

Original Article

Tracing Metastatic Evolutionary Patterns in Lung Adenocarcinoma: Prognostic Dissection Based on a Multi-state Model

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Purpose After surgery for lung adenocarcinoma, a patient may experience various states of recurrence, with multiple factors potentially influencing the transitions between these states. Our purpose was to investigate the effects of clinical and pathological factors on tumor recurrence, death, and prognosis across various metastasizing pathways.

Materials and Methods Our study group included 335 patients with all demographic and pathologic data available who underwent surgical resection for lung adenocarcinoma for more than 10 years. The following states of disease were defined: initial state, operation (OP); three intermediate states of local recurrence (LR), metastasis (Meta), and concurrent LR with metastasis (LR+Meta); and a terminal state, death. We identified eight transitions representing various pathways of tumor progression. We employed a multi-state model (MSM) to separate the impacts of multiple prognostic factors on the transitions following surgery.

Results After surgery, approximately half of patients experienced recurrence. Specifically, 142 (42.4%), 54 (16.1%), and seven (2.1%) patients developed Meta, LR+Meta, and LR, respectively. Clinical and pathological factors associated with the transitions were different. Impact of pathological lymph node remained a risk factor for both OP to Meta (λ_{02} , $p=0.001$) and OP to LR+Meta (λ_{03} , $p=0.001$).

Conclusion Lung adenocarcinoma displays a broad spectrum of clinical scenarios even after curative surgery. Incidence, risk factors, and prognosis varied across different pathways of recurrence in lung adenocarcinoma patients. The greatest implication of this MSM is its ability to predict the timing and type of clinical intervention that will have the greatest impact on survival.

Key words Non-small cell lung carcinoma, Multi-state model, Transition intensity

Introduction

Lung cancer is the leading cause of cancer-related death worldwide in both men and women [1]. However, a large proportion of lung cancer patients develop recurrence even after curative surgery, with reported rates as high as 68%, eventually leading to increased risk of death [2-4]. Recurrence patterns after surgery are heterogeneous as tumor recurrence encompasses multiple states such as local recurrence (LR), distal metastasis (Meta), and concurrent LR and distal Meta. In fact, a patient may develop several different states and move among the states throughout the course of the disease [5]. In particular, lung adenocarcinoma displays a broad spectrum of biological variations, ranging from indolent to aggressive forms, affecting prognostic results [6]. In other words, numerous clinical scenarios are evident in lung adenocarcinoma, leading to a wide range of treatment options.

Most lung cancer trials use the traditional end points of

overall survival and disease-free survival. These endpoints offer the advantages of simplicity and straightforwardness for describing patient mortality or cancer advancement. However, besides death, surviving patients may experience various states and multiple transitions between states during the course of the disease. For example, a patient may develop an ipsilateral metastatic lymph node (LN), classified as LR and receive limited treatment. Following limited treatment, the patient may be disease-free for many years, and then may develop distal Meta in other body regions, necessitating systemic therapy. Yet, this tumor trajectory is not revealed using traditional endpoints in lung adenocarcinoma. Thus, an improved understanding of the various metastasizing pathways and their risks can enhance patient care after surgery, allowing for a more personalized and effective treatment approach.

Multi-state model (MSM) analysis is used to analyze the movement of individuals between defined states over a period of time [7]. For example, MSM analysis has been used

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in prostate and oropharyngeal cancer studies when patients experience intermediate (transition) states corresponding to particular stages of disease [8-10]. As mentioned above, even after curative resection, the prognosis is extremely heterogeneous with diverse pathways and multiple treatment options in lung adenocarcinoma. Thus, for a more detailed understanding of metastatic evolutionary patterns, we implemented MSM analysis in lung adenocarcinoma patients. The main goal of this study was to investigate the effects of clinical and pathological factors on tumor recurrence, death, and prognosis in lung adenocarcinoma patients across various metastasizing pathways.

Materials and Methods

1. Patients

Data were retrospectively collected from patients who underwent operation (OP) for lung adenocarcinoma from October 2003 to August 2011. To conduct a comprehensive analysis of long-term survival after lung cancer surgery, we continued follow-up until the date of death or study end date (June 20, 2023), whichever was earliest, resulting in data collected over a period of more than a decade.

From a thoracic surgical database that exclusively focused on lung adenocarcinoma, 340 patients who had undergone complete surgical resection for invasive lung adenocarcinoma were identified. Five patients who had incomplete pathologic analysis and histologic subtyping were excluded. Thus, our final study group included 335 patients (186 men, 149 women). Demographic variables including age, sex, smoking history, adjuvant chemotherapy, and OP type were collected by reviewing electronic medical charts. Pathological variables such as overall tumor-node-metastasis (TNM) stage, tumor size, T status (pT), and LN status (pN) were evaluated. The pathologic staging was recorded based on the 7th edition TNM staging in non-small cell lung cancer (NSCLC) patients, at the beginning of this study.

Furthermore, a comprehensive evaluation of the pathological factors including tumor differentiation, predominant histologic pattern, pleural invasion, vascular invasion, lymphatic invasion, and perineural invasion was performed.

2. Definition of disease status

Electronic medical records were reviewed for date of last follow-up, documented LR or distal Meta, or death. Medical images including computed tomography (CT), magnetic resonance imaging (MRI), bone scan, ¹⁸F-fluorodeoxyglucose positron emission tomography/CT (¹⁸F-FDG PET/CT), and pathologic results were used to confirm recurrences. In this study, LR was defined as tumor recurrence in the entire ipsi-

lateral hemithorax (including the pleura and chest wall) or/and the ipsilateral mediastinal LNs [11,12]. When it came to identifying subsolid and solid nodules in the ipsilateral lung, we initially searched for pathologic results of biopsies or surgeries. If there were no pathologic results present, a comprehensive evaluation of multiple follow-up CT scans was performed. If the nodule continued to increase in size, and benign conditions such as infection or inflammation were excluded, the nodule was presumed to be recurrence from the date of initial detection on the CT scan by a thoracic radiologist. In addition, distinguishing multifocal primary lung cancers from intrapulmonary metastases is an important issue, yet can be very challenging. Especially in complex situations such as matching histology, the nodule was confirmed after extensive radiologic review and follow-up, comprehensive histologic assessment, and multidisciplinary tumor board discussion [13-16].

Any tumor recurrence occurring elsewhere than the ipsilateral hemithorax and ipsilateral LNs was considered distal Meta. S1 Table presents the information regarding confirmation of distal metastases. The coexistence of LR and distal metastasis (LR+Meta) was classified independently from LR and distal Meta. The Korean statistical information service was utilized to investigate the dates and reasons for death.

3. Statistical analysis

MSM is useful to investigate the effect of treatment on several paths from a study entry to intermediate to death. While classical methods such as log-rank test and Cox proportional hazard model focus on effect of treatment on a single event, MSM assesses the comprehensive patterns of the effects of treatment on the intermediate events resulting in the final outcome. The MSM consists of states and transitions between states. In this study, to represent several event types occurred after OP and the transition between events, five states are considered with one initial state (OP), three intermediate states (LR, Meta, and LR+Meta), and a terminal state (death). For notational simplicity, "metastasis" is denoted as Meta in the statistical analysis.

Under the assumption of the Markov property, a transition probability $\pi_{lk}(s, t) = \Pr(X(t)=k | X(s)=l)$ defining the probability of staying state l at $T=s$ and moving to state k at $T=t$. To reflect the effect of covariates on transition, a transition intensity is defined as

$$\lambda_{lk}(t) = \lim_{\Delta t \rightarrow 0} \frac{\pi_{lk}(t, t+\Delta t)}{\Delta t}, \quad \lambda_{kk} = -\sum_{k \neq l} \lambda_{lk}$$

which is a similar concept of Cox hazard function.

Fig. 1 shows the MSM with five states $K=\{0,1,2,3,4\}=\{\text{OP}, \text{LR}, \text{Meta}, \text{LR+Meta}, \text{Death}\}$ and eight transitions. The initial state is OP and there are three intermediate states (LR, Meta,

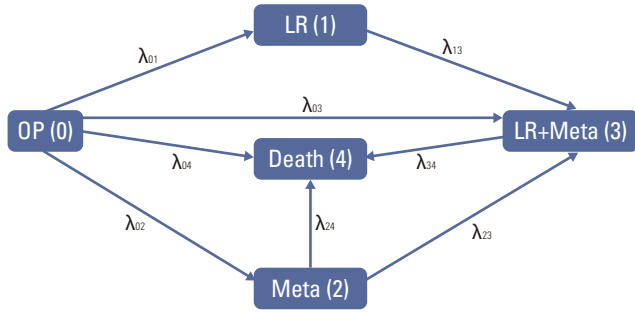


Fig. 1. Visualization of the multiple transitions consisting the multistate model with five states and eight transitions. Operation (OP) is the initial state and there are three intermediate states (local recurrence [LR], metastasis [Meta], concurrent local recurrence and metastasis [LR+Meta]) and a terminal state (Death). All patients start in state OP and may transit to one of the three intermediate states (transitions λ_{01} , λ_{02} , λ_{03}) or transit directly to a terminal state (transition λ_{04}) or stay on OP state without events.

LR+Meta) and a terminal event (Death) as an absorbing state. All patients start at OP (state 0) and may transfer to one of three intermediate states (state 1, 2, 3) or directly to a terminal state (state 4) or remain in OP state without events. Once patients move into one intermediate state, they are still at risk for other states or death. Therefore, they may also move forward to another intermediate state or death or stay. In detail, there are four possible transitions since OP. $0 \rightarrow 1$ denotes a transition $OP \rightarrow LR$ and the corresponding transition intensity is denoted as $\lambda_{01}(t)$. Similarly, $0 \rightarrow 2$ denotes $OP \rightarrow Meta$ with $\lambda_{02}(t)$; $0 \rightarrow 3$ represents $OP \rightarrow LR+Meta$ with $\lambda_{03}(t)$ and $0 \rightarrow 4$ means the transition $OP \rightarrow Death$ with $\lambda_{04}(t)$. Next, for the transition to as the intermediate states, $1 \rightarrow 3$ means the transition $LR \rightarrow LR+Meta$ with $\lambda_{13}(t)$, $2 \rightarrow 3$ represents the transition $Meta \rightarrow LR+Meta$ with $\lambda_{23}(t)$. Finally, some patients has experienced the terminal event, death. $2 \rightarrow 4$ represents the transition $Meta \rightarrow Death$ with $\lambda_{24}(t)$ and $3 \rightarrow 4$ means the transition $LR+Meta \rightarrow Death$ with $\lambda_{34}(t)$.

To estimate the effects of risk factors on each transition, the following proportional transition intensity model is assumed with a covariate vector $z = (z_1, \dots, z_p)$,

$$\lambda_{lk}(t|z) = \lambda_{lko}(t) \exp(\beta_{lk}'z),$$

where $\lambda_{lko}(t)$ is the baseline intensity function of the $l \rightarrow k$ transition and β_{lk} is the vector of the regression coefficient to measure the association between the $l \rightarrow k$ th transition and covariates z . All analyses were performed with R ver. 4.3.1 (R Foundation for Statistical Computing) and the function “probrtrans” from R package ‘mstate’ is implemented to estimate the transition probability and the function “coxph” from R package ‘survival’ package is used to estimate the

Table 1. Demographics of the study population

Variable	No. of patients (%) (n=335)
Age (yr), mean (25th to 75th percentile)	61 (54-68)
Sex	
Male	186 (55.5)
Female	149 (44.5)
Smoking	
Never-smoker	180 (53.7)
Current or former-smoker	155 (46.3)
Adjuvant chemotherapy	
No	291 (86.9)
Yes	44 (13.1)
Local recurrence^{a)}	
No	281 (83.9)
Yes	54 (16.1)
Distant metastasis	
No	171 (51.0)
Yes	164 (49.0)
Death	
No	186 (55.5)
Yes	149 (44.5)
Stage	
I	220 (65.7)
II	65 (19.4)
III	50 (14.9)
pT	
T1	156 (46.6)
T2	159 (47.4)
T3	20 (6.0)
pN	
N0	242 (72.2)
N1	48 (14.3)
N2	45 (13.5)
Tumor size (mm), mean (25th to 75th percentile)	28 (20-34)
Operation type	
Sublobar resection	18 (5.4)
Lobectomy / Pneumonectomy	317 (94.6)

^{a)}Including those with concurrent local recurrence and metastasis.

effect of covariates on each transition. Also, for comparing the time distributions of recurrent events at three OP types, F-test and Kruskal test are applied depending on the sample size. At all hypothesis tests, $p < 0.05$ was regarded as statistically significant.

Table 2. Frequency table of transitions

From	To				
	OP (state 0)	LR (state 1)	Meta (state 2)	LR+Meta (state 3)	Death (state 4)
OP (state 0) (n=335)	142 (42.4)	7 (2.1) (λ_{01})	142 (42.4) (λ_{02})	15 (4.5) (λ_{03})	29 (8.7) (λ_{04})
LR (state 1) (n=7)	0	0	0	7 (100) (λ_{13})	0
Meta (state 2) (n=142)	0	0	43 (30.3)	32 (22.5) (λ_{23})	67 (47.2) (λ_{24})
LR+Meta (state 3) (n=54)	0	0	0	1 (1.9)	53 (98.1) (λ_{34})

Values are presented as number of patients (%). Percentages reflect the proportion of patients in the state before transitioning. For example, among 335 patients from OP (state 0), 142 patients (42.4%) stayed at OP state without any further events. Seven patients (2.1%) developed LR (state 1). Another 142 patients developed Meta (42.4%), 15 patients developed LR+Meta (4.5%), and 29 patients (8.7%) died. Among 54 patients from LR+Meta (state 3), only one patient (1.9%) stayed at LR+Meta without any further event, and 53 patients (98.1%) died (state 4). Percent totals may not add up to 100% due to rounding error. LR, local recurrence; LR+Meta, concurrent local recurrence and metastasis; Meta, metastasis; OP, operation.

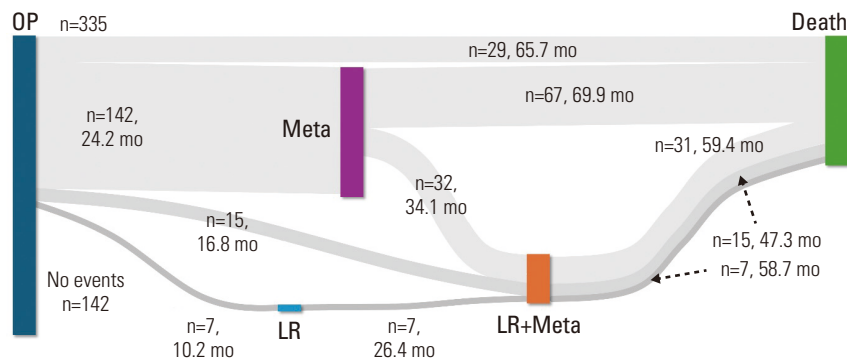


Fig. 2. Overflow of the various metastasizing pathways after operation and their corresponding patient numbers and median length of time to each status. The thickness of each transition line is proportional to the number of patients. LR, local recurrence; LR+Meta, concurrent local recurrence with metastasis; Meta, metastasis; mo, months; OP, operation.

Results

1. Patient characteristics and survival

Patient characteristics are summarized in Table 1. The final study group included 335 patients (186 men, 149 women) with a mean age of 61 years (25th to 75th percentile, 54 to 68 years). Regarding smoking history, 180 (53.7%) were never smokers and 155 (46.3%) were current or former smokers. Among the study group, 291 (86.9%) had never experienced adjuvant chemotherapy. Pathological TNM stages were classified as follows: stage I, 220 (65.7%); stage II, 65 (19.4%); and stage III, 50 (14.9%). The pT has three groups: T1, 156 (46.6%); T2, 159 (47.4%); and T3, 20 (6.0). The pN has also three groups: N0, 242 (72.2%); N1: 48 (14.3%); and N2, 45 (13.5%).

Mean tumor size was 28 mm (25th to 75th percentile, 20 to 34). Most patients underwent lobectomy or pneumonectomy (317 patients, 94.6%) and only 18 patients underwent sublobar resection.

Table 2 shows the numbers of patients corresponding to each transition path (Fig. 2). At the end of the study, among

335 patients starting from OP, 142 patients (42.4%) had no further events and survived until the end of the study, while 54 (16.1%) patients experienced LR+Meta and 142 patients (42.4%) experienced Meta, where the detection of LR and Meta may occur simultaneously or sequentially. Notably, all seven patients (2.1%) who experienced LR eventually developed concurrent Meta (transition λ_{13}).

Overall, 149 patients (44.5%) died by the end of the study. Among these, 67 patients (45.0%) died from Meta, 53 patients (35.6%) died from LR+Meta, and 29 patients (19.5%) died without intermediate events. Notably, with the exception of one patient, all other LR+Meta patients died.

For 142 patients who survived until the end of the study without any events, the mean follow-up period for these patients was 9.8±4.3 years after OP (S2 Table). The majority of these patients was diagnosed at early pathologic stages (stage I, 114 patients) and the mean tumor size was 2.7±1.3 cm. Considering predominant subtype, acinar type (79 patients, 55.6%) was the most frequent subtype in this group.

Table 3. Results of multivariate regression analysis of risk factors

Risk factor	Transitions							
	λ_{01} OP→LR	λ_{02} OP→Meta	λ_{03} OP→LR+Meta	λ_{04} OP→Death	λ_{13} LR→LR+Meta	λ_{23} Meta→LR+Meta	λ_{24} Meta→Death	λ_{34} LR+Meta→Death
Sex								
Female	0.645 (0.607)	-0.262 (0.280)	-0.768 (0.309)	0.303 (0.670)	0.279 (0.691)	-2.02 (< 0.001) ^{a)}	0.245 (0.537)	-0.036 (0.938)
Age	0.004 (0.412)	0.010 (0.244)	0.034 (0.232)	0.122 (< 0.001) ^{a)}	0.004 (0.412)	-0.015 (0.425)	0.062 (< 0.001) ^{a)}	-0.007 (0.696)
Smoking								
Never-smoker	-1.34 (0.254)	0.217 (0.391)	0.381 (0.576)	-0.964 (0.170)	-1.34 (0.254)	0.699 (0.111)	-0.552 (0.151)	-0.637 (0.117)
Adjuvant chemotherapy								
No	-37.6 (0.998)	0.608 (0.176)	1.957 (0.107)	1.075 (0.389)	-37.6 (0.998)	1.000 (0.186)	0.979 (0.121)	1.808 (0.009) ^{a)}
pT	0.208 (0.757)	0.360 (0.024) ^{a)}	0.362 (0.455)	0.463 (0.187)	-0.272 (0.99)	0.674 (0.070)	-0.066 (0.811)	0.595 (0.073)
pN	-1.88 (0.998)	0.729 (0.001) ^{a)}	1.957 (0.001) ^{a)}	0.762 (0.216)	-26.9 (0.998)	1.189 (0.005) ^{a)}	0.598 (0.059)	0.853 (0.015) ^{a)}
Size	0.276 (0.416)	0.093 (0.180)	0.115 (0.538)	0.278 (0.061)	27.91 (0.991)	-0.158 (0.218)	1.113 (0.281)	-0.014 (0.912)
Operation type								
Sublobar resection	-2.75 (0.015) ^{a)}	1.264 (0.079)	-1.094 (0.192)	-0.832 (0.163)	-16.4 (0.995)	0.338 (0.749)	-1.489 (0.171)	-0.445 (0.403)

Data are β coefficient values of risk factors and data in parentheses are p-values. Age, pT, pN, and size were regarded as continuous variables. LR, local recurrence; LR+Meta, concurrent local recurrence and metastasis; Meta, metastasis; OP, operation. ^{a)}p < 0.05.

2. Risk factors for LR, Meta, and/or death

Table 3 demonstrates the results of Cox regression models to evaluate risk factors for each transition. Female patients were more likely to transition from Meta to LR+Meta (transition λ_{23} , $\beta=-2.02$, $p < 0.001$). Patients receiving adjuvant therapy were more likely to transit from LR+Meta to death (transition λ_{34} , $\beta=1.808$, $p=0.009$).

Age was only a significant risk factor for the transition from OP to death (transition λ_{04} , $\beta=0.122$, $p < 0.001$) and the transition from Meta to death (transition λ_{24} , $\beta=0.062$, $p < 0.001$). The pT status was significantly correlated with the transition from OP to Meta (transition λ_{02} , $\beta=0.360$, $p=0.024$). After OP, pN status was significantly correlated with the two transitions to Meta (transition λ_{03} , $\beta=0.729$, $p=0.001$) and to LR+Meta (transition λ_{03} , $\beta=1.957$, $p=0.001$).

In terms of OP type, compared to lobectomy / pneumonectomy, sublobar resection was strongly associated with the transition to LR after OP (transition λ_{01} , $\beta=-2.72$, $p=0.015$).

3. Transition probabilities

Fig. 3A shows the stacked transition probabilities to four states over time after OP. At early times, the transition probability to Meta was the largest but death became more likely to occur as time passed. In addition, there were two transitions from Meta as shown in Fig. 3B. According to the transition probabilities over time of two competing states (death, LR+Meta), the transitions of two states have very different patterns. At 2 years since OP, the transition probabilities from Meta to LR+Meta (transition λ_{23}) and death (transition λ_{24}) were 0.23 and 0.36, respectively. These probabilities at 4 years and 6 years since OP were (0.17, 0.55) and (0.06, 0.73), respectively. In other words, the transition to LR+Meta has a higher probability at 2-4 years compared with other time periods.

Median and 25th and 75th percentiles of four transition times (transitions λ_{01} , λ_{02} , λ_{03} , and λ_{04}) occurred since OP are displayed (S3 Table). While a median Meta occurrence time is 24.2 months (about 2 years) since OP, 29 death cases occurred over a median of 65.7 months (about 5.4 years) since OP. As shown in Table 2 and Fig. 3A, B, the transition to LR has low incidence and a very small band between OP and Meta.

4. Event incidence according to OP type

Table 4 demonstrates the event frequency and time-to-event according to OP type. The three OP types displayed different recurrence patterns ($p < 0.001$). For checking the distribution of the occurrence time of four events (LR, Meta, LR+Meta, and death) according to OP type, there was no significant difference among events in the sublobar resection and pneumonectomy group. However, there was a significant difference in the lobectomy group. After OP, the median occurrence time of Meta was 2.05 years, the median time of

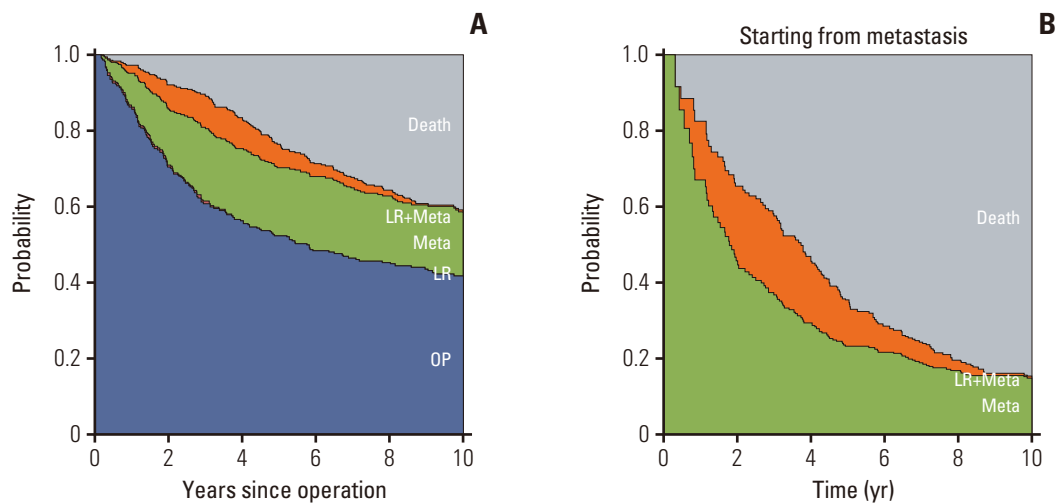


Fig. 3. (A) Transition probabilities starting from operation to death, concurrent local recurrence with metastasis (LR+Meta), metastasis (Meta), local recurrence (LR), or operation (OP). (B) Transition probabilities starting from metastasis to death, LR+Meta, or metastasis.

Table 4. Event frequency and time-to-event according to operation type

Operation type	Event type	Frequency		Time-to-event (yr)	
		Sample size (n)	Test-statistics ^{a)}	Median (25%-75% percentile)	Test-statistics
Sublobar resection (n=18)	No event	7	Fisher's exact test p < 0.001	11.65 (10.59-13.44)	$\chi^2=2.209$ (df=3) p=0.530
	LR(0→1)	2		1.53 ^{b)}	
	Meta(0→2)	2		1.48 ^{b)}	
	LR+Meta(0→3)	2		0.89 ^{b)}	
	Death(0→4)	5		4.79 (1.93-8.59)	
Lobectomy (n=317)	No event	133	F=16.81 (df1=3, df2=172) p < 0.001	9.89 (5.76-12.58)	
	LR(0→1)	5		0.84 (0.67-1.37)	
	Meta(0→2)	136		2.05 (1.04-3.69)	
	LR+Meta(0→3)	13		1.38 (1.14-1.92)	
	Death(0→4)	22		6.28 (2.24-10.63)	
Pneumonectomy (n=317)	No event	2	$\chi^2=0.214$ (df=1) p=0.643	10.33 ^{b)}	
	LR(0→1)	0		-	
	Meta(0→2)	4		0.424 ^{b)}	
	LR+Meta(0→3)	0		-	
	Death(0→4)	2		0.563 ^{b)}	

LR, local recurrence; LR+Meta, concurrent local recurrence and metastasis; Meta, metastasis. ^{a)}H₀: Three operation types have homogeneous frequencies of events; Fisher's exact test statistics, ^{b)}(25%-75%) quantile points are not available at n=2 and n=4.

LR+Meta was 1.38 years and the median time of death was 6.28 years, respectively. Fig. 4 shows the boxplot of the occurrence time of four recurrent events after lobectomy.

5. Analysis of comprehensive pathological data

An independent analysis of patients with comprehensive pathological data was performed. S4 Table shows the number of patients corresponding to each transition pathway. All five patients who transitioned from OP to LR subsequently

moved on to LR+Meta. Thus, this transition (λ_{13}) was disregarded in the pathological analysis due to the extremely high regression coefficient value.

Table 5 shows the results of multivariate regression analysis of pathological risk factors for each transition. The presence of any vascular, lymphatic, or perineural invasion was a risk factor for transitions from OP to Meta (transition λ_{02} , $\beta=0.635$, $p < 0.001$) and OP to LR+Meta (transition λ_{03} , $\beta=1.882$, $p=0.014$).

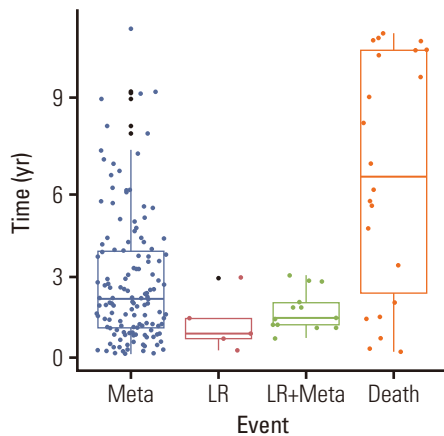


Fig. 4. Boxplot of time by event after lobectomy operation. After operation, the median occurrence time of metastasis (Meta) is 2.05 years, the median time of concurrent local recurrence (LR) and metastasis (LR+Meta) is 1.38 years and the median time of death is 6.28 years, respectively.

Discussion

Our findings can be summarized as follows: (1) After OP, approximately half of the patients in our study group developed recurrence with Meta as the most common route. To be specific, 142 (42.4%), 54 (16.1%), and seven (2.1%) patients developed Meta, LR+Meta, and LR, respectively; (2) The prognosis and transition patterns from OP to intermediate states (LR, Meta, and LR+Meta) were different; and (3) Clinical and pathological factors had different effect on each transition. (4) The presence of any vascular, lymphatic, or perineural invasion was a risk factor for transitions from OP to Meta and OP to LR+Meta. The key strength of our study is that we revealed multiple tumor recurrence pathways, each with its own prognosis. Moreover, we were able to separate the impact of multiple prognostic factors on the transitions following lung adenocarcinoma surgery. Initially, the transition probability to Meta is the largest, but the probability of death increases with time.

Our results revealed that nearly 50% of patients developed recurrence, with the most frequent pathway being Meta, followed by LR+Meta and LR. This confirms the results of earlier studies, which indicated that recurrence rates for stages I to III of NSCLC ranges from 30% to 75%, depending on pathologic stage and the length of follow-up [2,17-19]. In a large study by Boyd et al. [20], the incidences of recurrence after surgery were highest in distant Meta followed by local and distant Meta, and finally that confined to local regions. Distinguishing between LR, LR+Meta, and Meta is crucial because an increasing number of clinicians are adopting radical local treatment options that support systemic therapy,

underscoring its importance [5].

Consistent with previous research, LR was found to occur quickly after surgery, with reported ranges of 50%-90% within 2 years of the initial OP [21]. In addition, a separate study demonstrated that 24% of patients had LR after lung cancer surgery [11]. The incidence of LR was lower (2.1%) in our study. This is probably because our study was conducted at a nationwide top tier, tertiary hospital that specializes in thoracic surgery and treatment. It should be noted that all patients with LR concurrently showed LR+Meta. Despite the small number of patients in our samples, our findings suggest that LR patients are at risk for developing Meta, so careful monitoring should be performed in this subgroup. Furthermore, all but one LR+Meta patients died, indicating poor prognosis.

In patients with Meta, the transition to LR+Meta has a higher probability at 2-4 years compared with other time periods. Hence, based on our findings, it is important to closely monitor metastatic patients for LR at 2-4 years. In a meta-analysis, Fedor et al recommended that patients with distant recurrence should be carefully examined for local lesions, as the presence of distant recurrence may imply that LR has had sufficient time to develop [11].

Age was a risk factor for OP to death (transition λ_{04}) and Meta to death (transition λ_{24}) in our study. Aging may present as a challenge after OP as the respiratory system undergoes physiologic changes and multiple chronic conditions tend to coexist in older patients. Furthermore, the immune system functionally declines in elderly patients, increasing the risk of respiratory tract infections [22]. Hence, elderly patients are a heterogeneous group that can be at risk for both over and under-treatment in lung cancer patients. However, age itself was not a risk factor for OP to LR (transition λ_{01}) or OP to Meta (transition λ_{02}) in our study. This may reflect that lung tumors in elderly patients tend to be biologically less aggressive. In a large study, Sacher et al. [23] found that younger NSCLC patients were more likely to have a targetable genotype, but the survival rate for young patients was unexpectedly poor compared to other age groups, indicating more aggressive disease biology.

Our results further emphasize the significant role of pT and pN, two important staging descriptors. Instead of the initial TNM staging, we assessed the effects of pT and pN separately in this study. The pT was a risk factor for OP to Meta (transition λ_{02}). The impact of pN was still evident even after surgery, as it remained a risk factor for both OP to Meta (transition λ_{02}) and OP to LR+Meta (transition λ_{03}). In addition, pN was also a risk factor for Meta to LR+Meta (transition λ_{23}). The presence of cancer cells in the LNs is a significant prognostic factor for most cancers, but the exact mechanism remains uncertain. Originally, the commonly

Table 5. Results of multivariate regression analysis of pathological risk factors (n=307)

Risk factor	Reference	Transitions					
		λ_{01}	λ_{02}	λ_{03}	λ_{04}	λ_{23}	λ_{24}
		OP→LR	OP→Meta	OP→LR+Meta	OP→Death	Meta→LR+Meta	Meta→Death
Tumor differentiation	Well and moderate	-14.95 (0.989)	0.163 (0.469)	-0.668 (0.357)	0.857 (0.087)	-0.170 (0.728)	0.636 (0.069)
Predominant histologic pattern	Lepidic, acinar, and papillary	1.238 (0.195)	0.199 (0.369)	0.492 (0.426)	-0.619 (0.259)	0.536 (0.256)	-0.369 (0.294)
Pleural invasion	No	-0.556 (0.559)	0.363 (0.056)	0.627 (0.288)	-0.262 (0.511)	0.571 (0.219)	-0.417 (0.151)
Vascular, lymphatic, or perineural invasion	No	-0.412 (0.654)	0.635 (< 0.001) ^{a)}	1.882 (0.014) ^{a)}	0.396 (0.326)	-0.212 (0.600)	0.076 (0.796)

Data are β coefficient values of risk factors and data in parentheses are p-values. LR, local recurrence; LR+Meta, concurrent local recurrence and metastasis; Meta, distal metastasis; OP, operation. ^{a)}p < 0.05.

accepted concept regarding metastatic progression was that it follows a sequential pattern, with the presence of tumor cells in regional LNs leading to an increased chance of tumor cells throughout the lymphatic system, ultimately leading to distant metastases [24]. In contrast, Naxerova et al. [25] found that a considerable portion of colorectal cancer patients exhibited distinct genetic origins for their LNs and distant lesions. These findings propose that there are two distinct lineage relationships between lymphatic and distant metastases [25].

Prior studies have established lobectomy as the gold standard for lung cancer surgery, as it results in a lower risk of LR compared to wedge resection or segmentectomy [18]. In the decades since those initial studies, advancements in imaging techniques have made it possible to detect tumors at earlier stages and smaller sizes, leading to controversy and debates regarding sublobar resection in patients with early lung cancer. A recent large, randomized trial concluded that sublobar resection is recommended solely for NSCLC patients with a tumor size of 2 cm or smaller, as well as confirmed absence of LN involvement [26]. The evidence from our study reinforces this fact, as the risk of LR after sublobar resection was found to be higher, despite the small number of patients undergoing sublobar resection.

It is worth noting that 142 patients (42.4%) had no tumor recurrence and survived until the end of the study period. People who live for more than 5 years following a lung cancer diagnosis have been referred to as long-term lung cancer patients. Our results exceed the average 5-year survival rates reported worldwide, ranging from 10%-20% in most regions, and the highest rate of 32.9% observed in Japan [27]. This might be attributed to early detection through lung cancer screening and advances in treatment options in Korea. In our study, 80% of patients who survived without tumor recurrence were found to have pathologic stage I disease. Studies have confirmed that patients diagnosed with lung cancer through annual screening programs and those diagnosed in the early stages have a higher lung cancer-specific survival rate [28,29].

Finally, we performed an independent analysis of patients with comprehensive pathological data. Based on our results, the detection of any vascular, lymphatic, or perineural invasion is likely to be more closely related to the development of metastases. Earlier research by Higgins et al. [30] has also indicated that the presence of lymphovascular invasion is a significant adverse prognostic factor for both the development of distant metastases and long-term survival outcomes. Despite being recognized as significant risk factors for unfavorable outcomes in lung adenocarcinoma patients, factors such as tumor differentiation, predominant histologic pattern, and the presence of pleural invasion were not

identified as risk factors among the transitions in this study. Pleural invasion is a commonly acknowledged risk factor, and according to the latest staging system, tumors that are 3cm or smaller with visceral pleural invasion are upstaged to T2 status, influencing the type of surgery conducted [31]. Tumors identified as high risk based on their differentiation or predominant histologic pattern serves as an indicator for more intense adjuvant treatment strategies. Consequently, we believe that these factors of pleural invasion, predominant histologic type, and tumor differentiation were already incorporated into the surgical procedure and subsequent treatment, compensating their significance.

Two traditional statistical models, the log-rank test and Cox proportional hazard model, are often used for the analysis of survival or time-to-event outcomes. However, these models only allow for evaluation of the impact of covariates on a single outcome, such as death. In this regard, MSM enables clinicians to partition prognostic factors according to various outcomes as well as to elucidate the evolutionary pattern over time. To date, only a few studies have employed this approach in oncology studies. In a study of colorectal cancer patients, MSM separated the effects of prognostic factors on recurrence and mortality [32]. Ferrer et al. [33] applied MSM to prostate cancer patients and were able to formulate a complete model of prostate cancer progression that considers both classical prognostic factors and prostate-specific antigen dynamics between clinical health states. Jeong et al. [34] also applied a multi-state model to describe the transition probability and to estimate the covariate effect on each transition. The significant contribution of our study was to consider the concurrence of Meta and local recurrence (LR+Meta). That is, they considered only two events (LR and Meta) and five transition pathways after OP [34]. Our study included three events and eight transitions between the states. Hence, our study provides a wider range of clinical scenarios as we tried to reflect the complexity of the real-world data. However, compared with the previous study of 949 patients, our dataset has smaller sample size, which may result in fewer occurrences in OP to LR and LR to LR+Meta.

There were several limitations in this study. First, although patient data from a specialized cancer hospital were analyzed, this was a retrospective study based on the data from a single institution, and the findings may not be universal and needs to be verified in a larger multicenter study. Second, imaging studies such as CT, MRI, ¹⁸F-FDG PET/CT, and bone scan were performed at varying intervals during follow-up or upon clinical suspicion. In line with typical observational studies when compared to clinical trials, our results may have been influenced by lead time bias caused by the time gap between the date of diagnosis and true progression of the disease. However, our institute is highly spe-

cialized in cancer treatment and maintains a very high level of patient compliance. Hence, the majority of patients was treated according to standard protocols and underwent regular follow-up examinations. Third, new techniques such as detecting circulating tumor DNA in the blood have shown potential and accuracy in monitoring and detecting recurrence in cancer patients. However, due to the retrospective design of this study, we were unable to correlate our findings with cancer profile blood levels. Fourth, a considerable proportion of patients simply underwent surgery without additional chemotherapy. The explanation for this was that some patients were too elderly and in poor general condition and some patients decided against undergoing chemotherapy. Some patients refrained from undergoing chemotherapy due to financial reasons. It is important to highlight that the results we obtained is from the real-world data. In addition, treatments such as 3rd generation tyrosine kinase inhibitors and immunotherapy agents has been widely adopted for lung cancer treatment because of their high selectivity and minimal adverse effects in recent years. However, our study cohort had an extensive follow-up period of more than 10 years, meaning it was established before the widespread availability of current treatments. Thus, further investigations including a more recent patient cohort which includes the recent treatment options would be interesting. Finally, we were unable to examine the presence of spread through air spaces, as our patient cohort included patients who underwent OPs more than ten years prior, when spread through air spaces was not an essential part of assessment process.

In conclusion, lung adenocarcinoma displays a broad spectrum of clinical scenarios even after curative surgery. The incidence, risk factors, and prognosis varied across different pathways of recurrence in patients with lung adenocarcinoma. The greatest implication of this MSM is its ability to predict the timing and type of clinical intervention that will have the greatest impact on survival in lung adenocarcinoma patients.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Ethical Statement

This study was conducted in accordance with the 1964 Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB approval number: 2017-09-045). Written informed consent was waived due to the retrospective nature of this study.

Author Contributions

Conceived and designed the analysis: Lee G, Kim YJ, Lee HY.

Collected the data: Lee G, Lee HY.

Contributed data or analysis tools: Lee G, Kim YJ, Sohn I, Kim JH, Lee HY.

Performed the analysis: Kim YJ.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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