Optimal method for measuring invasive size that predicts survival in invasive mucinous adenocarcinoma of the lung

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Key words

Invasive mucinous adenocarcinoma, invasive size, lepidic component, TNM classification

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Abbreviation List

AIC = Akaike' information criteria; CI = confidence interval; CPE = concordance probability estimate; ELM = excluding lepidic method; ILM = including lepidic method; IMA = invasive mucinous adenocarcinoma; OS = overall survival; T-ELM = T stages based on ELM; T-ILM = T stages based on ILM; WHO = World Health Organization

Abstract

Purpose

The purpose of this study was to determine the optimal method for measuring pathological invasive size that predicts prognosis in invasive mucinous adenocarcinoma (IMA).

Methods

We analyzed patients who underwent complete surgical resection for lung IMA. The invasive size of IMA was measured using two methods: (1) excluding lepidic method (ELM), that is, lepidic component was excluded from the invasive area regardless of alveolar mucin and (2) including lepidic method (ILM), that is, lepidic component was included as invasive area if alveolar space was filled with mucin. The prognostic predictability of ELM and ILM on survival was assessed using univariable and multivariable Cox regression models. The discriminative power was assessed using concordance probability estimate (CPE) and Akaike's information criteria (AIC), and the prognostic impact of the newly redefined pathological stage according to ELM or ILM was also assessed.

Results

A total of 101 patients were included. The median invasive size via ELM and ILM was 1.4 cm (range, 0.0-7.7 cm) and 2.1 cm (range, 0.0-14.2 cm), respectively. ELM had better discriminative power than ILM (ELM, HR = 1.38, AIC = 110.19, CPE = 0.671; ILM, HR = 1.19,

AIC = 111.52, CPE = 0.655). Although the survival curves based on ILM crossed between T3 and T4, the overall survival (OS) curves based on ELM were sufficiently distinct from one another.

Conclusions

ELM has higher discriminative power for OS, and thus the optimal method for measuring the pathological invasive size of IMA should exclude the lepidic component regardless of alveolar mucin.

Introduction

Invasive mucinous adenocarcinoma (IMA) of the lung is a variant of adenocarcinoma characterized by a goblet or columnar cell morphology with abundant intracytoplasmic mucin.(Travis et al. 2011, 2015a) IMA was newly classified as a variant of adenocarcinoma in the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma in 2011 and the World Health Organization (WHO) Classification of Lung Tumors in 2015.(Travis et al. 2011, 2015b, a)

In the 8th edition of the TNM classification of lung cancer published in 2017,(Brierley et al. 2017) tumor size is determined according to the invasive size excluding the lepidic growth component in pathological findings because the lepidic growth pattern is considered a non-invasive lesion in lung non-mucinous adenocarcinoma.(Yoshizawa et al. 2011; Nakagiri et al. 2014; Kadota et al. 2014; Travis et al. 2016; Kameda et al. 2018)

However, there is no evidence whether this rule could be applied to IMA(Travis et al. 2016) where a lepidic growth area is sometimes filled with alveolar mucin that may also spread to alveolar spaces.(Travis et al. 2013; Isaka et al. 2017; Boland et al. 2018) Thus, the lepidic growth pattern of IMA might be an invasive component, but the prognostic significance of this component is unclear.(Travis et al. 2011; Hwang et al. 2017)

Given that IMA widely spreads with lepidic growth pattern with alveolar mucin,(Casali et al. 2010; Travis et al. 2013, 2015b) the invasive size differs largely between cases, particularly when this area is included or excluded in the measurement of invasive component. Therefore, the invasive size of IMA has not been clearly defined yet. The purpose of this study was to define the optimal method for measuring the pathological invasive size that predicts prognosis in IMA.

Materials and methods

Patient selection

Among patients who underwent complete surgical resection for lung adenocarcinoma between January 2004 and December 2015 at National Cancer Center Hospital East, Chiba, Japan, we included those who met the following criteria: (1) more than 10% goblet cells; (2) pathologically negative lymph node and distant metastasis; and (3) did not receive preoperative therapy. Data were retrospectively collected from medical records. The diagnosis of IMA was confirmed by two pathologists (TO and GI) according to the 2015 WHO classification. This study was approved by the Institutional Review Board of the National Cancer Center Hospital East in 2017 (approval number 2017-428), and comprehensive informed consent was obtained from all individual participants.

Histological studies

The surgical specimens were fixed in 10% formalin, embedded in paraffin, and sliced into 4-mm sections. The sections were then stained with hematoxylin and eosin. All the histological materials included in this series were reviewed by two pathologists (TO and GI). IMA was defined as an adenocarcinoma with tumor cells that had a goblet or columnar morphology, abundant intracytoplasmic mucin, and basally oriented nuclei (Figure 1) according to the 2015 WHO Classification of Lung Tumors.(Travis et al. 2015b, a) In accordance with this definition, the term of "goblet cells" in this study represented tumor cells having above histological characteristics. All tumors consisted of more than 10% of goblet cells. Therefore, IMA in this study pertains to pure invasive mucinous adenocarcinoma (goblet cell proportion ≥90%), mixed invasive mucinous and non-mucinous adenocarcinoma (goblet cell proportion ≥10% and non-mucinous component ≥10%), minimally invasive mucinous adenocarcinoma, and mucinous adenocarcinoma in situ.

Measurement of invasive size of IMA

The invasive size of lung adenocarcinoma was defined in the International Association for the Study of Lung Cancer /American Thoracic Society /European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma in 2011(Travis et al. 2011) as follows:

(1) any histologic subtype other than a lepidic pattern (such as acinar, papillary, micropapillary, and solid) or (2) tumor cells infiltrating the myofibroblastic stroma. In addition, we also measured the invasive size of IMA using two methods: (1) excluding lepidic method (ELM), that is, the lepidic component was excluded from the invasive area regardless of alveolar mucin and (2) including lepidic method (ILM), that is, the lepidic component was included in the invasive area when the alveolar space was filled with mucin (Figure 1). The pathological stage was determined based on the 8th edition of the TNM classification of the Union for International Cancer Control. Two patterns of T stage were decided according to the two measurement methods. The discrepancies in interpretation between observers were resolved by consensus.

Patient follow-up

Patients were followed-up at 3-month intervals for the first 2 years after surgery and at 6-month intervals thereafter on an outpatient basis. The follow-up evaluation included physical examination, chest radiography, and blood testing, including for pertinent tumor markers. Whenever any signs of symptoms of recurrence were detected, further evaluations were conducted, including CT of the chest and abdomen, brain magnetic resonance imaging, and positron emission tomography. Recurrence or survival information was obtained as far as

possible by a follow-up letter in the case of patients who could not make regular clinic visits for up to 10 years. Overall survival (OS) was calculated from the date of surgical intervention to the last follow-up date or death due to any cause. Observations were censored at the last follow-up when the patient was alive or lost to follow-up.

Statistical analysis

The prognostic impact of each clinicopathological variable on OS was estimated using univariable Cox regression model and summarized as hazard ratios (HRs) and their 95% confidence intervals (CIs). For ELM and ILM, we also created a multivariable regression model adjusted for the potential predictive variables that were significant (i.e., those with p values < 0.05 calculated using Wald statistics) in univariable Cox regression analysis. As discriminative measures, the concordance probability estimate (CPE)(Gönen and Heller 2005; Heller and Mo 2016) estimated from the multivariable Cox regression model and Akaike' information criteria (AIC) in the regression analyses were also assessed.

Survival curves were estimated using the Kaplan-Meier method and compared using log-rank test. All tests were two-sided, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using either EZR version 1.32 (Saitama Medical Center, Jichi Medical

University, Saitama, Japan) or CPE package in R version 3.2.4 (The R Foundation for Statistical Computing, Vienna, Austria).

Result

Clinicopathological characteristics of the IMA patients

The cohort comprised 101 patients with a median age of 66 years (range, 43-85 years) at the time of surgery. A total of 49% of the patients were men. The median follow-up time after surgery was 6 years (range, 3-15 years). The clinicopathological characteristics of the 101 patients are shown in Table 1. The median pathological tumor size was 2.8 cm (range, 0.5 to 14.2 cm). A total of 49% of the patients had lepidic component with alveolar mucin that filled the alveolar space.

Difference in invasive size between ELM and ILM

The distribution of invasive size measured via ELM and ILM is shown in Table 1 and Supplementary figure 1. The median invasive size measured via ELM and ILM was 1.4 cm (range, 0.0-7.7 cm) and 2.1 cm (range, 0.0-14.2 cm), respectively.

Comparison between T stage based on ELM and ILM

The pathological T stages based on ELM (T-ELM) and based on ILM (T-ILM) are shown in Table 1 and Supplementary table 1. The T-ILM of 18 patients was upstaged to an advanced level on T-ELM.

Comparison of hazard ratios for OS between invasive size measured via EL and ILM

Table 2 summarizes the results of Cox regression analyses for OS. For multivariable analyses, variables ly and pm were adjusted. In multivariable analysis, the HR of invasive size measured via EL was higher than that measured via ILM (1.38 vs 1.19).

Comparison of the discriminative power and the predictive accuracy between invasive size measured via EL and ILM

Table 3 shows the CPE and AIC by each method. The low level of AIC denoted the goodness of model fit. Invasive size measured via ELM had a better discriminative power than that measured via ILM. With respect to the discriminative power and the predictive accuracy as evaluated according to CPE, the CPE of invasive size measured via ELM was higher than that of invasive size measured via ILM in both univariable and multivariable analyses, although the 95% CI overlapped due to the small number of events. These results showed that ELM was superior to ILM for predicting prognosis.

Comparison of survival curves and hazard ratios between T-ELM and T-ILM

Figure 2A and 2B show the estimated survival curves according to T-ELM and T-ILM, respectively. Compared to T-ILM, T-ELM showed better distinction. Particularly, the survival curves of T-ILM crossed between T3 and T4, and the HR of T3 was higher than that of T4.

Evaluation of the patients with stage migration according to the measurement method

The T stage evaluated according to the invasive size was higher when ILM was used than when ELM was used in 18 patients (Figure 3A). Because the invasive size measured via ILM was bigger than or equal to that measured via ELM, stage migration of T-ILM was to higher stages in T-ELM. Despite the advanced stages of the migration group, there were no differences in survival between the patients with stage migration (n = 18) and the patients without stage migration (n = 83) (log-rank test, p = 0.94; Figure 3B).

Discussion

In this study, we evaluated the invasive size that most adequately predicted the prognosis in IMA of the lung. Lepidic growth pattern of lung adenocarcinoma was shown to be associated with favorable survival by several studies(Yokose et al. 2000; Borczuk et al. 2009; Yoshizawa et

al. 2011; Nakagiri et al. 2014) and was defined as a preinvasive lesion by the International Association for the Study of Lung Cancer /American Thoracic Society /European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma in 2011.(Travis et al. 2011, 2015a, b) In the 8th edition of the TNM classification published in 2017, the tumor size, which was the main factor for T staging, was defined as the invasive size excluding the lepidic component.(Brierley et al. 2017; Kameda et al. 2018) However, the prognostic significance of lepidic component in IMA was not well documented, and thus the invasive size of this tumor has not been defined to date.(Kadota et al. 2014; Travis et al. 2016)

While there is a consensus on the invasive area in IMA (i.e., histologic subtype other than a lepidic pattern or tumor cells infiltrating the myofibroblastic stroma), the tumor cells in IMA secrete mucin that fill the alveolar space and sometimes spread throughout the entire alveolar spaces.(Isaka et al. 2017; Boland et al. 2018) Thus, the lepidic growth pattern with mucin filling alveolar space might be an invasive component in IMA.(Hwang et al. 2017; Motono et al. 2017) Therefore, we created two methods to measure the invasive size of IMA: (1) ELM (exclusion of lepidic component from invasive area regardless of alveolar mucin and (2) ILM (inclusion of lepidic component to invasive area when alveolar space was fulfilled by mucin). The area not comprising tumor cells and only filled by mucin was considered as a non-tumor area because the alveolar walls of such area were not destroyed in all cases.

The findings showed that invasive size measured via ELM showed better model fitness, discriminative power, and the predictive accuracy than that measured via ILM. Therefore, ELM was superior to ILM to predict prognosis. In T staging, T-ELM showed a better distinction than T-ILM.

Although the mechanism by which ELM more accurately predicts prognosis than ILM is unclear, we developed the following hypothesis: the difference in invasive size between that measured via ELM and via ILM is due to the lepidic component with mucin filling alveolar spaces. Because the lepidic components of IMA did not destroy existing alveolar structures even if mucin filled the alveolar spaces and because tumor cells had low nuclear atypia,(Cha and Shim 2017) they might have low invasiveness.

With respect to the discrepancy in T stage between ELM and ILM measurement, IMA tends to widely spread with lepidic pattern; thus, the prognostic impact of lepidic component might particularly appear in the advanced stages such as T3 and T4. Furthermore, the patients who had an advanced stage in T-ILM did not show worse prognosis than the non-migration group, indicating that the lepidic component did not contribute to prognosis in IMA. These findings indicate that staging should be according to the invasive size measured via ELM than ILM.

Our study had several limitations. First, the retrospective nature of this study cannot preclude a selection bias. The patients were included from our single institution, and all the patients were

surgical cases. Therefore, the application of our findings might be limited in those with diseases higher than stage III. Second, the pathological stage could not be classified to substages due to the small number of patients. However, our study was remarkable with respect to the number of cases included despite the rarity of IMA. Third, as the current TNM classification was constructed for non-mucinous adenocarcinoma, a new classification for IMA may be needed to accurately predict prognosis according to each stage.

Conclusion

ELM showed higher prognostic impact and discriminative power for OS than ILM. Thus, measurement of the pathological invasive size in IMA should exclude the lepidic component.

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Conflict of Interest: All authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Comprehensive informed consent was obtained from all individual participants included in the study.

Figure legends

Figure 1 *Measurement methods of invasive size*

A) The solid line shows an invasive size measured by excluding the lepidic component from the invasive area regardless of alveolar mucin (ELM). The dotted line shows an invasive size measured by including the lepidic component to the invasive area if the alveolar space was filled with mucin (ILM). This case was classified as T1mi on ELM measurement, but was upstaged to T1b on ILM measurement.

B) The scheme of figure A). Gray zone shows the invasive area composed of any histologic subtype other than a lepidic pattern. The dotted zone shows the lepidic growth area with alveolar spaces was filled with mucin.

C) High-power view of figure A) (square area in Figure A). The tumor cells grew with lepidic pattern and alveolar spaces were filled with mucin.

D) Alcian blue period acid-Schiff stain of the area same as figure C. Alveolar space was filled with abundant mucin.

Figure 2 *Kaplan-Meier survival curves and hazard ratios according to T stage*

A) T stage was decided according to the invasive size measured by excluding the lepidic component (T-ELM).

B) T stage was decided according to the invasive size measured by including the lepidic component (T-ILM).

p values are from Cox proportional hazard model.

OS, overall survival; HR, hazard ratio; CI, confidence interval; Inf, infinity; Ref, reference.

Figure 3 *Evaluation of the patients with stage migration according to each measurement method*

A) T stage based on invasive size measured via ELM (T-ELM) and via ILM (T-ILM).

B) Kaplan-Meier survival curves according to stage migration.

p values are from log-rank test.

Table 1: Clinicopathological characteristics of the IMA patients with negative for lymph node and distal metasitasis

Characteristics		n=101 (%)
Medin age at surgery, years (range)		66 (43-85)
Sex	Man	49 (49)
Smoking history	Present	53 (53)
Predominant pattern	lepidic	64 (63)
	papillary	26 (26)
	acinar	9 (9)
	solid	2 (2)
Lepidic component with alveolar mucin	Present	49 (49)
v	Present	5 (5)
ly	Present	3 (3)
pl	Present	5 (5)
pm	Present	7 (7)
Pathological tumor size, cm (range)		2.8 (0.5-14.2)
Invasive size by ELM, cm (range)		1.4 (0.0-7.7)
Invasive size by ILM, cm (range)		2.1 (0.0-14.2)
T stage based on ELM	Tis	4 (4)
	T1	69 (68)
	T2	14 (14)
	T3	9 (9)
	T4	5 (5)
T stage based on ILM	Tis	2 (2)
	T1	59 (58)
	T2	21 (21)
	T3	8 (8)
	T4	11 (11)

ELM, excluding lepidic method; ILM, including lepidic method

Table 2: Comparison of hazard ratios for OS between invasive size measured via ELM and ILM (n = 101)

		Univariate analysis		Multivariate analysis			
Factors	Group	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	years	1.04 (0.99-1.1)	0.13				
Sex	Man / Woman	1.30 (0.47-3.59)	0.61				
Smoking history	Present / Absent	2.03 (0.69-5.94)	0.2				
Invasive size ELM	cm	1.56 (1.23-1.98)	<0.01	1.38 (1.07-1.79)	0.01		
Invasive size ILM	cm	1.20 (1.07-1.35)	<0.01			1.19 (1.03-1.36)	0.02
Predominant pattern	Others / Lepidic	2.42 (0.86-6.81)	0.10				
v	+ / -	1.13 (0.15-8.8)	0.91				
ly	+ / -	6.36 (1.41-28.76)	0.02	3.44 (0.59-20.25)	0.17	6.53 (1.34-31.77)	0.02
pl	+ / -	3.05 (0.68-13.62)	0.14				
pm	+ / -	6.27 (1.96-20.03)	<0.01	5.15 (1.44-18.38)	0.01	6.19 (1.85-20.68)	<0.01

ELM, excluding lepidic method; ILM, including lepidic method; HR, hazard ratio; CI, confidence interval; p values are from Cox proportional hazard model

Table 3: Comparison of AIC and CPE between invasive size measured via ELM and ILM (n = 101)

	Univariate analysis		Multivariate analysis	
	AIC*	CPE (95%CI)	AIC*	CPE (95%CI)
Reference			114.26	0.570 (0.529-0.611)
Invasive size ELM	111.97	0.679 (0.604-0.753)	110.19	0.671 (0.598-0.744)
Invasive size ILM	117.00	0.615 (0.548-0.683)	111.52	0.655 (0.584-0.726)

ELM, excluding lepidic method; ILM, including lepidic method; AIC, Akaike information criterion; CPE, concordance probability estimate; CI, confidence interval; Reference was calculated by multivariate analysis including ly and pm

*smaller is better

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Figure 1

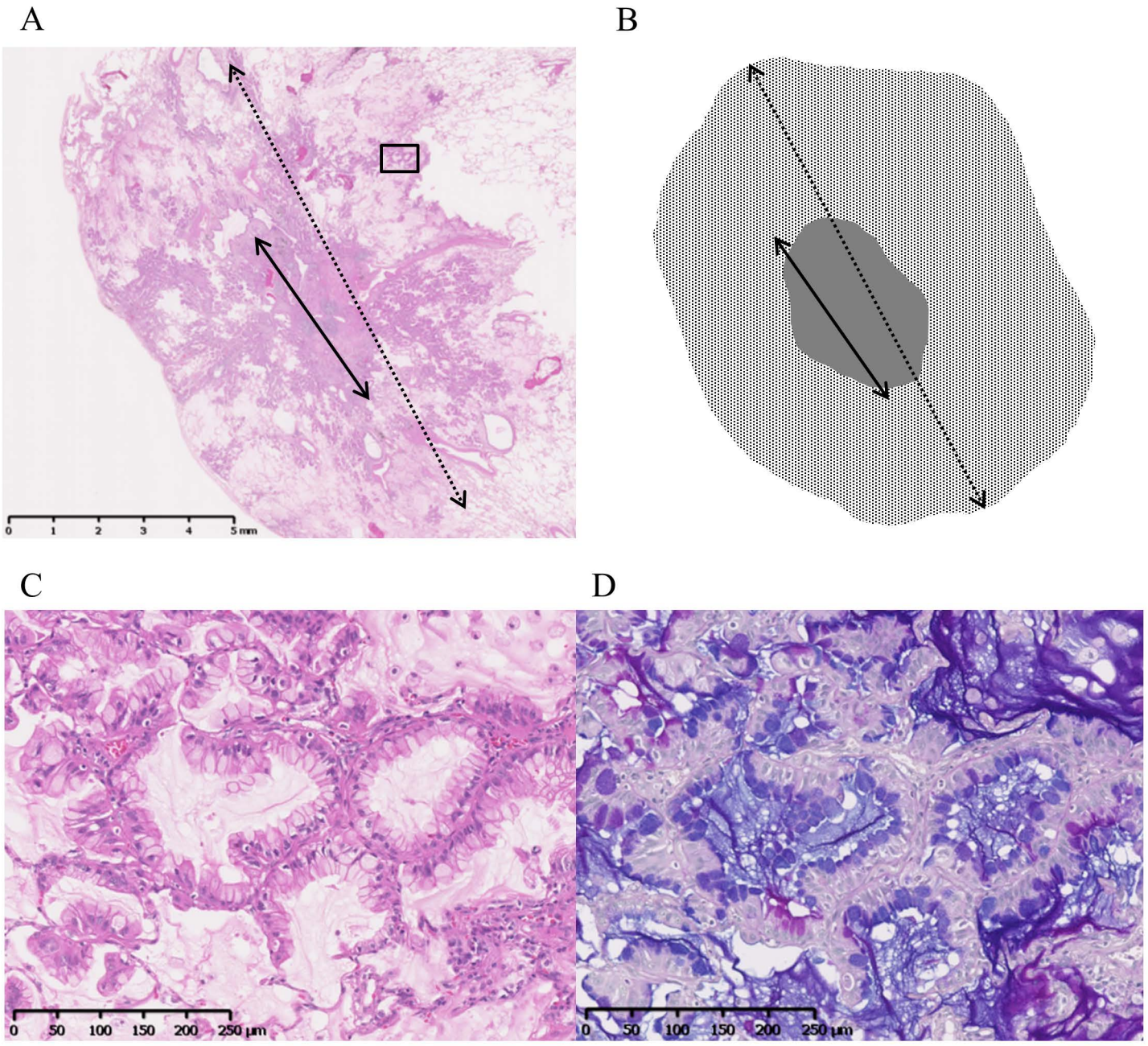
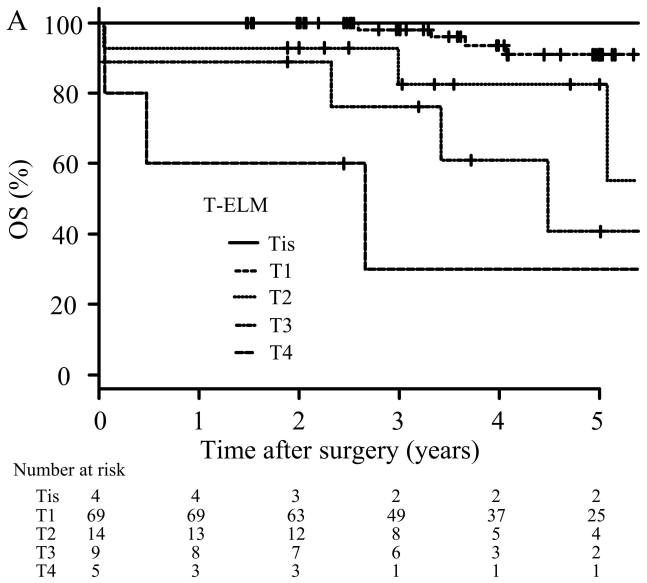
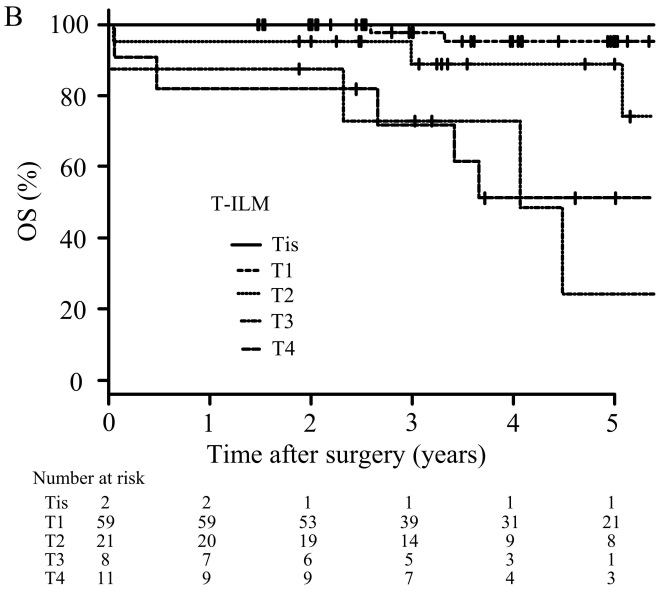


Figure 2

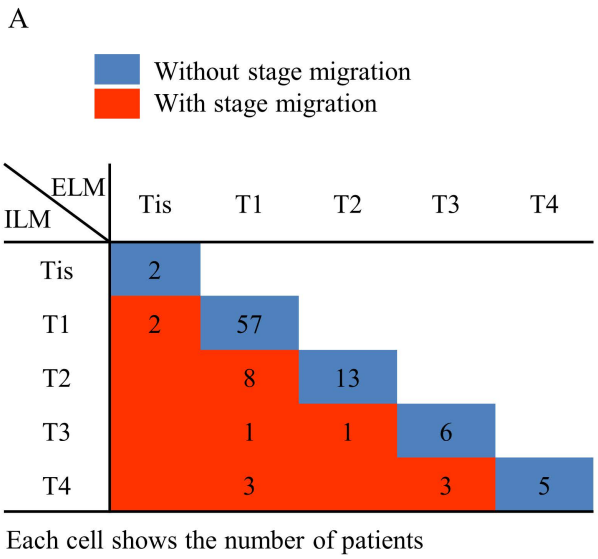


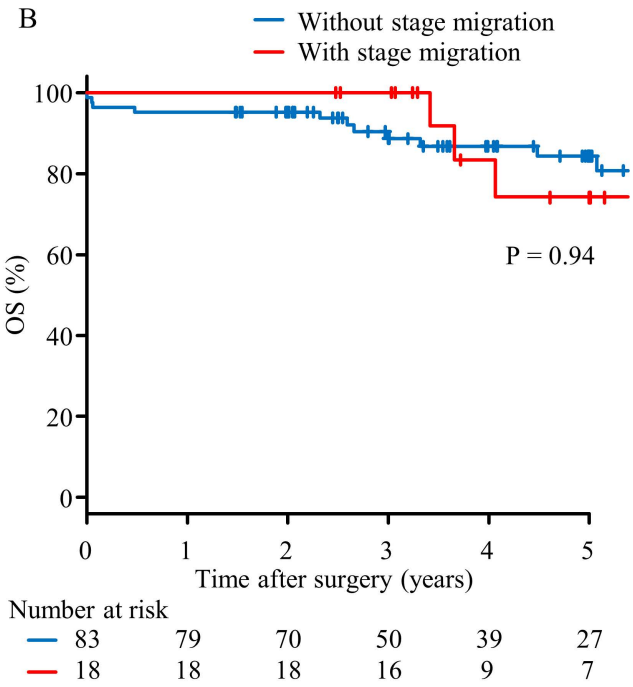


T-ELM	HR (95%CI)	p value
Tis	0.00 (0.00-Inf)	1.00
T1	Ref	
T2	3.48 (0.83-14.64)	0.09
T3	8.54 (2.24-32.58)	<0.01
T4	16.61 (3.83-71.97)	<0.01

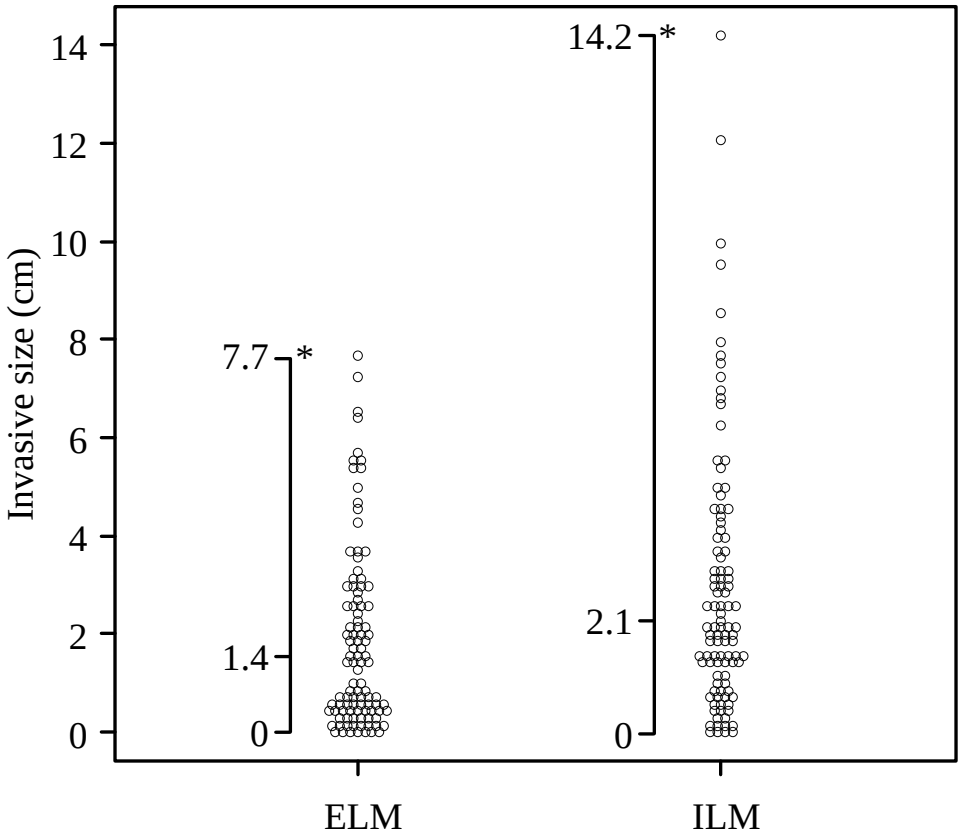
T-ILM	HR (95%CI)	p value
Tis	0.00 (0.00-Inf)	1.00
T1	Ref	
T2	3.10 (0.62-15.36)	0.17
T3	14.66 (3.22-66.81)	<0.01
T4	9.98 (2.38-41.89)	<0.01

Figure 3


A
Without stage migration
With stage migration
ELM
ILM
Tis
T1
T2
T3
T4
Tis
2
T1
2
57
T2
8
13
T3
1
1
6
T4
3
3
5
Each cell shows the number of patients


B
Without stage migration
With stage migration
100
80
60
40
20
0
OS (%)
P = 0.94
0
1
2
3
4
5
Time after surgery (years)
Number at risk
83
79
70
50
39
27
18
18
18
16
9
7

Supplementary figure 1



*Minimum, median, and maximum of invasive size

Supplementary table 1: Pathological T stages based on ELM and ILM

T stage	ELM n=101 (%)	ILM n=101 (%)
Tis	4 (4)	2 (2)
T1	69 (68)	59 (58)
T2	14 (14)	21 (21)
T3	9 (9)	8 (8)
T4	5 (5)	11 (11)

ELM, excluding lepidic method; ILM, including lepidic method