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Tumor spread through air spaces (STAS) is a predictor of occult lymph node metastasis in clinical stage IA lung adenocarcinoma

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Abstract

Introduction: In patients with stage IA lung adenocarcinoma (ADC), sublobar resection and tumor spread through air spaces (STAS) are associated with high rates of locoregional recurrence, half of which occur within the regional lymph nodes (LNs). Our objective was to investigate the association between occult LN metastasis (ONM) and STAS and to assess their prognostic value in patients with clinical stage IA lung ADC.

Methods: The association between STAS and ONM was analyzed in patients who underwent lobectomy and LN dissection for clinical stage IA lung ADC (n=809). Multivariable logistic regression analysis was conducted to identify predictors of ONM. Site-specific recurrence by surgical procedure was investigated in patients with pathologic N0 disease (n=1055) using a competing-risks approach.

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Results: ONM was identified in 129 patients (16%)—one-third of ONMs were located only in intrapulmonary nodes. STAS was more common in patients with ONM (67% vs. 39%; $P<0.001$) and in patients with multiple ONMs (86%−89% vs. 60%−67%). STAS was a significant predictor of ONM on multivariable analysis, independent of tumor size, maximum standardized uptake value, and lymphovascular invasion. In STAS-positive (high ONM risk) patients, the risk of recurrence in the treated lobe and regional lymph nodes increased as the extent of resection decreased (recurrence risk: lobectomy < segmentectomy < wedge resection). In STAS-negative patients, the risk of locoregional recurrence did not differ by procedure type.

Conclusion: Presence of STAS predicts ONM in patients with clinical stage IA lung ADC and can help stratify risk of recurrence by extent and type of resection.

Keywords

Lung adenocarcinoma; non-small cell lung cancer; lymph node metastasis; sublobar resection; pathological staging

Introduction

Lobectomy with hilar and mediastinal lymph node (LN) dissection is the standard of care for the management of patients with early-stage non-small cell lung cancer (NSCLC).[1] This follows the results of the Lung Cancer Study Group randomized trial from 1995,[2] which showed that sublobar resection was associated with a higher risk of locoregional recurrence than lobectomy for patients with T1N0M0 NSCLC.

An analysis of patients with stage I NSCLC from the Surveillance, Epidemiology, and End Results database (1998–2009) showed that both the incidence of early-stage NSCLC and the use of sublobar resection (segmentectomy and wedge resection) have been increasing[3] despite ongoing concerns about the high risk of recurrence associated with these procedures.[2,4,5] Lung adenocarcinoma (ADC) is the most common histologic type of NSCLC, and 25% of cases of lung ADC are diagnosed at stage IA.[6] In patients with small, peripheral lung ADC, which is often treated with sublobar resection, accurate staging to confirm node-negative (N0) status is key. (18) F-fluorodeoxyglucose–positron emission tomography (PET) is routinely used in lung cancer workup on the basis of its higher sensitivity for the primary tumor, mediastinal LN metastasis, and distant metastasis, compared with conventional staging.[1,7–9] However, even in patients with clinical N0 lung ADC identified on both computed tomography (CT) and PET, occult LN metastasis (ONM) still occurs at a high rate (both N1 and N2, 15%−21%; only N2, 9%−14%).[10–13]

Lung ADC is associated with a higher risk of ONM than other histologic types of NSCLC.[11,14] We previously established that increasing percentage of micropapillary (MIP) subtype is associated with a higher risk of mediastinal ONM in patients with early-stage lung ADC without PET-positive mediastinal LNs.[15] We also found that the presence of MIP subtype (≥5% of the tumor) was associated with a higher risk of locoregional recurrence in patients with small lung ADCs undergoing sublobar resection.[16] On the basis of this observation, we investigated the lung parenchyma surrounding the tumor and identified a previously unrecognized pattern of invasion: tumor spread through air spaces (STAS), which is defined

as tumor cells existing within air spaces in the lung parenchyma beyond the tumor edge. We were the first to report that STAS is significantly associated with a higher risk of locoregional recurrence following sublobar resection for lung ADC.[17] In addition, we reported that in patients with stage IA lung ADC who underwent sublobar resection, a resection margin equal to more than the tumor diameter does not protect against locoregional recurrence, unlike in patients who underwent lobectomy.[5] The prognostic importance of STAS has been validated in cohorts from multiple institutional databases[18–23] and for other lung cancer histologic subtypes.[24–27]

Given that approximately half of locoregional recurrences occur within regional LNs, we hypothesized that STAS might be associated with the risk of ONM in patients with clinical N0 lung ADC. In the present study, we investigated the incidence, number, location, and size of ONMs in patients with clinical stage (c-Stage) IA lung ADC (N0 on CT and PET) and evaluated the association between ONM and STAS. Additionally, we hypothesized that the incidence of locoregional recurrence would be higher in STAS-positive patients undergoing sublobar resection than in those undergoing lobectomy.

Methods

Study Cohort and Data Collection

This retrospective study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSK). The MSK Thoracic Surgery Service's prospectively maintained lung cancer database was reviewed to identify consecutive patients who had been surgically treated for c-Stage IA lung ADC between January 1, 2000, and December 31, 2014. Exclusion criteria are shown in Figure 1. CT and (18) F-fluorodeoxyglucose–PET analyses performed within 3 months before surgery were reviewed for 1822 patients. Patients with tumor diameter >3 cm or LN short-axis diameter >1 cm on CT scan or patients with suspected hilar or mediastinal LN metastasis on PET scan (maximum standardized uptake value [SUVmax] ≥2.5)[28–30] were excluded from the analysis. Patient demographic information was obtained from the MSK Thoracic Surgery Service's prospectively maintained lung cancer database. Data on clinicopathological variables were obtained by reviewing patient medical records specifically for the purposes of this study, to determine clinical characteristics and follow-up status. Staging was based on the eighth edition of the *American Joint Committee on Cancer Staging Manual*.[31]

Patient follow-up status was updated as of July 2017. All recurrences were confirmed by clinical, radiologic, and pathologic assessment and were classified as local, regional LN, regional lung, or distant.[32] Local recurrence was defined as recurrence in the staple line or the lung parenchyma within the treated lobe. Regional LN recurrence was defined as recurrence within the ipsilateral hilar or mediastinal LNs. Regional lung recurrence was defined as recurrence within the ipsilateral lobes other than the resected lobe.[32] In cases where a new tumor developed in the lung or pleura and a biopsy specimen was available, the histologic profile was reviewed to determine whether the new tumor was a metachronous primary tumor, a recurrence, or a metastasis; this was completed in accordance with the method developed by our group.[33] In total, 1194 patients with c-Stage IA lung ADC met the inclusion criteria.

Histologic Evaluation

All available hematoxylin and eosin–stained tumor and LN slides were reviewed by two pathologists (S.L. and W.D.T.), who were blinded to patient clinical outcomes, using an Olympus BX51 microscope (Olympus, Tokyo, Japan) with a standard 22-mm diameter eyepiece. Any discrepancies among the pathologists during assignment of predominant subtypes were later resolved via consensus using a multihead microscope.

Presence of tumor STAS was defined as tumor cells in clusters, solid nests, or aggregates of single cells within air spaces beyond the edge of the main tumor.[17] Artifacts were excluded on the basis of previously described criteria.[17] The percentage of each histologic pattern was recorded in 5% increments. Tumors were classified, in accordance with the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society classification and the 2015 World Health Organization classification, as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma, which was subdivided into lepidic-predominant (LEP), acinar-predominant (ACI), papillary-predominant (PAP), MIP-predominant, solid-predominant (SOL), colloid-predominant (COL), and invasive mucinous (IMA) adenocarcinoma.[34,35] Tumors were grouped by architectural grade as low (AIS, MIA, or LEP), intermediate (PAP or ACI), or high (MIP, SOL, COL, or IMA).[36] Visceral pleural invasion (VPI), lymphovascular invasion (LVI), and necrosis were also investigated. In cases with LN metastasis, the largest diameter of metastatic area was measured using a ruler.

Evaluation of ONM

ONM was evaluated in 809 patients who underwent lobectomy with mediastinal LN evaluation. Pathologic reports were reviewed and the presence and location of ONM were evaluated for all cases. The location of ONM was classified, on the basis of nodal station,[31] as either intrapulmonary (only #12-#14), hilar (#10, #11, with or without intrapulmonary LNs), and mediastinal (#2-#9, with or without N1 [#10–14] nodes). The number of metastatic LN stations was recorded. The size of the ONM was defined as the largest diameter among the metastatic areas.

Site-Specific Risk of Recurrence by Type of Resection

To investigate whether recurrence pattern is associated with risk of ONM, site-specific CIR was evaluated in patients with pathologic N0 disease (n=1055) who underwent lobectomy, segmentectomy, and wedge resection with pathologic mediastinal LN evaluation by either dissection or sampling and in patients who underwent wedge resection without mediastinal LN evaluation. Recurrence was classified as local (treated lobe, including the resection line), regional LN (ipsilateral hilar or mediastinal LN), regional lung (other ipsilateral lobe), or distant recurrence.[32]

Statistical Analysis

Patient clinicopathologic characteristics were summarized and compared using Fischer's exact test and the χ^2 test (for categorical variables), the Wilcoxon rank-sum test (to compare continuous variables between two groups), or the Kruskal-Wallis test (to compare continuous variables among more than two groups). Logistic regression analysis was used to

identify risk factors for ONM. Multivariable models were constructed starting with variables with $P<0.1$ in the univariable analyses. To assess the marker of interest (STAS), the multivariable model building procedure was conducted in three phases: (1) identify a set of preoperative factors associated with ONM; (2) include STAS in the model from part 1, assuming STAS can be detected intraoperatively using frozen section analysis[37]; and (3) include postoperative factors in the model to investigate whether STAS can predict ONM independently of other pathologic factors, such as LVI. Recurrence patterns were summarized using a CIR approach and were compared between surgery types using Gray's test for competing-risks events. Two statistical comparisons were conducted: (1) between three procedures (lobectomy, segmentectomy, and wedge resection) with mediastinal LN evaluation and (2) between four procedures (including wedge resection without LN evaluation). All *P* values were two-sided with a 5% alpha level. Statistical tests were conducted using Stata 13.1 (StataCorp, College Station, TX) and R 3.1.1 (R Development Core, Vienna, Austria).

Results

Patient Clinicopathologic Characteristics and ONM Status

The clinicopathologic characteristics of patients who underwent lobectomy are reported in Table 1. Of the 809 patients who underwent lobectomy, 129 (16%) had ONM identified. Of the 129 patients with ONM, 31% had only intrapulmonary ONM, 19% had hilar ONM, and 50% had mediastinal ONM. Fifty-seven percent had ONM in 1 station, 29% had 2 stations, and 15% had ≥3 stations. The median size of ONM was 3 mm (25th-75th percentile, 2–6 mm).

The presence of ONM was significantly associated with female sex, larger tumor CT size, higher tumor SUVmax, presence of STAS, larger pathologic total and invasive tumor size, presence of LVI, presence of VPI, and a lower proportion of low-grade and a higher proportion of high-grade histologic subtypes (Table 1). The location and incidence of ONM, by resected lobes, are shown in supplemental data, Table S1.

STAS and ONM

Of the 809 patients who underwent lobectomy, 350 (43%) had STAS identified. The presence of STAS was significantly associated with current smoker status, higher pack-year index, higher tumor SUVmax, higher number of ONMs, larger pathologic total and invasive tumor size, presence of LVI, presence of VPI, presence of necrosis, and a lower proportion of low-grade and a higher proportion of high-grade histologic subtypes (Table 1).

Figure 2 demonstrates the relationship between ONM status and incidence of STAS. The incidence of STAS was higher in patients with ONM than in those without ONM (67% vs. 39%; $P<0.001$) and higher in patients with multiple ONMs (N1b or N2b) than in those with a single ONM (N1a or N2a) (86%−89% vs. 60%−67%). The incidence of STAS increased with increasing number of ONMs (0=39%, 1=62%, 2=73%, 3=79%; $P<0.001$).

Predictors of ONM

In univariable logistic analysis, female sex, larger CT tumor size, higher tumor SUVmax, presence of STAS, larger pathologic total and invasive tumor size, presence of LVI, presence of VPI, and higher-grade histologic subtypes were significantly associated with ONM (Table 2).

In the first multivariable model, which included only preoperative factors, female sex, larger CT tumor size, and higher SUVmax were independent risk factors for ONM. In the second multivariable model, which included STAS in addition to preoperative factors, STAS was a significant risk factor for ONM (odds ratio, 2.82 [95% confidence interval, 1.87–4.28]; $P<0.001$), independent of sex, CT tumor size, and SUVmax. In the third multivariable model, which included both preoperative and postoperative pathologic factors, STAS remained a significant risk factor for ONM (odds ratio, 1.89 [95% confidence interval, 1.23–2.93]; $P=0.004$), independent of sex, SUVmax, invasive tumor size, and LVI.

ONM Risk-Based Recurrence Pattern Assessment: Site-Specific 5-Year CIR by Procedure

Table 3 shows site-specific 5-year CIR by type of resection. The top panel shows the results from the overall cohort of patients. Patients were divided into two groups on the basis of risk of ONM as determined by STAS status: patients with STAS were considered high ONM risk (middle panel), and patients without STAS were considered low ONM risk (bottom panel).

In the overall cohort, the incidence of local (treated lobe) and regional LN recurrence were lowest in patients who underwent lobectomy; the incidence increased as the extent of resection decreased (recurrence risk: lobectomy < segmentectomy < wedge resection) and was highest in patients who underwent wedge resection without mediastinal LN evaluation. There was no statistically significant difference in the incidence of distant recurrence across the four procedures.

Differences in local and regional LN recurrence across procedures were more evident in the high ONM risk cohort (patients with STAS) than in the overall cohort. Of note, the incidence of regional LN recurrence was significantly higher after sublobar resection than after lobectomy; the risk was highest after wedge resection, regardless of mediastinal LN evaluation.

In the low ONM risk cohort (patients without STAS), risk of local recurrence was higher after sublobar resection than after lobectomy but was similar after segmentectomy and wedge resection with mediastinal LN evaluation. The risk of regional LN recurrence did not differ by extent of resection, with the exception of a higher risk in patients treated with wedge resection without mediastinal LN evaluation.

Table 4 shows patient clinicopathologic characteristics and a comparison of the four surgical procedures. Greater extent of resection (lobectomy > segmentectomy > wedge) was associated with younger age, lower pack-year index, larger CT tumor size, higher tumor SUVmax, larger pathologic total and invasive tumor size, and a lower proportion of low-grade subtypes.

Discussion

The novelty of the present study is reflected in its evaluation of detailed characteristics of ONM, including location, number, and size, using a large cohort of patients with c-Stage IA lung ADC. Of significance, (1) one-third of ONMs were located in intrapulmonary LNs without hilar and mediastinal LN metastasis, and half of ONMs were 3 mm or smaller, suggesting potential difficulty in detecting ONMs by hilar and mediastinal sampling during sublobar resection; (2) STAS was associated with a high risk of ONM, especially multiple ONMs, and was a significant predictor of ONM on multivariable analysis, independent of tumor size, SUVmax, and LVI; and (3) in patients with STAS, risk of recurrence within treated lobes and regional LNs was higher after sublobar resection than after lobectomy, suggesting that lobectomy may be the most appropriate procedure for patients with STAS.

Previous studies have reported radiologic or pathologic predictors of ONM, such as larger tumor size, higher SUVmax, presence of LVI, and MIP histologic subtype.[11,15,38] Although pathologic findings are strongly associated with ONM, it would be difficult to use these factors for pre- or intraoperative decisions regarding resection type. We have reported that detection of MIP histologic subtype on frozen section analysis[39] had low sensitivity (37%) despite high specificity (94%). However, we also assessed the potential utility of frozen section analysis for detecting STAS intraoperatively and found that frozen section analysis for STAS had better sensitivity and similar specificity, compared with frozen section for MIP subtype, with substantial interpathologist agreement.[37] Our three-phase multivariable models for predicting ONM demonstrated that (1) SUVmax and tumor size were independent predictors of ONM; (2) STAS was an independent predictor of ONM, suggesting that intraoperative detection of STAS (assuming frozen section analysis is feasible) will be useful for predicting ONM, in addition to preoperative radiological findings; and (3) STAS remained a significant predictor of ONM, independent of LVI and invasive tumor size, when preoperative and postoperative factors were included in the analysis. Together, these findings suggest that STAS is a clinically useful and significant factor for predicting ONM in patients with c-Stage IA lung ADC.

To avoid locoregional recurrence following sublobar resection, various options have been proposed, such as selecting patients by imaging studies,[40] achieving adequate surgical margins,[41] performing segmentectomy rather than wedge resection,[42] and including adequate LN evaluation.[43] In the present study, we evaluated site-specific risk of recurrence by risk of ONM (based on STAS status). The results of this analysis showed that (1) wedge resection without mediastinal LN evaluation was associated with a significantly higher risk of locoregional recurrence, regardless of the risk of ONM, supporting the importance of adequate mediastinal LN evaluation in all patients undergoing sublobar resection; (2) in patients with a high risk of ONM (based on positive STAS status), decreased extent of resection was associated with an increased risk of recurrence within the treated lung and regional LNs; and (3) in patients with a low risk of ONM (based on negative STAS status), the risk of regional LN recurrence was similar between sublobar resection with mediastinal LN evaluation and lobectomy and the risk of any type of recurrence was similar between segmentectomy and wedge resection (with mediastinal LN evaluation). These findings suggest that assessing the risk of ONM by STAS status—in addition to performing

mediastinal LN evaluation to detect ONM—may help to identify appropriate candidates for sublobar resection. A multi-institutional, prospective study determining the accuracy and predictive value of detecting STAS on frozen section is a first step, as confirmation of presence of STAS can help determine the type of resection for small-sized lung ADC. The information derived from such a study (location, extent, and histological subtypes of STAS cells) can help determine the nature of the prospective, therapeutic study investigating the appropriate extent of resection for high-risk, small-sized lung ADC. The presence of STAS in other NSCLC histologic subtypes has been reported. The utility of STAS in predicting ONM in NSCLC other than lung ADC is an ongoing area of investigation.

One of the limitations of the present study was the potential selection bias between surgical procedures. Another limitation was the relatively small number of patients who underwent sublobar resection. These limitations might have affected our results. Nevertheless, the association between STAS and ONM demonstrated in our study is provocative and needs to be investigated in a prospective study. Following the results of the National Lung Screening Trial, which showed that screening with low-dose CT reduces mortality attributable to lung cancer, the detection of early-stage lung cancer has been expected to increase.[44] In addition, the age of patients with lung cancer in the United States has been increasing, with associated higher risks of postoperative morbidity and noncancer-specific mortality.[45,46] The above factors underscore the importance of investigating the risk factors for ONM.

In conclusion, we have demonstrated that, in patients with c-Stage IA lung ADC, ONMs are small and frequently located in intrapulmonary LNs, suggesting a potential difficulty in detecting ONM by LN sampling during sublobar resection. STAS is a significant predictor of ONM, independent of SUVmax, tumor size, and LVI. In patients who are eligible for both lobar and sublobar resection, intraoperative identification of STAS can help to determine the most appropriate type of resection to perform.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACI	acinar predominant
ADC	adenocarcinoma
AIS	adenocarcinoma in situ

CIR	competing risks analysis
COL	colloid predominant
CT	computed tomography
N0	node-negative
LEP	lepidic predominant
LN	lymph node
LVI	lymphovascular invasion
MIA	minimally invasive adenocarcinoma
MIP	micropapillary predominant
MUC	mucinous predominant
NSCLC	non-small cell lung cancer
ONM	occult lymph node metastasis
PAP	papillary predominant
PET	positron emission tomography
SOL	solid predominant
STAS	spread through air spaces
SUVmax	maximum standard uptake value
VPI	visceral pleural invasion

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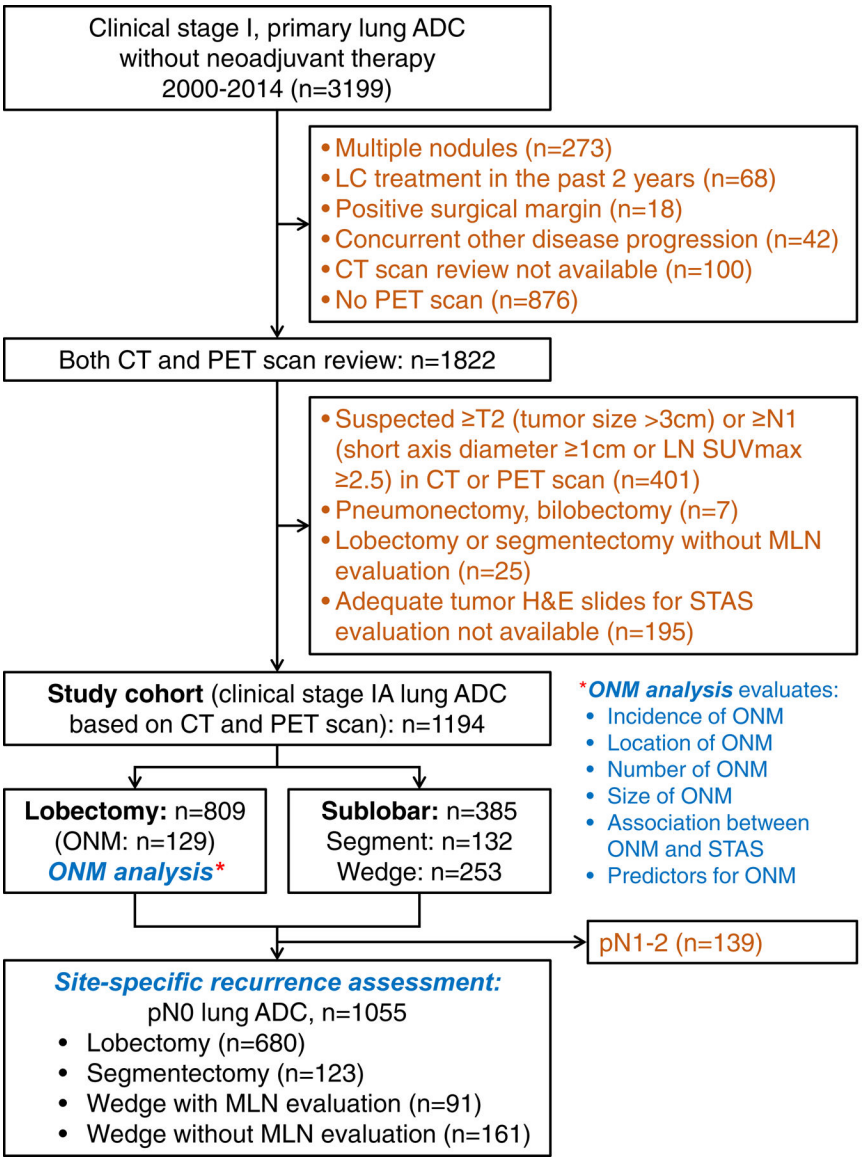

Figure 1.

CONSORT diagram. ADC, adenocarcinoma; CT, computed tomography; LC, lung cancer; MLN, mediastinal lymph node; ONM, occult lymph node metastasis; PET, positron emission tomography; STAS, spread through air spaces; SUVmax, maximum standardized uptake value.

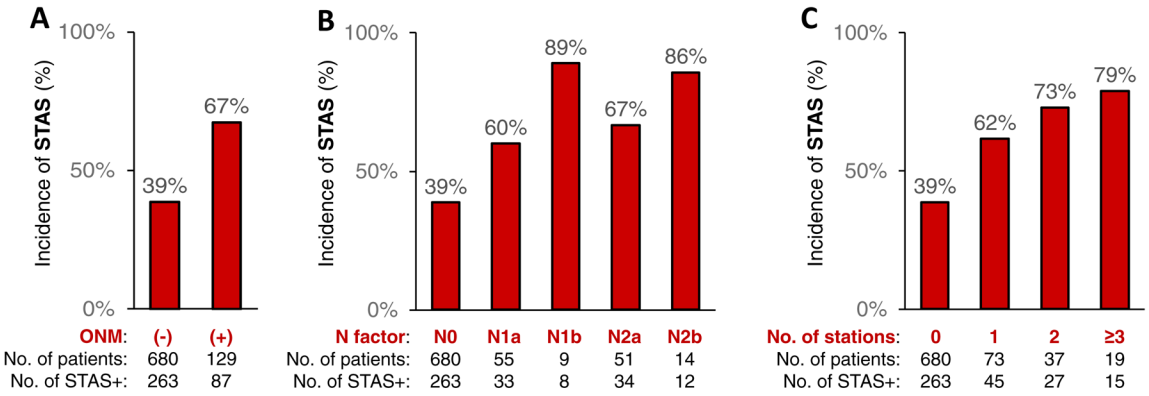

Figure 2.

Percentage of STAS-positive patients by ONM status – A) incidence of STAS by ONM, B) incidence of STAS in N1 and N2 lymph nodes, and C) incidence of STAS and number of positive lymph node stations. ONM, occult lymph node metastasis; STAS, spread through air spaces.

Table 1.

Patient clinicopathologic characteristics in the lobectomy cohort and their association with occult lymph node metastasis and spread through air spaces status

Variable	Overall cohort (N=809)	ONM (−) (N=680)	ONM (+) (N=129)	*P*	STAS (−) (N=459)	STAS (+) (N=350)	*P*
Age, years	68 (61–75)	68 (61–75)	68 (63–73)	0.5	68 (61–75)	68 (61–74)	0.7
Sex							
Female	530 (66)	434 (64)	96 (74)	**0.020**	305 (66)	225 (64)	0.6
Male	279 (34)	246 (36)	33 (26)		154 (34)	125 (36)	
Smoking							
Never	167 (21)	144 (21)	23 (18)	0.5	111 (24)	56 (16)	**0.003**
Former	548 (68)	460 (68)	88 (68)		305 (66)	243 (69)	
Current	94 (12)	76 (11)	18 (14)		43 (9)	51 (15)	
Pack-year index	25 (4–50)	25 (4–50)	30 (9–50)	0. 5	23 (1–45)	30 (11–50)	**0.003**
CT tumor size, cm	2.0 (1.5–2.5)	1.9 (1.5–2.4)	2.2 (1.7–2.7)	<**0.001**	1.9 (1.5–2.4)	2.0 (1.5–2.5)	0.15
Tumor SUVmax	2.7 (1.5–5.2)	2.4 (1.3–4.4)	4.7 (3.0–7.9)	<**0.001**	2.1 (1.1–3.9)	3.8 (2.0–6.9)	<**0.001**
ONM							
Present	129 (16)				42 (9)	87 (25)	<**0.001**
Location							
Intrapulmonary[a]	40 (5)				14 (3)	26 (7)	<**0.001**
Hilar[b]	24 (3)				9 (2)	15 (4)	
Mediastinal[c]	65 (8)				19 (4)	46 (13)	
Number of metastatic stations							
1	73 (9)				28 (6)	45 (13)	<**0.001**
2	37 (5)				10 (2)	27 (8)	
≥3	19 (2)				4 (1)	15 (4)	
Size of metastatic area, mm[d]	3 (2–6)				4 (2–5)	3 (1–6)	0. 3
pN (8th ed.)							
N1a (single N1)	55 (7)				22 (5)	33 (9)	<**0.001**
N1b (multiple N1)	9 (1)				1 (0)	8 (2)	
N2a (single N2)	51 (6)				17 (4)	34 (10)	

Variable	Overall cohort (N=809)	ONM (−) (N=680)	ONM (+) (N=129)	*P*	STAS (−) (N=459)	STAS (+) (N=350)	*P*
N2b (multiple N2)	14 (2)				2 (0)	12 (3)	
STAS present	350 (43)	263 (39)	87 (67)	<**0.001**			
Pathologic tumor size, cm	1.8 (1.4–2.4)	1.7 (1.3–2.2)	2.0 (1.6–2.5)	<**0.001**	1.7 (1.2–2.2)	1.9 (1.5–2.5)	<**0.001**
Invasive tumor size, cm	1.5 (1.0–2.0)	1.4 (1.0–2.0)	2.0 (1.5–2.5)	<**0.001**	1.2 (0.8–1.8)	1.8 (1.3–2.3)	<**0.001**
LVI	377 (47)	269 (40)	108 (84)	<**0.001**	155 (34)	222 (63)	<**0.001**
VPI	140 (17)	96 (14)	44 (34)	<**0.001**	53 (12)	87 (25)	<**0.001**
Necrosis (n=792)	96 (12)	80 (12)	16 (13)	0.7	38 (8)	58 (17)	**0.003**
Predominant subtype							
AIS	1 (0)	1 (0)	0 (0)	<**0.001**	1 (0)	0 (0)	<**0.001**
MIA	47 (6)	47 (7)	0 (0)		47 (10)	0 (0)	
Lepidic	59 (7)	55 (8)	4 (3)		53 (12)	6 (2)	
Acinar	369 (46)	308 (45)	61 (47)		205 (45)	164 (47)	
Papillary	123 (15)	110 (16)	13 (10)		69 (15)	54 (15)	
Micropapillary	56 (7)	36 (5)	20 (16)		11 (2)	45 (13)	
Solid	130 (16)	99 (15)	31 (24)		54 (12)	76 (22)	
IMA	22 (3)	22 (3)	0 (0)		17 (4)	5 (1)	
Colloid	2 (0)	2 (0)	0 (0)		2 (0)	0 (0)	
Histologic grade							
Low	107 (13)	103 (15)	4 (3)	<**0.001**	101 (22)	6 (2)	<**0.001**
Intermediate	493 (61)	419 (62)	74 (57)		274 (60)	219 (63)	
High	209 (26)	158 (23)	51 (40)		84 (18)	125 (36)	
Mutation status (n=683)							
Wild-type	337 (49)	288 (49)	49 (52)	0.7	184 (48)	153 (51)	0.3
EGFR	150 (22)	133 (23)	17 (18)		93 (24)	57 (19)	
KRAS	196 (29)	168 (29)	28 (30)		107 (28)	89 (30)	

Data are no. (%) or median (25–75 percentile). AIS, adenocarcinoma in situ; CT, computed tomography; IMA, invasive mucinous adenocarcinoma; LVI, lymphovascular invasion; MIA, minimally invasive adenocarcinoma; ONM, occult lymph node metastasis; STAS, spread through air spaces; SUVmax, maximum standardized uptake value; VPI, visceral pleural invasion.

[a] Only intrapulmonary lymph node metastasis (#12-#14), without hilar and mediastinal metastasis.

[b] Hilar lymph node metastasis (#10, #11) without mediastinal metastasis, with or without intrapulmonary metastasis.

[c] Mediastinal lymph node metastasis (#2-#9), with or without hilar/intrapulmonary metastasis.

[d] Largest diameter of the metastatic area.

Table 2.

Univariable and multivariable logistic regression analysis for predicting occult lymph node metastasis

				Multivariable models								
	Univariable analysis			Preoperative factors			Preoperative + STAS			Both pre- and postoperative		
Factor	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Preoperative factors												
Age (per 1-year increase)	1.00	0.98–1.02	0.7									
Male (vs female)	0.61	0.40–0.93	**0.021**	0.60	0.39–0.93	**0.023**	0.57	0.37–0.90	**0.015**	0.50	0.31–0.78	**0.003**
Smoking (vs never)												
Former	1.20	0.73–1.97	0.5									
Current	1.48	0.75–2.92	0.3									
Pack-year index (per 1 index increase)	1.00	0.99–1.01	1.0									
CT tumor size (per 1-cm increase)	2.04	1.46–2.86	<**0.001**	1.55	1.08–2.21	**0.016**	1.59	1.10–2.29	**0.013**			
Tumor SUVmax (per 1 value increase)	1.16	1.11–1.22	<**0.001**	1.15	1.09–1.21	<**0.001**	1.12	1.06–1.18	<**0.001**	1.06	1.00–1.12	**0.037**
STAS												
Present (vs absent)	3.28	2.20–4.90	<**0.001**				2.82	1.87–4.28	<**0.001**	1.89	1.23–2.93	**0.004**
Postoperative factors												
Pathologic tumor size (per 1-cm increase)	1.82	1.43–2.31	<**0.001**									
Invasive tumor size (per 1-cm increase)	2.29	1.80–2.91	<**0.001**							1.42	1.06–1.90	**0.019**
LVI (vs absent)	7.86	4.80–12.85	<**0.001**							5.21	3.08–8.83	<**0.001**
VPI (vs absent)	3.15	2.06–4.81	<**0.001**									
Necrosis (vs absent)	1.13	0.63–2.00	0.7									
Histologic grade (vs low)												
Intermediate	4.55	1.63–12.73	**0.004**									
High	8.31	2.92–23.69	<**0.001**									
Mutation (vs wild-type)												
EGFR	0.75	0.42–1.35	0.3									
KRAS	0.98	0.59–1.62	0.9									

CI, confidence interval; CT, computed tomography; LVI, lymphovascular invasion; OR, odds ratio; STAS, spread through air spaces; SUVmax, maximum standardized uptake value; VPI, visceral pleural invasion.

Table 3

Site-specific 5-year cumulative incidence of recurrence between procedures in patients with pN0 lung adenocarcinoma: Occult lymph node metastasis risk-based recurrence pattern assessment

	MLN evaluation (+)[a]				MLN evaluation (−)[c]	
Cohort, site	**Lobectomy**	**Segmentectomy**	**Wedge**	***P*[b]**	**Wedge**	***P*[d]**
Overall	N=680	N=123	N=91		N=161	
Local (treated lobe)	0 (N/A)	3 (1–9)	5 (2–14)	**<0.001**	14 (9–21)	**<0.001**
Regional LN (ipsilateral hilar/mediastinal)	1 (1–3)	4 (1–10)	8 (3–19)	**0.011**	14 (9–21)	**<0.001**
Regional lung (ipsilateral another lobe)	3 (2–5)	2 (0–7)	1 (0–9)	0.7	7 (3–13)	0.053
Distant	9 (7–12)	7 (4–14)	12 (6–23)	0.5	12 (8–20)	0.3
High ONM risk (STAS positive)	N=263	N=37	N=34		N=75	
Local (treated lobe)	0 (N/A)	3 (0–20)	8 (2–32)	**<0.001**	23 (14–36)	**<0.001**
Regional LN (ipsilateral hilar/mediastinal)	2 (1–6)	9 (3–26)	21 (9–50)	**<0.001**	22 (14–35)	**<0.001**
Regional lung (ipsilateral another lobe)	5 (3–10)	6 (1–22)	3 (0–24)	0.9	11 (5–23)	0.4
Distant	14 (10–19)	11 (4–29)	22 (10–50)	0.7	21 (13–35)	0.5
Low ONM risk (STAS negative)	N=417	N=86	N=57		N=86	
Local (treated lobe)	0 (N/A)	3 (1–12)	4 (1–17)	**0.002**	7 (3–15)	**<0.001**
Regional LN (ipsilateral hilar/mediastinal)	1 (0–3)	2 (0–12)	0 (N/A)	0.8	6 (3–15)	**<0.001**
Regional lung (ipsilateral another lobe)	1 (0–3)	0 (N/A)	0 (N/A)	0.5	3 (1–10)	0.3
Distant	6 (4–9)	6 (2–15)	7 (3–19)	0.7	5 (2–13)	0.9

Data are % (95% confidence interval). LN, lymph node; MLN, mediastinal lymph node; N/A, not applicable; ONM, occult lymph node metastasis; STAS, spread through air spaces.

[a] Pathologic evaluation of at least one MLN by either dissection or sampling.

[b] Comparison between three procedures with MLN evaluation.

[c] No pathologic evaluation of MLNs.

[d] Comparison between four procedures, including wedge resection without MLN evaluation.

Table 4.

Patient clinicopathologic characteristics and comparison between surgical procedures in patients who underwent lobectomy, segmentectomy, and wedge resection for pN0 lung adenocarcinoma

	MLN Evaluation (+)[a]		MLN Evaluation (−)[b]		
Characteristic	**Lobectomy (N=680)**	**Segmentectomy (N=123)**	**Wedge (N=91)**	**Wedge (N=161)**	**P**
Age, years	68 (61–75)	68 (61–75)	71 (65–76)	70 (63–77)	**0.004**
Sex					
Female	434 (64)	85 (69)	63 (69)	101 (63)	0.5
Male	246 (36)	38 (31)	28 (31)	60 (37)	
Smoking					
Never	144 (21)	25 (20)	9 (10)	25 (16)	0.14
Former	460 (68)	81 (66)	70 (77)	116 (72)	
Current	76 (11)	17 (14)	12 (13)	20 (12)	
Pack-year index	25 (4–50)	25 (5–60)	31 (15–56)	36 (10–56)	**0.045**
CT tumor size, cm	1.9 (1.5–2.4)	1.7 (1.3–2.2)	1.5 (1.2–1.9)	1.5 (1.1–1.8)	**<0.001**
Tumor SUVmax	2.4 (1.3–4.4)	2.4 (1.2–4.1)	2.1 (1.2–2.9)	1.9 (0.0–3.6)	**0.001**
T factor					
Tis	1 (0)	0 (0)	0 (0)	2 (1)	**<0.001**
T1a	129 (19)	34 (28)	22 (24)	52 (32)	
T1a(mi)	47 (7)	17 (14)	16 (18)	26 (16)	
T1b	304 (45)	52 (42)	34 (37)	49 (30)	
T1c	90 (13)	6 (5)	0 (0)	2 (1)	
T2a	97 (14)	14 (11)	19 (21)	29 (18)	
T2b	4 (1)	0 (0)	0 (0)	0 (0)	
T3	8 (1)	0 (0)	0 (0)	1 (1)	
Pathologic tumor size, cm	1.7 (1.3–2.2)	1.5 (1.1–2.0)	1.3 (1.0–1.8)	1.2 (1.0–1.6)	**<0.001**
Invasive tumor size, cm	1.4 (1.0–2.2)	1.1 (0.7–1.5)	1.0 (0.5–1.5)	1.0 (0.6–1.4)	**<0.001**
LVI	269 (40)	41 (33)	26 (29)	59 (37)	0.2
VPI	96 (14)	11 (9)	19 (21)	29 (18)	0.051
Necrosis (n=1041)	80 (12)	9 (7)	5 (6)	10 (6)	0.053
STAS	263 (39)	37 (30)	34 (37)	75 (47)	**0.043**
Predominant subtype					
AIS	1 (0)	0 (0)	0 (0)	2 (1)	**0.022**
MIA	47 (7)	17 (14)	16 (18)	26 (16)	
Lepidic	55 (8)	12 (10)	12 (13)	14 (9)	
Acinar	308 (45)	51 (41)	31 (34)	63 (39)	
Papillary	110 (16)	14 (11)	10 (11)	22 (14)	
Micropapillary	36 (5)	5 (4)	6 (7)	7 (4)	
Solid	99 (15)	17 (14)	11 (12)	23 (14)	
IMA	22 (3)	7 (6)	5 (5)	4 (2)	
Colloid	2 (0)	0 (0)	0 (0)	0 (0)	
Histologic grade					

	MLN Evaluation (+)[a]		MLN Evaluation (−)[b]		
Characteristic	**Lobectomy (N=680)**	**Segmentectomy (N=123)**	**Wedge (N=91)**	**Wedge (N=161)**	**P**
Low	103 (15)	30 (24)	28 (31)	42 (26)	**0.001**
Intermediate	419 (62)	64 (52)	41 (45)	85 (53)	
High	158 (23)	29 (24)	22 (24)	34 (21)	
Mutation status (n=890)					
Wild-type	288 (49)	49 (51)	36 (49)	61 (47)	0.11
EGFR	133 (23)	17 (18)	7 (10)	26 (20)	
KRAS	168 (29)	31 (32)	30 (41)	44 (34)	

Data are no. (%) or median (25–75 percentile). AIS, adenocarcinoma in situ; CT, computed tomography; IMA, invasive mucinous adenocarcinoma; LVI, lymphovascular invasion; MIA, minimally invasive adenocarcinoma; MLN, mediastinal lymph node; ONM, occult lymph node metastasis; STAS, spread through air spaces; SUVmax, maximum standardized uptake value; VPI, visceral pleural invasion.

[a]Pathologic evaluation of at least one MLN by either dissection or sampling.

[b]No pathologic evaluation of MLNs.