Original Article

Various recurrence dynamics for non-small cell lung cancer depending on pathological stage and histology after surgical resection

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Background: Although there are numerous postoperative surveillance guidelines for non-small cell lung cancer (NSCLC), most guidelines recommend the same protocol for patients with different recurrence dynamics. In this study, we investigated the recurrence dynamics of NSCLC patients according to their clinical factors.

Methods: We retrospectively reviewed the data from NSCLC patients who underwent complete resection between 2007 and 2017. Recurrence dynamics were estimated using the hazard rate and displayed with kernel smoothing method according to tumor stage, sex, and histology.

Results: During the period, a total of 6,012 patients were enrolled: 3,687 (61.3%) in stage I, 1,194 (19.9%) in stage II, and 1,131 (18.8%) in stage III. The highest recurrence hazard rate was shown at about 12 months, regardless of tumor stage, but the maximum of hazard rate for stage III was 7 times higher than that in stage I. Depending on tumor histology, the highest peak of hazard curve was observed at different periods, 9 months in squamous cell carcinoma and 15 months in adenocarcinoma. These trends were similar when analyzed based on sex, 9 months in male patients and 15 months in female patients. In stage I adenocarcinoma, recurrence hazard rates were significantly different depending on histologic subtypes and tumor differentiation grade.

Conclusions: Adopting the same follow-up strategy may be undesirable in NSCLC patients who have different clinical and pathological characteristics. Adequate consideration of these factors will help clinicians develop detailed follow-up strategy in lung cancer patients with different recurrence dynamics.

Keywords: Lung cancer; follow-up; surveillance; recurrence

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Introduction

Despite recent developments in multimodality approaches and targeted therapies, non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide (1). This is partly due to the high recurrence rates and the incremental risk of developing new primary lung cancers after complete resection (2). Thus, periodic surveillance for lung cancer survivors is a vital component of comprehensive survivorship care. Various organizations have suggested the differing postoperative surveillance regimens (3-8), but the optimal one for NSCLC survivors remains unclear.

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To establish a rational surveillance regimen for NSCLC, a detailed insight of the timing and patterns of recurrences should be given priority. Previously, cumulative incidence curves, which represents the cumulative failure rates over time due to a particular cause, have been used frequently to obtain information on tumor recurrence. However, this method is not suitable for identifying the propensity change of an event failure depending on time it has reached (i.e., event dynamics), which can be computed by event-specific hazard rates over the follow-up time interval (9). In addition, most surveillance guidelines adopted the same protocol for all patients who received surgical resection (3-8), without distinguishing between tumor stage and histology that are known to have different recurrence rates (10,11).

In this study, we sought to investigate the recurrence pattern and timing of NSCLC patients who received complete resection using the hazard rate estimates. To develop an individualized surveillance protocol, we compared the recurrence dynamics of those patients according to their pathological stage, tumor histology, histologic grade, and histologic subtype. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1028/rc).

Methods

Patients

From January 2007 and December 2017, we retrospectively reviewed the data from patients with primary NSCLC who received surgical resection at Asan Medical Center, Seoul, South Korea. Patients with concurrent malignancies, neoadjuvant therapy, incomplete resection, stage IV, lung cancer history, and deaths within 30 days after surgery or during the initial hospitalization were excluded from the study (Figure S1). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of Asan Medical Center in Seoul, South Korea (IRB No. 2021–0166). The requirement for individual patient consent was waived due to the retrospective nature of this study.

Patient work-up for diagnosis, staging, and surgical resection were conducted according to well-established, widely accepted protocols, the details of which are previously described elsewhere (12). Sublobar resection was generally performed when patients had a tumor size of 2 cm or less without suspicious lymph node metastasis. Patients with a borderline pulmonary reserve (forced expiratory volume in 1 second <60% and diffusing capacity of the lungs for carbon monoxide <60%) and comorbidities were also considered candidates for sublobar resection. Whether to perform wedge resection or segmentectomy was decided according to the depth of the nodule to the lung surface (i.e., feasibility of sufficient resection margin). The pathological staging was performed retrospectively, based on the 8th edition of American Joint Committee on Cancer (AJCC) criteria (13). For the simplicity of the study, adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma (MIA) was considered stage IA1.

Follow-up information on the patients was obtained through clinic follow-up notes every 3 months for the first two years after surgery, every 6 months for the next three years, and annually thereafter (8). Chest CT was performed concomitantly with clinic visits. When cancer recurrence was suspected on chest CT images, patient's symptoms, or physical exam, positron emission tomography-computed tomography (PET-CT) was additionally performed. Whole-brain CT or brain magnetic resonance imaging (MRI) and other imaging techniques were not routinely performed in patients with early-stage NSCLC. For pathological stage III NSCLC, brain assessment with imaging at 6 and 12 months postoperatively was routinely performed. Extrathoracic recurrence including bone, liver, adrenal gland, and kidney was detected by chest CT, and additional imaging modalities were performed accordingly. Recurrence was diagnosed based on patient's symptoms, physical examinations, imaging findings, and, if necessary, biopsy specimens. Recurrence in the ipsilateral hemithorax and mediastinum was defined as local recurrence, whereas that in the contralateral lung or outside the hemithorax and mediastinum was distant recurrence. Second primary lung cancers [defined as: (I) different histologic type; (II) different lung site, in the absence of mediastinal node involvement; or (III) time to occurrence >4 years] were excluded in this study (14,15). Recurrence-free survival (RFS) was defined as the interval between the date of operation and recurrence, and patients who did not occur recurrence were censored at the latest time known to be recurrence-free. Treatment modalities and chemotherapeutic regimens in relapsed cases were determined at the discretion of the attending physician.

Statistical analysis

Continuous variables are presented as medians and

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interquartile range, and categorical variables are shown as percentages. Using the Kaplan-Meier method, RFS was analyze and the differences were calculated through the log-rank test. Bonferroni correction was adopted to assess the P values of log-rank test for multiple comparisons of the survival curves (≥3 curves). For the simplicity of the study, histologic subtypes of adenocarcinoma were grouped into four categories (AIS/MIA *vs.* lepidic *vs.* acinar/papillary *vs.* solid/micropapillary) based on internal exploratory data analysis. In terms of recurrence dynamics, the life-table method was used to measure the hazard rate for recurrence, that is, the conditional probability of manifesting recurrence within a certain time interval. To display easier underlying pattern, some instability owing to random variation in the hazard rate estimates was dealt with the kernel smoothing method at 2-month intervals (16). With the kernel smoothing approach and discrete hazards, smoothed risk estimates were obtained using a flexible piecewise exponential regression model (17). We used natural cubic splines, i.e., with linearity constraints on the tails, to place internal knots equidistantly within the month range (0–72 months). The number of knots, which represented to the number of basic cubic spline functions, was selected depending on the Akaike Information Criteria.

All statistical analyses were performed using R version 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). P values less than 0.05 were considered statistically significant.

Results

Overall patients

A total of 6,012 patients fitting the inclusion criteria were identified (Figure S1). The mean follow-up after surgery was 58.5±30.4 months. During the study period, 27.6% (1,658/6,012) of patients had developed recurrence. In detail, 409 patients had only local recurrence, 1,074 patients had only distant recurrence, and 188 patients showed mixed pattern (local plus distant recurrence simultaneously). The clinicopathologic characteristics of the patients are summarized in *Table 1*. There were 3,687 (61.3%), 1,194 (19.9%), 1,131 (18.8%) patients with pathological stage I, II, and III. Adjuvant chemoradiotherapy, chemotherapy, and radiotherapy was performed in 309 (5.1%), 933 (15.5%), and 320 (5.3%) patients in overall cohort and the detailed rates according to pathological stage are described in Table S1. The most frequent recurrence site was chest wall (32.3%) in loco-regional metastasis and the contralateral lung in distant metastasis (48.2%) (Table S2). Among patients with cancer recurrence (n=1,658), there were 441 (26.6%) cases of pathologically confirmed recurrence. According to the recurrence pattern, cases of pathologically confirmed recurrence were 30.2% (130/431), 25.1% (272/1,084), and 21.0% (39/186) in patients with local, distant, and mixed recurrence. The details of the mode for recurrence detection are described in the Table S3.

Recurrence dynamics

Figure 1 describes the RFS and the hazard rate for recurrence based on the pathological stage. Survival curves for recurrence between patients with stage I, stage II, and stage III were significantly different (all P<0.001, *Figure 1A*). In spite of different hazard rates depending on pathological stage, all hazard rate curves displayed similar patterns with the highest peak at around 12 months and the second peak at around 33 months after surgery (*Figure 1B*). When patients with stage II and II were divided according to the performance of adjuvant therapy, all hazard rate curves still showed a similar pattern with the highest peak at about 12 months, although there were slight differences (Figure S2). In accordance with the recurrence pattern, the rate of distant recurrence was higher than that of local or mixed recurrence, regardless of pathological stage (*Figure 2*). In addition, the highest peak for distant recurrence was shown around 9–12 months, whereas the peak for local recurrence was observed at around 15 months in patients with stage II and III (*Figures 2B,2C*). As for histological type, the 5-year RFS rate for adenocarcinoma was higher than squamous cell carcinoma in stage I (82.4% *vs.* 77.5%), but it was reversed in stage III (31.7% *vs.* 49.9%) (*Figure 3A,3B*). The highest peak of hazard rate was also observed at different period, which was 9 months for squamous cell carcinoma and 15 months for adenocarcinoma (*Figures 3C,3D*). Similar to histological type, the 5-year RFS rate for female patients was higher than male patients in stage I (83.8% *vs.* 79.7%), but it was reversed in stage III (30.1% *vs.* 40.1%) (*Figure 4A,4B*). In addition, the highest peak of hazard rate was shown at 9 months in female patients and 15 months in male patients (*Figure 4C,4D*). When it comes to histologic subtypes among patients with stage I adenocarcinoma, a phased degradation was found within the RFS curves from AIS/MIA to solid/micropapillary (*Figure 5A*). Each curve of RFS according to the grade of histologic differentiation was also different in stage I adenocarcinoma (*Figure 5B*). Stage I adenocarcinoma with

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Table 1 Characteristics of enrolled patients (N=6,012)

Variable	Number (%) or median [IQR]
Age (years)	63 [56–70]
Sex	
Male	3,578 (59.5)
Female	2,434 (40.5)
Smoking status	
Smoker	3,226 (53.7)
Never-smoker	2,786 (46.3)
Histologic structure	
ADC	4,395 (73.1)
SqCC	1,290 (21.5)
Others	327 (5.4)
Tumor location	
Right upper	1,700 (28.3)
Right middle	401 (6.7)
Right lower	1,440 (23.9)
Left upper	1,421 (23.6)
Left lower	1,050 (17.5)
Surgical approach	
VATS	4,303 (71.6)
Thoracotomy conversion	254 (4.2)
Thoracotomy	1,455 (24.2)
Pathologic tumor size (mm)	26 [18–38]
Operative method	
Wedge resection	635 (10.6)
Segmentectomy	405 (6.7)
Lobectomy	4,242 (77.2)
Bilobectomy	209 (3.5)
Pneumonectomy	121 (2.0)
8th pathologic stage	
IA1	338 (5.6)
IA2	1,215 (20.2)
IA3	1,026 (17.1)
IB	1,108 (18.4)
IIA	287 (4.8)
IIB	907 (15.1)
IIIA	910 (15.1)
IIIB	221 (3.7)
EGFR mutation	
Present	668 (11.1)
Absent	791 (13.2)
Unknown	4,553 (75.7)
Adjuvant therapy	
Chemoradiotherapy	309 (5.1)
Chemotherapy	933 (15.5)
Radiotherapy	320 (5.3)

IQR, interquartile range; ADC, adenocarcinoma; SqCC, squamous cell carcinoma; VATS, video-assisted thoracoscopic surgery; EGFR, epidermal growth factor receptor.

solid/micropapillary pattern had a distinct peak of recurrence hazard rate at 12 months, but other subtypes did not (*Figure 5C*). The highest peak of hazard rate was displayed at 9 months in well differentiated stage I adenocarcinoma, whereas it was at 15 months in moderately differentiated tumor (*Figure 5D*).

Discussion

In this study, we investigated the recurrence dynamics of NSCLC patients who received complete resection according to their pathological stage, tumor histology, sex, histologic grade, and histologic subtype. Based on the results in our study, the main findings could be summarized as follows. First, irrespective of pathological stage, the highest recurrence hazard rate was shown at about 12 months and distant recurrence accounted for the largest portion of the overall recurrence pattern. However, the maximum of hazard rate for stage I was only one-seventh of that in stage III. Second, depending on tumor histology, the highest peak of recurrence hazard curve was observed at different periods, 9 months in squamous cell carcinoma and 15 months in adenocarcinoma. These trends based on tumor histology were similar when analyzed based on sex, 9 months in male patients and 15 months in female patients. Lastly, RFS and recurrence hazard rate were significantly different in accordance with histologic subtype and tumor differentiation grade in stage I adenocarcinoma. These findings indicate that adopting the same follow-up strategy may be undesirable in NSCLC patients who have different clinical and pathological characteristics.

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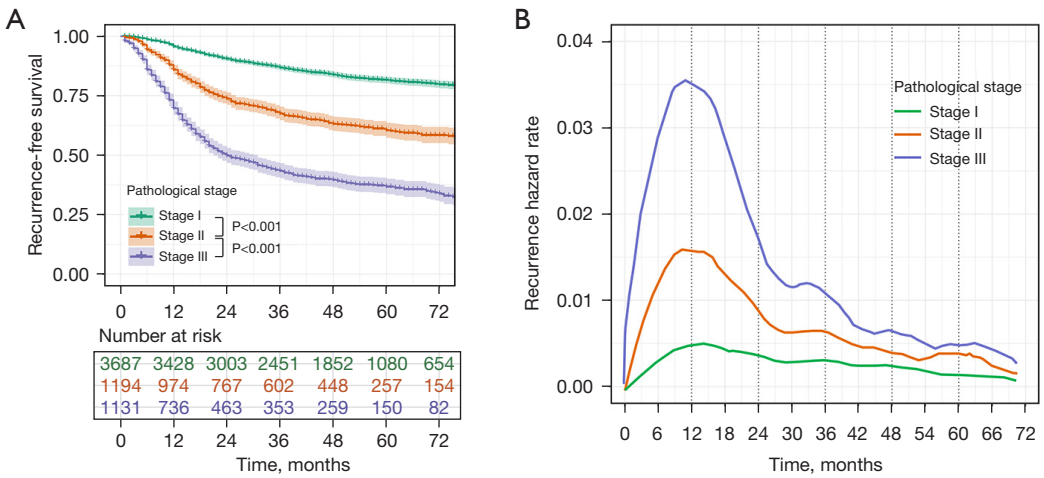

Figure 1 Recurrence-free survival (A) and the hazard rate for recurrence (B) based on the pathological stage in patients with non-small cell lung cancer.

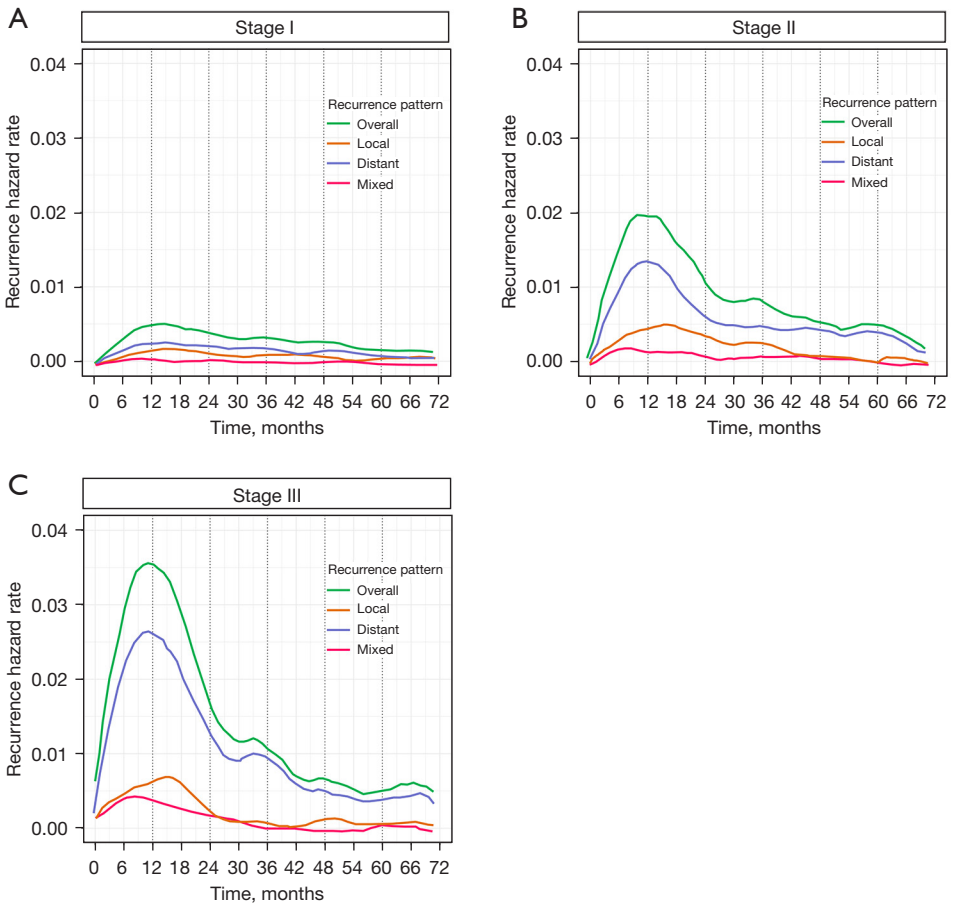

Figure 2 The hazard rate for recurrence following the recurrence pattern in patients with pathological stage I (A), stage II (B), and stage III (C) non-small cell lung cancer.

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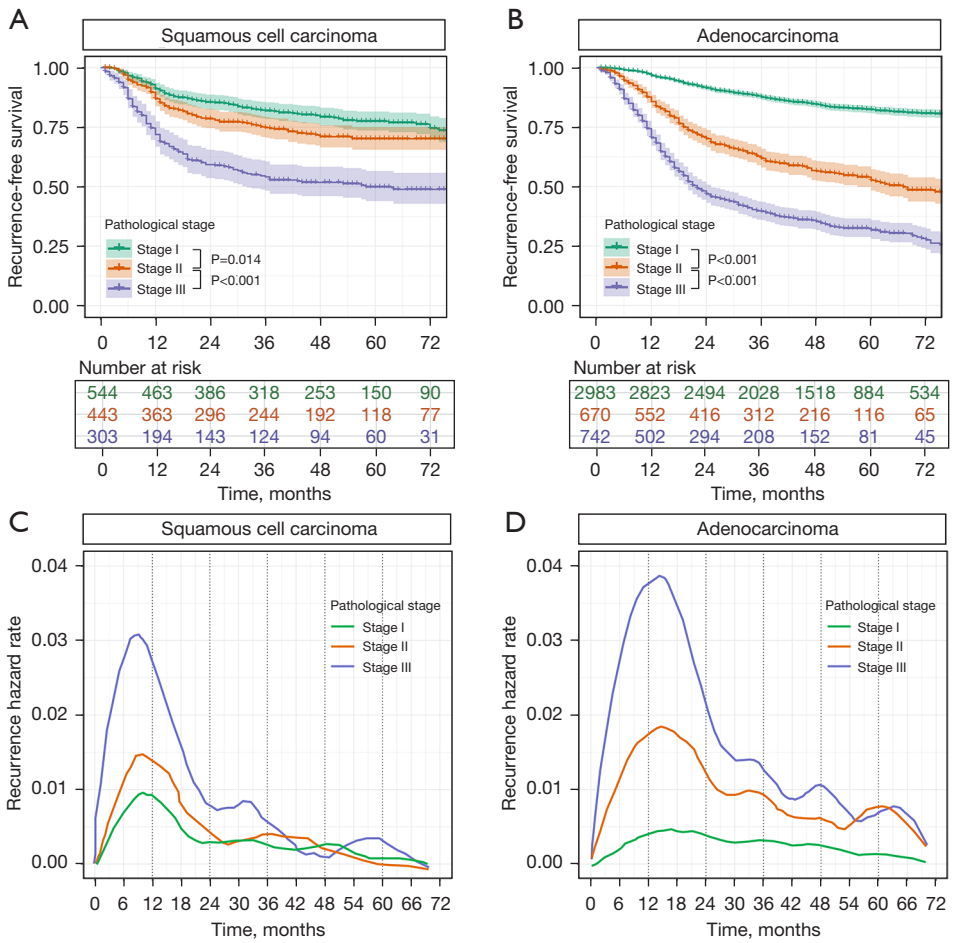

Figure 3 Recurrence-free survival following the pathological stage in patients with squamous cell carcinoma (A) and adenocarcinoma (B). The hazard rate for recurrence following the pathological stage in patients with squamous cell carcinoma (C) and adenocarcinoma (D).

As with our findings, several studies have reported a structured recurrence pattern with multiple peaks in NSCLC (18-20). This pattern contradicts the conventional notion that tumor cells continue to proliferate in disorder, leading to disease progression. Demicheli *et al.* adopted the hypothesis of a metastasis growth model based on breast cancer to explain this specific recurrence pattern in NSCLC (18). It was that the first peak of recurrence at around 1 year is closely related to disruption of homeostasis and proliferation of dormant tumor cells triggered by surgical invasion (21). Accordingly, the subsequent peaks of recurrence could be explained by the proliferation of residual tumor cells and the development of micro-metastasis after entering a temporary state of dormancy (20). However, the detailed mechanisms for the hypothesis of tumor dormancy have not been fully elucidated to date.

It should be noted that the recurrence dynamics of patients who undergo curative surgical treatment for NSCLC might be changed by various confounding factors, such as the frequency of the follow-up visits and radiologic examinations, the diagnostic modalities, and the interruption. In our institution, patients were strictly followed up every 3 months for the first 2 years after surgery and every 6 months thereafter. Chest CT was performed concomitantly with clinic visits, which seems more frequent than those recommended in any guidelines, such as National Comprehensive Cancer Network, European Society for Medical Oncology, and American Association of Thoracic Surgeons (3-8). Many previous studies examined optimal surveillance strategies that potentially contribute to overall survival (22). Westeel *et al.* reported that symptomatic patients with recurrence had worse survival than asymptomatic patients in whom recurrence was diagnosed on intensive imaging studies after

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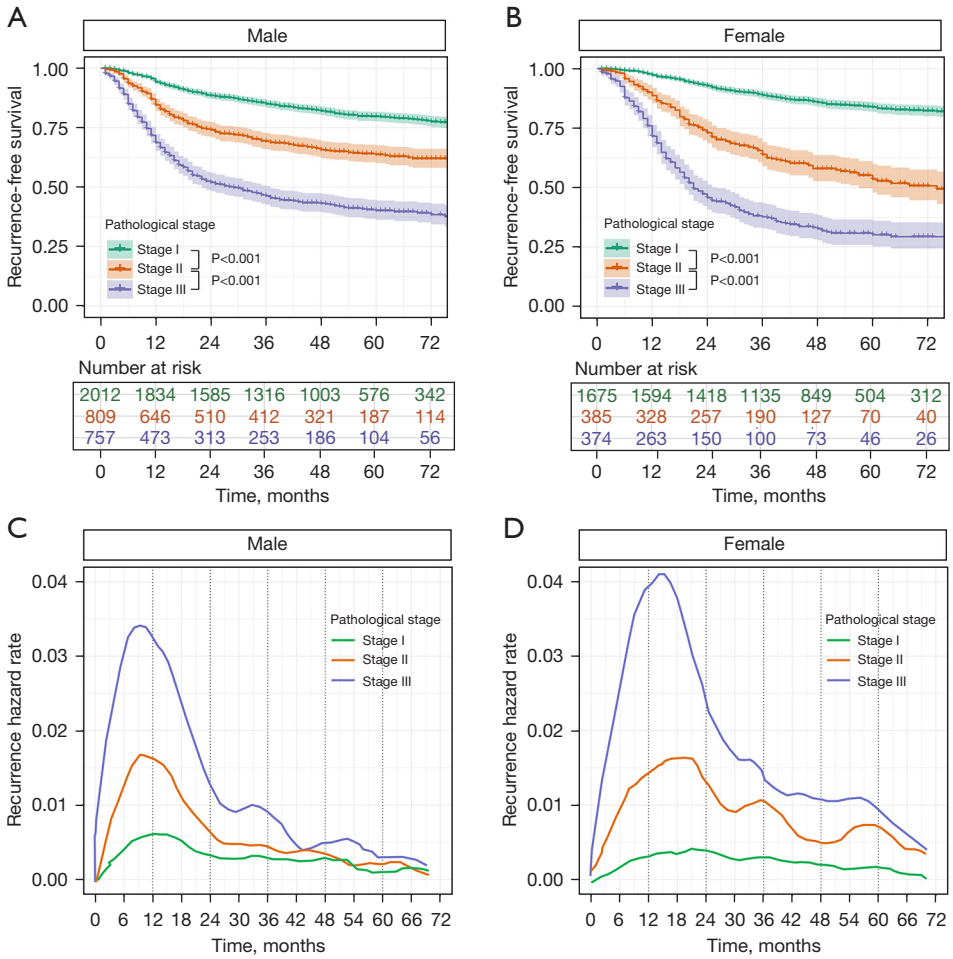

Figure 4 Recurrence-free survival following the pathological stage in male (A) and female (B) patients. The hazard rate for recurrence following the pathological stage in male (C) and female (D).

surgery (23). Williams *et al.* also insisted that symptomatic patients at the time of recurrence have more than doubled the risk of death compared to asymptomatic patients, which supports intensive follow-up after complete resection (24). Accumulated evidence from prospective randomized studies and meta-analysis suggests intensive local therapy for oligo–recurrence may improve outcomes in a meaningful way (25-27). Furthermore, the adoption of molecular targeted therapy with an epidermal growth factor receptor (EGFR) gene mutation and an anaplastic lymphoma kinase (ALK) gene mutation for recurrent NSCLC has improved post-recurrence survival (28-30). However, the benefit of postoperative surveillance was also questioned from the perspectives of efficacy and cost-effectiveness (8,31). To date, there have been no large, prospective, randomized trials comparing different surveillance strategies in patients with NSCLC, and it remains unclear whether the early detection of recurrence contributes to improved outcomes. Consequently, it should be cautious to recommend individualized postoperative surveillance protocol according to clinical factors. However, we believe several tips based on our findings will help clinicians develop appropriate follow-up strategy for NSCLC patients with various clinical information.

First, given that no apparent peak of recurrence hazard curve has emerged in stage I patients, it does not seem mandatory to follow-up aggressively (e.g., hospital visit for every 3 months over the first 2 years or standard dose CT for 5 years) for these patients, as do patients in higher stages. Second, we have shown different hazard rates for recurrence depending on histologic subtype and tumor differentiation grade in stage I adenocarcinoma. Thus,

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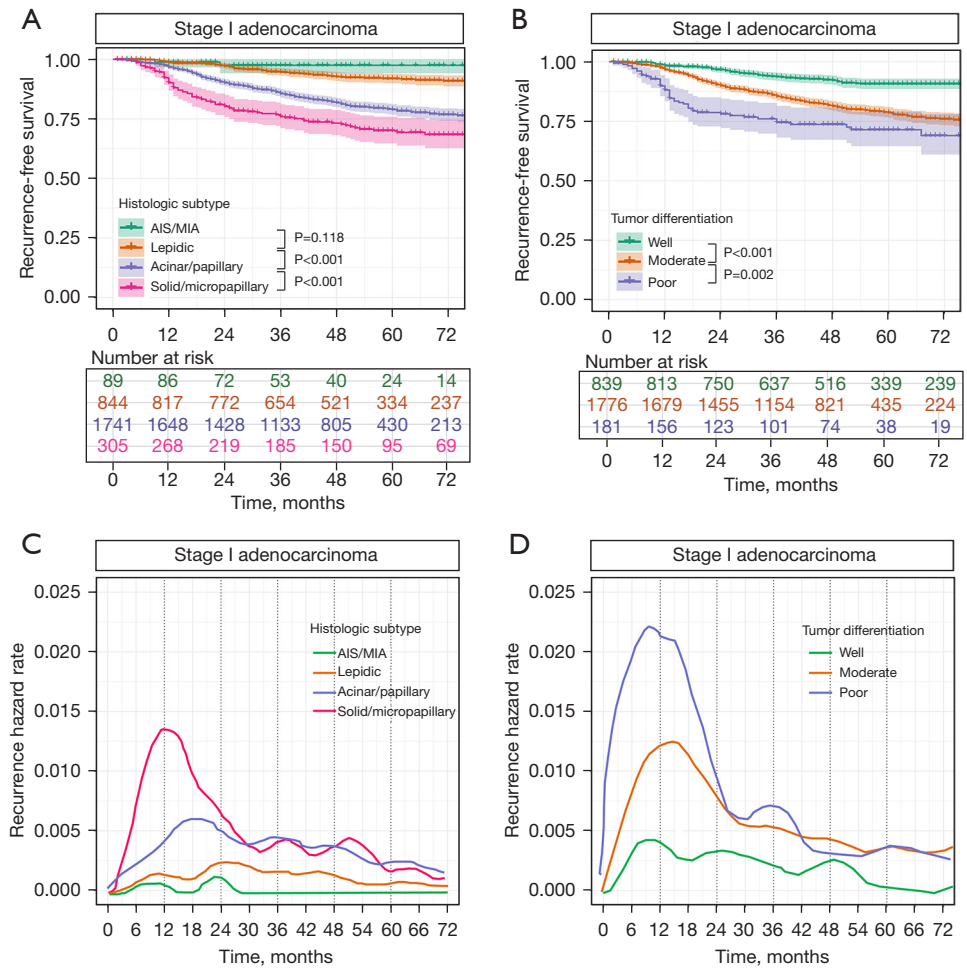

Figure 5 Recurrence-free survival following the histologic subtype (A) and tumor differentiation (B) in patients with stage I adenocarcinoma. The hazard rate for recurrence following the histologic subtype (C) and tumor differentiation (D).

aggressive surveillance should be maintained even in stage I adenocarcinoma, if patients have poor prognostic indicators, such as solid/micropapillary histologic subtype or poor tumor differentiation. Last, considering that the timing at which the peak of hazard curve was seen differed according to tumor histology and sex, it is suggested to take the intensive follow-up strategy longer in adenocarcinoma and female, compared to squamous cell carcinoma and male.

This study has some limitations. Selection bias may be present due to the retrospective, single-center design of the study. Although intensive surveillance system was adopted in our study, especially for the first two years, the timing of the first event obviously depends on the timing of imaging studies or hospital visits. Thus, we acknowledge there might be lead-time and length-time bias on our results. In addition, given that this study is focusing on descriptive analysis, no conclusions about further effects on survival outcomes, cost-effectiveness, or patient's quality of life can be made. The impact on these outcomes would necessarily be performed with randomized prospective design.

In summary, patients who received complete surgical resection for NSCLC have various recurrence dynamics depending on clinical factors, such as pathological stage, sex, tumor histology and its subtype, and tumor differentiation grade. Adequate consideration of these factors will help clinicians develop detailed follow-up strategy in lung cancer patients with different recurrence dynamics.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1028/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1028/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1028/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of Asan Medical Center in Seoul, South Korea (IRB No. 2021–0166). The requirement for individual patient consent was waived due to the retrospective nature of this study.

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Supplementary

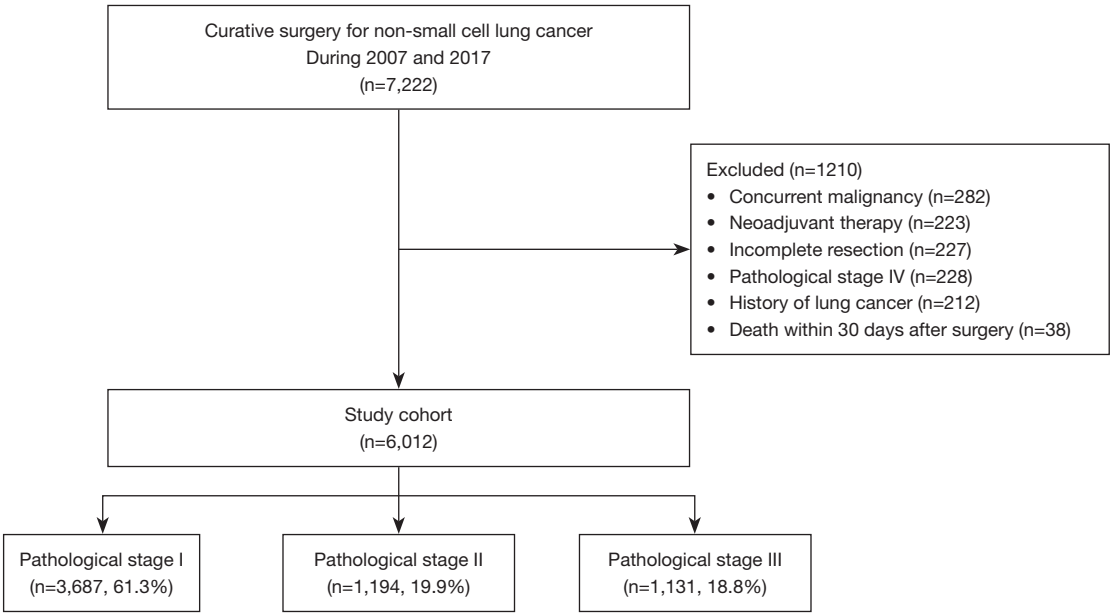

Figure S1 Inclusion criteria.

Table S1 Detailed rates of adjuvant therapy according to pathological stage

	pStage I (n=3,687)	pStage II (n=1,194)	pStage III (n=1,131)	P value
Chemotherapy	85 (2.3%)	399 (33.4%)	449 (39.7%)	<0.001
Radiotherapy	9 (0.2%)	52 (4.4%)	259 (22.9%)	<0.001
Chemoradiotherapy	2 (0.1%)	43 (3.6%)	264 (23.3%)	<0.001
None	3,591 (97.4%)	700 (58.6%)	284 (25.1%)	<0.001

pStage, pathological stage.

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Table S2 Recurrence pattern for overall patients with non–small cell lung cancer

			Recurrence pattern		
			Loco-regional	Distant	Mixed
Total patients (n=1658)			431 (26.0%)	1084 (65.4%)	186 (11.2%)
Recurrence site	Loco-regional	Mediastinal lymph node	64 (14.8%)		99 (53.2%)
		Bronchus stump	69 (16.0%)		31 (16.7%)
		Lung	70 (16.2%)		40 (21.5%)
		Chest wall	139 (32.3%)		11 (5.9%)
		Others	89 (20.6%)		6 (3.2%)
	Distant	Brain		192 (17.7%)	9 (4.8%)
		Bone		196 (18.1%)	40 (21.5%)
		Liver		65 (6.0%)	17 (9.1%)
		Mediastinal lymph node		76 (7.0%)	41 (22.0%)
		Adrenal gland		47 (4.3%)	5 (2.7%)
		Kidney		8 (0.7%)	2 (1.1%)
		Lung		522 (48.2%)	70 (37.6%)
		Other lymph node		119 (11.0%)	46 (24.7%)
		Others		112 (10.3%)	39 (21.0%)

Table S3 Details of the recurrence detection mode

	Total	Recurrence pattern		
		Loco-regional	Distant	Mixed
The number of cases	1658	431	1084	186
The presence of recurrence–related symptom	472 (28.5%)	15 (3.5%)	385 (35.5%)	72 (38.7%)
Unplanned visit for recurrence[a]	196 (11.8%)	9 (2.1%)	132 (12.2%)	55 (29.6)
Pathologically confirmed cancer recurrence	441 (26.6%)	130 (30.2%)	272 (25.1%)	39 (21.0%)
Initial modality for recurrence detection				
- Symptom	85 (5.1%)	3 (0.7%)	34 (31.4%)	48 (25.8%)
- Physical examination	9 (0.5%)	0	2 (0.2%)	7 (3.7%)
- Chest CT	1168 (70.4%)	416 (96.5%)	720 (66.4%)	32 (17.2%)
- PET scan	187 (11.3%)	10 (2.3%)	45 (4.2%)	132 (71.0%)
- Brain MRI	245 (14.8%)	0	177 (16.3%)	68 (36.6%)
- Bone scan	37 (2.2%)	0	9 (0.8%)	28 (15.1%)

[a], A recurrence diagnosed not by a scheduled outpatient clinic, such as emergency room or unplanned outpatient clinic visit after follow–up loss. CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging.

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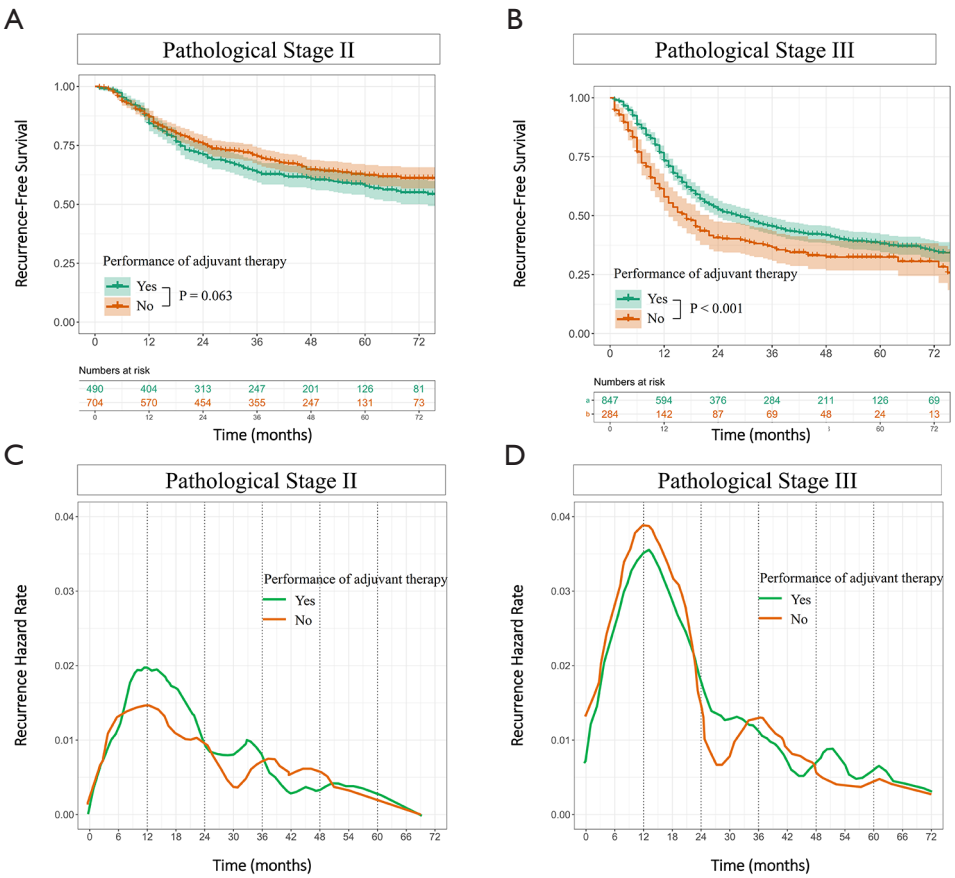

Figure S2 Recurrence-free survival following the performance of adjuvant therapy in patients with pathological stage II (A) and III (B). The hazard rate for recurrence following the performance of adjuvant therapy in patients with pathological stage II (C) and III (D).

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