagnostic process, the N stage was determined through consensus among specialists in thoracic radiology, nuclear medicine, pulmonology, thoracic surgery, and oncology in multidisciplinary care team for lung cancer. Central tumor was defined as the inner one-third of the hemithorax adopted by drawing concentric lines from the midline.[21] We defined solidity in lung nodules based on the presence of solid components, categorizing them into solid and part-solid nodules. Solid nodules are characterised by a CT (consolidation to tumor) ratio of 1, indicating a completely solid composition. In contrast, subsolid nodules, defined by a CT ratio of less than 1, exhibit a combination of solid and ground-glass opacity components. Good performance status was defined as an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

Outcomes

The primary outcome of the study was 5-year OS of the IMNS and non-IMNS group. The 5-year OS rate was calculated from the date of treatment of NSCLC to the date of death from any cause or the last follow-up date. The date of death was based on the CDW annual data retrieval of death records from the National Statistics Korea (KOSTAT). The secondary outcome was recurrence-free survival (RFS) of the IMNS and non-IMNS group, where the patients were followed from the date of surgery to the date of recurrence, death, or

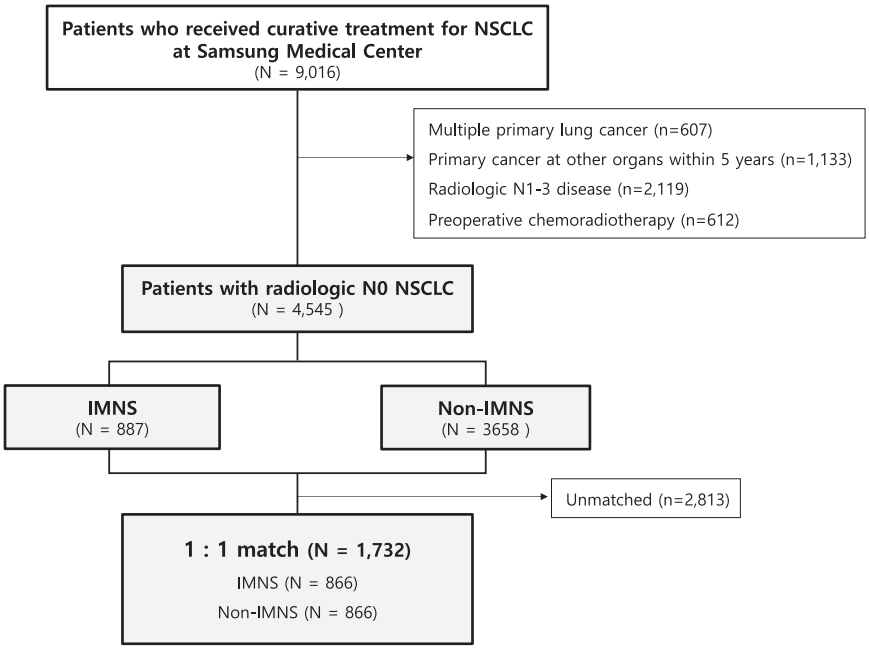

***Fig. 1:* Study flow diagram**. NSCLC, Non-small-cell lung cancer; IMNS, Invasive mediastinal nodal staging.

last surveillance without evidence of recurrence. In addition, we assessed the incidence of unforeseen N2 and its associated survival. The unforeseen N2 disease was defined that the N2 disease was confirmed by postoperative pathologic N2 disease without any suspicion of nodal involvement in preoperative evaluation.

Statistical analysis

This is a retrospective study utilizing registry data, where all patients who underwent curative treatment during the study period were identified and selected as study participants based on specific inclusion and exclusion criteria. And the analysis was conducted using a meticulously collected registry, which ensured that there were no missing values in the data.

Patients were characterised according to demographic and clinical characteristics (including age, sex, performance status, tumor size [cm], centrality, solidity, forced expiratory volume in 1 s, FDG uptake in PET-CT, histological examination of the tumor before surgery, other types of cancers, and double primary cancer diagnosis). Differences in patient characteristics among the groups were evaluated using the chi-square test for categorical variables and the *t*-test for continuous variables.

Due to variations in patient characteristics among the IMNS groups, the treatment assignment was subject to selection bias, which might not be completely accounted for in the multivariate logistic regression model. Therefore, the logistic regression model with clustered data (within clinicians) was used to construct propensity scores, an index representing the probability of receiving each type of IMNS diagnosis. We created the propensity scores and plotted a pre-match and post-match boxplot to determine the matching outcomes with and without IMNS. (Appendix p 1) This statistical methodology is commonly used in observational studies to control for nonrandom treatment assignment by adjusting for differences in covariates between treatment groups.[22] Where possible, each patient who underwent IMNS was matched with one patient who did not, and who had a nearest-neighbor propensity score value. The variables used in propensity score matching were age, sex, performance status, tumor size [cm], centrality, solidity, forced expiratory volume in 1 s, FDG uptake in PET-CT, and histological examination of the tumor before surgery. Propensity score matching was used to reduce bias in treatment assignment, mimicking the effects of randomisation in non-randomised studies. We used the standardised mean difference (SMD) as a measure of balance. The SMD of a variable is the weighted difference between the mean of the variable for participants who received the treatment and those who did not, divided by the pooled SD.[23] Paired t-tests is typically used to assess the mean differences between two groups. The survival of the IMNS groups was compared using the Kaplan–Meier estimate and the log-rank test. Univariate and multivariate Cox proportional hazards regression models were assessed to determine the factors associated with survival.

All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant. Statistical

analyses were performed using Stata, and propensity score matching was conducted using the psmatch2 package (StataCorp 2021. Stata Statistical Software: Release 17, StataCorp LLC, College Station, TX, USA).

Role of the funding source

There was no funding source for this study. YJJ and JK had access to the dataset. The corresponding authors had final responsibility for the decision to submit for publication.

Results

Baseline characteristics of the participants

In total, 4545 patients were enrolled in this study. Table 1 shows the clinical characteristics of all patients. Among them, 887 (19.5%) underwent IMNS. The IMNS and non-IMNS groups did not significantly differ in terms of age (mean: 62 years). The IMNS group were more likely to include men (68.2% vs. 56.6%; $p < 0.0001$) and have a poor performance status (1.1% vs. 0.4%; $p < 0.0001$), central tumor (54% vs. 35.8%; $p < 0.0001$), solid tumor (67.9% vs. 37.9%; $p < 0.0001$), and FDG-avid tumor (97.9% vs. 75.3%; $p < 0.0001$) compared with the non-IMNS group. Based on the propensity score matching, 866 patients were assigned in the IMNS group and 866 in the non-IMNS group. The distribution of co-variables after propensity score matching was well-balanced.

The clinical characteristics of the two cohorts were shown in Table 2. Variables including age, sex, performance status, lung function, centrality, solidity, tumor size, and FDG avidity were matched. In the matched cohort, the patients' mean age was 62 years, and one-third were women. All patients had good performance status and lung function. Regarding tumor characteristics in radiology, 54% and 67% of patients in the matched cohort had central and solid tumors, respectively. The mean tumor size was 3.7 cm, and 98% of patients had FDG-avid tumors.

The clinical T1 stage was more prevalent in the non-IMNS group (40.19%) compared to the IMNS group (33.55%, $p = 0.009$). There was no statistically significant variation in the clinical T2, 3, and 4 stages. In terms of the clinical N stage, all patients of both cohorts were classified as stage N0, resulting in no significant difference ($p > 0.99$). In addition, there were no significant differences in the pathologic T stage distributions between the groups ($p = 0.11$). However, the pathologic N stage had a statistically significant difference ($p = 0.009$), with the IMNS group showing a higher proportion of patients in pN1 and pN2 (Appendix p 2).

Survival status

All patients were followed-up until death or up to December 2021. The median follow-up duration was 5.8 years. The IMNS group had a worse overall survival (OS) than the non-IMNS group before propensity score matching (Appendix p 3).

Characteristic	IMNS (N = 887)	Non-IMNS (N = 3658)	p-value	SMD
Mean age (SD) – yr	62 (9)	62 (10)	0.63	0.06
Female sex – no. (%)	282 (32)	1589 (43)	<0.0001	0.256
ECOG 0–1 – no. (%)	877 (98.9)	3542 (99.6)	0.0013	0.152
Central – no. (%)	479 (54)	1274 (36)	<0.0001	0.381
Solid – no. (%)	602 (68)	1339 (38)	<0.0001	0.628
Mean tumor size (SD) – cm	3.7 (1.9)	2.7 (1.5)	<0.0001	0.619
FDG-avid – no. (%)	863 (98)	2592 (75)	<0.0001	0.719
FEV1 >70% predicted – no. (%)	871 (98)	3515 (95)	0.0031	0.186
Histological examination of the tumor before surgery – no. (%)	696 (78)	1327 (38)	<0.0001	0.89

IMNS, invasive mediastinal nodal staging; SMD, Standardized Mean Difference; PS, propensity score; SD, standard deviation; FDG, fluoro-deoxyglucose; FEV1, forced expiratory volume in 1 s.

Table 1: **Characteristics of IMNS procedures in all patients.**

After propensity score matching, the 5-year OS and RFS did not differ between the IMNS and non-IMNS groups. The 5-year OS rate, as estimated from Kaplan–Meier curves, was 73.9% (95% confidence interval, CI: 71%–77%) for the IMNS group and 71.7% (95% CI: 68.6%–74.9%) for the non-IMNS group. A log-rank test resulted in a p-value of 0.231 and the hazard ratio (HR) for IMNS relative to non-IMNS was 0.90, with a 95% CI ranging from 0.77 to 1.07 (Fig. 2A).

Moreover, the 5-year RFS rate was determined to be 64.7% (95% CI: 61.5%–68.2%) for those in the IMNS group and 67.5% (95% CI: 64.3%–70.9%) for the non-IMNS group. The log-rank test indicated no significant difference between the two groups, with a p-value of 0.35. The HR was 1.08, with a 95% CI ranging from 0.92 to 1.27 (Fig. 2B).

In addition to the matching method, the hazard ratio for IMNS vs. non-IMNS. of the model controlled by creating propensity scores in quintiles (HR = 0.98, 95% CI: 0.85–1.14) and the hazard ratio of the model controlled by the restricted cubic splines technique (HR = 0.98, 95% CI: 0.84–1.13) were not statistically significant, as were the results of the matched model (HR = 0.90, 95% CI: 0.77–1.07) (not shown).

The timing and sites of recurrence were not different in both groups (Appendix p 4 and 5).

Then, the factors associated with survival outcomes were analysed. In a subgroup analysis after propensity score matching, age >65 years, male sex, tumor size >3 cm, centrality, solidity, and FDG avidity were associated with survival.

Subgroup analyses

Table 3 shows that OS was similar between IMNS group for all subgroups on age over 65 years ($p = 0.12$), sex ($p = 0.18$), central ($p = 0.44$), solid (=0.45), FDG-avid (=0.58), and tumor size over 3 cm ($p = 0.96$).

Characteristic	IMNS (N = 866)	Non-IMNS (N = 866)	p-value	SMD
Mean age (SD) – yr	62 (9)	62 (11)	0.61	−0.024
Female sex – no. (%)	276 (32)	290 (34)	0.47	−0.034
ECOG 0–1 – no. (%)	866 (100)	866 (100)	>0.99	NA
Central – no. (%)	469 (54)	463 (54)	0.77	0.014
Solid – no. (%)	585 (68)	574 (66)	0.57	0.027
Mean tumor size (SD) – cm	3.7 (1.8)	3.7 (1.9)	0.63	0.015
FDG-avid – no. (%)	847 (98)	847 (98)	>0.99	0
FEV1 >70% predicted – no. (%)	866 (100)	866 (100)	>0.99	NA
Histological examination of the tumor before surgery – no. (%)	679 (78)	691 (80)	0.48	−0.034

IMNS, invasive mediastinal nodal staging; PS, propensity score; SMD, standardized mean differences; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; NA, not applicable FDG, fluoro-deoxyglucose; FEV1, forced expiratory volume in 1 s.

Table 2: **Characteristics of IMNS procedures in PS-matched pairs.**

Incidence of unforeseen N2 and its associated survival

Although the survival outcomes between two groups were similar, the incidence of unforeseen N2 disease differed.

Of 4378 patients undergoing surgery for rN0 disease, 317 (7.2%) presented with pathologic N2 disease. Of 863 patients who underwent IMNS, 91 (10.5%) had pathologic N2 disease. Of them, only 30 (3.5%) presented with pN2 disease based on IMNS before surgery (cTxN2M0) and received neoadjuvant therapy before surgery. Further, 61 (7.1%) patients were not diagnosed with metastases of the mediastinal node even after preoperative IMNS (cTxN0M0). Unforeseen pN2 diseases were eventually found after surgery (not shown).

Considering the risk factors of unforeseen N2 disease, the incidence rates of pN2 disease in patients with >3 cm tumor and central tumor, solid tumor, and FDG-avid tumor were 11.9%, 9.54%, 12.2%, and 9.5%, respectively (not shown).

In terms of N2 burden, there was no statistically significant difference in the distribution between the non-IMNS and IMNS groups. In the non-IMNS group, 41.3% had single station (skip) N2, while 50.5% in the IMNS group, with a p-value of 0.4644. For single station (N1 + N2) N2, the percentages were 40% for non-IMNS and 33.7% for IMNS. Regarding multiple station N2, it was 18.8% for non-IMNS compared to 15.8% for IMNS. (Appendix p 2).

There was also no difference in survival rate depending on the N2 burden between the non-IMNS and IMNS groups. For single station (skip) N2, the 5-year OS rate was 62.8% (95% CI: 50.8%–77.5%) for the IMNS group and 63.4% (95% CI: 48.8%–82.3%) for the non-IMNS group (p = 0.77). For single station (N1+N2) N2, the 5-year OS rate was 56.3% (95% CI: 41.4%–76.4%) for the IMNS group and 61.3% (95% CI: 46.3%–81.3%) for the non-IMNS group (p = 0.37). In patients with multiple station N2, the 5-year OS rate was 43.8% (95% CI: 25.1%–76.3%) for the IMNS group and 46.7% (95% CI: 27.2%–80.2%) for the non-IMNS group (p = 0.77; Appendix p 6).

The 5-year survival rate of patients with pN2 disease undergoing upfront surgery (60.2% [95% CI: 54.8%–66%]) was similar to that of patients receiving

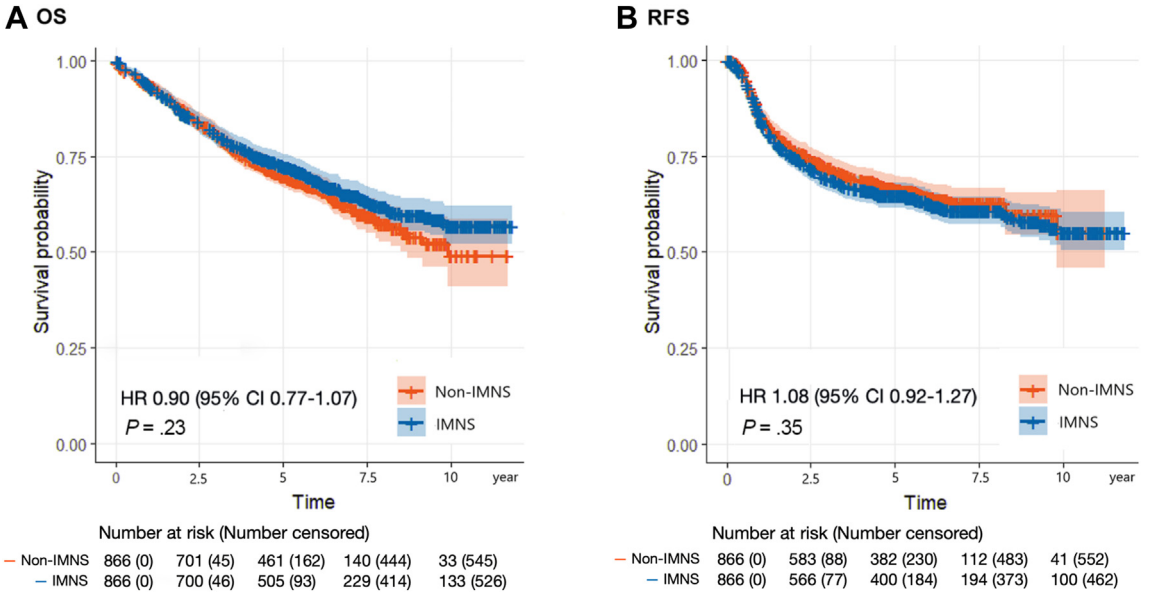

Fig. 2: **Survival outcome according to the IMNS and Non-IMNS Groups (matched)**. (A) Overall Survival; (B) Recurrence-free Survival Kaplan–Meier estimates of survival in IMNS (blue) and non-IMNS (red) group. p-value calculated by log-rank test.

Subgroup	No. of patients	HR (95% CI)	P for interaction
Total	1732	0.90 (0.77–1.07)	
Age (years)			0.12
≤ 65	975	1.11 (0.86–1.44)	
>65	757	0.84 (0.68–1.04)	
Sex			0.18
Female	566	1.05 (0.74–1.50)	
Male	1166	0.84 (0.70–1.02)	
Central			0.44
No	800	0.81 (0.61–1.07)	
Yes	932	0.96 (0.78–1.19)	
Solid			0.45
No	573	1.02 (0.72–1.42)	
Yes	1159	0.87 (0.72–1.05)	
FDG-avid			0.58
No	38	0.63 (0.11–3.80)	
Yes	1694	0.91 (0.77–1.07)	
Tumor size (cm)			0.96
≤3	662	0.89 (0.64–1.25)	
>3	1070	0.90 (0.74–1.09)	

PS, propensity score; FDG, fluoro-deoxyglucose.

Table 3: **Subgroup analysis after PS matching.**

neoadjuvant therapy followed by surgery (56.7% [95% CI: 41.4%–77.5%]) (p = 0.63; Appendix p 7).

Discussion

This study used data from a large, prospectively designed registry. Results showed that IMNS did not affect the OS and RFS of patients with radiographic N0 disease after adjusting for confounding factors. Hence, IMNS may not be required before surgery if there is no detectable FDG-avid LN enlargement on CT and PET-CT scan.

Initially, we compared survival by performing IMNS in an unmatched manner. Results showed that the survival rates of the IMNS group were worse than those of the non-IMNS group. However, this was caused by the characteristics of the patients, not by IMNS itself. Since 2008, IMNS has been performed only on patients who were less likely to benefit from local treatment. Compared with the non-IMNS group, the IMNS group had a higher number of empirically selected male patients with a poorer performance status and FDG-avid tumor. Hence, the IMNS group had a poor survival outcome based on the unmatched analysis.

Thus, propensity score matching was used to decrease the effect of confounding preoperative variables, in which baseline characteristics were well-balanced between the subgroups. We found that IMNS was not associated with OS and RFS.

This finding can be attributed to several reasons. First, the incidence of occult mediastinal LN metastasis itself in patients with radiographic N0 disease is as low as <10%. This can explain the difference in survival in patients with or without IMNS. In this study, the overall incidence of occult mediastinal LN metastasis was only 7%. Considering advancements in functional radiology, the incidence of unforeseen N2 disease on radiologic assessment might even decrease.[24]

Second, most unforeseen metastatic lesions are micrometastatic, with a maximal diameter of <3–5 mm. The current techniques for IMNS are not accurate enough to localise and/or detect such tiny lesions.[25] We have performed more than five thousands of endosonographic biopsy procedures for N2 nodes. However, the sensitivity of endosonographic biopsy in rN0 disease is only 49%.[6] Conversely, pathologic examination of the whole nodes resected via cervical mediastinoscopy can be reliable.[18] Nevertheless, considering the low incidence of N2 disease, it could be inefficient with non-negligible risk.[26–28] Moreover, considering the time required for multiple sample preparation and meticulous inspection of unlocalised tiny lesions, frozen section biopsy, which should be performed within ≤30 min, is less efficient.[29]

Third, the risk of occult systemic metastasis may not be similar between patients with micrometastatic lesions in the LNs and those with macrometastasis. Several breast cancer studies showed that micrometastasis in the sentinel LN was associated with a significantly lower incidence of proximal downstream axillary LN and a fairly good prognosis.[30,31] Although the number of studies is limited and the results are inconclusive, similar findings were suggested in lung cancer.[32–35] Hence, micrometastatic lesions may be in a state of dormancy, during which proliferation and colonization processes do not progress.[36,37]

Fourth, there was no difference in terms of survival based on the mode of systemic treatments (neoadjuvant therapy followed by surgery after N2 disease confirmation via IMNS, adjuvant therapy after upfront surgery despite N2 disease confirmation via IMNS, or adjuvant therapy after upfront surgery with node dissection without preoperative IMNS). Nonetheless, based on a retrospective study without a sufficient number of patients, it is a completely acceptable (or agreeable) finding. in fact, several reports have shown an acceptable survival outcome in patients who received adjuvant chemotherapy after upfront surgery for unforeseen N2 disease.

Recently, neoadjuvant chemoimmunotherapy has notably emerged as a novel and significant modality in the spectrum of neoadjuvant treatments. We postulate that the decision-making process surrounding IMNS is connected to the indications for neoadjuvant chemo-immunotherapy. If neoadjuvant immunotherapy demonstrates superior recurrence-free and survival outcomes compared to adjuvant immunotherapy in cases of occult N1/N2 disease, aggressive IMNS should be pursued. However, if this is not the case, we believe

that upfront surgery is justifiable in the same context as this study. Further research is required on this matter.

This study has several limitations. At first, the retrospective design of the study and its reliance on a limited patient cohort might not comprehensively capture the nuances of varying treatment modalities. Secondly, the initial survival analysis, conducted in an unmatched manner, may reflect a selection bias favoring patients less likely to benefit from local treatment, indicating a need for cautious interpretation of these results. Third, this study did not differentiate between mediastinoscopy and EBUS as methods of IMNS, failing to reflect the differences in invasiveness and diagnostic yield between the two techniques. Finally, this study was conducted at a single-institution, and thus may not be directly applicable to other settings or general populations. These limitations underscore the necessity for multicentre RCTs to provide more definitive evidence. Multicentre RCTs could help validate and expand upon these findings by controlling for various confounding factors, offering a more robust comparison of treatment outcomes, and potentially exploring the effectiveness of IMNS.

There have been concerns about the application of obsolete and hazardous surgery with uncertain survival benefit in patients with unforeseen N2 disease. Hence, the need for IMNS in routine diagnostic procedures has become questionable. However, considering the risk of procedure-related complications, medical cost, and potential treatment delays, efforts have been made to identify IMNS indications in patients at high risk of unforeseen N2 disease. 25 Nonetheless, due to the abovementioned data, IMNS may not have survival benefits even in such groups. Due to the increasing prevalence of early-stage lung cancer, this question could no longer be answered.

In conclusion, if there is no LN suspicious of metastasis on CT and PET-CT scan, patients might be able to have upfront surgery or receive definitive radiotherapy without worry of obsolete surgery. During surgery, meticulous and systematic nodal evaluation is important, and adjuvant systemic treatment would be considered for N2 disease. Further RCTs are required to validate the findings of the present study.

Contributors

HKK, YJJ, SH, and JK contributed to the conception of the study or the study design, or both. S-WU, HYL, Y-LC, JHC, YSC, JIZ, YMS, SHS, HK, KSL, TJK, and JH contributed to generation of data. YJJ and JK have access to and verify the underlying study data. YJJ and SH contributed to the statistical analyses. All authors contributed to the interpretation of the data. HKK, YJJ, SH and JK wrote the initial version of the manuscript. All authors reviewed the initial version, revised it critically for important intellectual content, and approved the final version.

Data sharing statement

The data that support the findings of this study are not publicly available. De-identified individual data can be made available to researchers who provide a research proposal. It is available from the corresponding author, JKK, upon reasonable request after publication.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102478.

References

1 Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of chest physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl): e211S–e250S.
2 Kudo S, Imai K, Ishiyama K, et al. New CT criteria for nodal staging in non-small cell lung cancer. *Clin Imaging*. 2014;38(4):448–453.
3 Li X, Zhang H, Xing L, et al. Mediastinal lymph nodes staging by 18F-FDG PET/CT for early stage non-small cell lung cancer: a multicenter study. *Radiother Oncol*. 2012;102(2):246–250.
4 Bousema JE, Aarts MJ, Dijkgraaf MGW, Annema JT, van den Broek FJC. Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer. *Eur Respir J*. 2021;57(4): 2001549.
5 Resio BJ, Canavan M, Mase V, Dhanasopon AP, Blasberg JD, Boffa DJ. Invasive staging procedures do not prevent nodal metastases from being missed in stage I lung cancer. *Ann Thorac Surg*. 2020;110(2):390–397.
6 Shin SH, Jeong BH, Jhun BW, et al. The utility of endosonography for mediastinal staging of non-small cell lung cancer in patients with radiological N0 disease. *Lung Cancer*. 2020;139: 151–156.
7 Beyaz F, Verhoeven RLJ, Schuurbiers OCJ, Verhagen A, van der Heijden E. Occult lymph node metastases in clinical N0/N1 NSCLC; A single center in-depth analysis. *Lung Cancer*. 2020;150:186–194.
8 De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardio Thorac Surg*. 2014;45(5):787–798.
9 Ettinger DS, Wood DE, Aggarwal C, et al. NCCN guidelines insights: non-small cell lung cancer, version 1.2020. *J Natl Compr Canc Netw*. 2019;17(12):1464–1472.
10 Kim HK, Choi YS, Kim J, Shim YM, Kim K. Outcomes of unexpected pathologic N1 and N2 disease after video-assisted thoracic surgery lobectomy for clinical stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2010;140(6):1288–1293.
11 Koike T, Koike T, Yamato Y, Yoshiya K, Toyabe S. Predictive risk factors for mediastinal lymph node metastasis in clinical stage IA non-small-cell lung cancer patients. *J Thorac Oncol*. 2012;7(8):1246–1251.
12 Eapen GA, Shah AM, Lei X, et al. Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE registry. *Chest*. 2013;143(4):1044–1053.
13 Jeon YJ, Lee J, Shin S, et al. Prognostic impact of micropapillary and solid histological subtype on patients undergoing curative resection for stage I lung adenocarcinoma according to the extent of pulmonary resection and lymph node assessment. *Lung Cancer*. 2022;168:21–29.
14 Kim MJ, Kim HJ, Kang D, et al. Preliminary attainability assessment of real-world data for answering major clinical research questions in breast cancer brain metastasis: framework development and validation study. *J Med Internet Res*. 2023;25:e43359.
15 Park HK, Jeon K, Koh WJ, et al. Occult nodal metastasis in patients with non-small cell lung cancer at clinical stage IA by PET/CT. *Respirology*. 2010;15(8):1179–1184.
16 Billé A, Pelosi E, Skanjeti A, et al. Preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer: accuracy of integrated positron emission tomography and computed tomography. *Eur J Cardio Thorac Surg*. 2009;36(3):440–445.
17 Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abraira V, Roqué IFM. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. *Cochrane Database Syst Rev*. 2014;2014(11): Cd009519.

18 Shim SS, Lee KS, Kim BT, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. *Radiology*. 2005;236(3):1011–1019.
19 Kim YK, Lee KS, Kim BT, et al. Mediastinal nodal staging of nonsmall cell lung cancer using integrated 18F-FDG PET/CT in a tuberculosis-endemic country: diagnostic efficacy in 674 patients. *Cancer*. 2007;109(6):1068–1077.
20 Cho YS, Choi JY, Lee KS, et al. FDG PET/CT criteria for diagnosing mediastinal lymph node metastasis in patients with non-small cell lung cancer. *J Nucl Med*. 2007;48(2 Suppl):85P.
21 Shin SH, Jeong DY, Lee KS, et al. Which definition of a central tumour is more predictive of occult mediastinal metastasis in nonsmall cell lung cancer patients with radiological N0 disease? *Eur Respir J*. 2019;53(3):1801508.
22 Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research. *JAMA*. 2020;323(5):466–467.
23 Langworthy B, Wu Y, Wang M. An overview of propensity score matching methods for clustered data. *Stat Methods Med Res*. 2023;32(4):641–655.
24 Bousema JE, van Dorp M, Noyez V, Dijkgraaf MGW, Annema JT, van den Broek FJC. Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. *J Thorac Oncol*. 2019;14(6):979–992.
25 Zhi X, Chen J, Xie F, Sun J, Herth FJF. Diagnostic value of endobronchial ultrasound image features: a specialized review. *Endosc Ultrasound*. 2021;10(1):3–18.
26 Paleru C, Danaila O, Bolca C, Cordos I. [Complications of mediastinoscopy]. *Pneumologia*. 2009;58(1):39–40.
27 Zakkar M, Hunt I. Complication rates in mediastinoscopy and training: video versus conventional mediastinoscopy. *Ann Thorac Surg*. 2012;94(1):337.
28 Vyas KS, Davenport DL, Ferraris VA, Saha SP. Mediastinoscopy: trends and practice patterns in the United States. *South Med J*. 2013;106(10):539–544.
29 Yeh YC, Nitadori J, Kadota K, et al. Using frozen section to identify histological patterns in stage I lung adenocarcinoma of </= 3 cm: accuracy and interobserver agreement. *Histopathology*. 2015;66(7):922–938.
30 Chang JM, Leung JWT, Moy L, Ha SM, Moon WK. Axillary nodal evaluation in breast cancer: state of the art. *Radiology*. 2020;295(3):500–515.
31 Barkur S, Notingher I, Rakha E. Intra-operative assessment of sentinel lymph nodes for breast cancer surgery: an update. *Surg Oncol*. 2022;40:101678.
32 Shimada Y, Saji H, Kakihana M, et al. Retrospective analysis of nodal spread patterns according to tumor location in pathological N2 non-small cell lung cancer. *World J Surg*. 2012;36(12):2865–2871.
33 Riquet M, Rivera C, Pricopi C, et al. Is the lymphatic drainage of lung cancer lobe-specific? A surgical appraisal. *Eur J Cardio Thorac Surg*. 2015;47(3):543–549.
34 Hishida T, Miyaoka E, Yokoi K, et al. Lobe-specific nodal dissection for clinical stage I and II NSCLC: Japanese multi-institutional retrospective study using a propensity score analysis. *J Thorac Oncol*. 2016;11(9):1529–1537.
35 Adachi H, Sakamaki K, Nishii T, et al. Lobe-specific lymph node dissection as a standard procedure in surgery for non-small cell lung cancer: a propensity score matching study. *J Thorac Oncol*. 2017;12(1):85–93.
36 Salvador F, Llorente A, Gomis RR. From latency to overt bone metastasis in breast cancer: potential for treatment and prevention. *J Pathol*. 2019;249(1):6–18.
37 Neophytou CM, Kyriakou TC, Papageorgis P. Mechanisms of metastatic tumor dormancy and implications for cancer therapy. *Int J Mol Sci*. 2019;20(24):6158.