Peer Review File

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● Reviewer A:

Comment 1. We sometimes experience brain recurrence after surgery. Examination of brain recurrence is difficult by CT or PET-CT. Did you routinely perform brain MRI in postoperative surveillance? If you did not perform examination of brain recurrence, you may describe the reasons in Discussion.

Response 1. Thank you for your valuable comment. In our current practice, 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. Chest CT was performed concomitantly with clinic visits. When cancer recurrence was suspected on chest CT images, patient's symptoms, or physical exam, 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. However, brain assessment with imaging at 6 and 12 months postoperatively was routinely performed in patients with pathological stage III NSCLC. Extrathoracic recurrence including bone, liver, adrenal gland, and kidney was detected by chest CT, and additional imaging modalities were performed accordingly. We added these comments in the Method section.

Change 1.

Methods

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. Chest CT was performed concomitantly with clinic visits. When cancer recurrence was suspected on chest CT images, patient's symptoms, or physical exam, 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.

● **Reviewer B:**

Comment 1. You didn't report the EGFR mutation status of the patients, which may have some prognostic implications.

Response 1. Thank you for your valuable comment. In our institution, target therapy for EGFR mutations has been routinely performed since 2012. Considering that the patients included in this study were from 2007 to 2017, many patients lack information on EGFR mutation. In addition, EGFR mutation was not routinely performed in patients with early–stage NSCLC. As a result, information on EGFR mutation was identified in 1459 of 6012 (24.2%) patients and EGFR mutation was present in 668/1459 (45.8%) patients. We added this information in Table 1.

Comment 2. Do you have the CTR data? CTR less than 0.5 will have a lower risk of recurrence?

Response 2. Unfortunately, we did not collect information for GGO. Thus, we could not analyze the recurrence rate according to the cutoff value 0.5 of CTR.

Instead, we have previously reported the surgical outcome in patients who underwent pulmonary resection for GGO–dominant nodules measuring ≤2 cm with a CTR ≤0.25 based on computed tomography. As a result, there were no significant differences in the 5-year DFS rate (100%, 100%, 92.7%, respectively; p=0.76) or 5-year OS rate (100%, 100%, 100%; p=0.223) among the wedge resection, segmentectomy, and lobectomy groups (1).

1. Ha KJ, Yun JK, Lee GD, et al. Surgical Outcomes of Radiographically Noninvasive Lung Adenocarcinoma according to Surgical Strategy: Wedge Resection, Segmentectomy, and Lobectomy. Korean J Thorac Cardiovasc Surg 2018;51:376-83.

Comment 3. A total of 10% of the patients underwent wedge resections, which may impact the local recurrence rates relative to patients who underwent anatomical resection. Did the wedge resection patients have mixed ground glass tumors with low CTRs? Were they small tumors less than 2 cms?

Response 3. Thank you for pointing this out. Although there were no definite criteria, sublobar resection was generally considered for patients with a tumor size of less than or equal to 2 cm and clinical N0 disease. Many patients who had a borderline pulmonary reserve (forced expiratory volume in 1 second <60% and diffusing capacity of the lungs for carbon monoxide <60%) and comorbidities also underwent sublobar resection. The decision to undergo wedge resection or segmentectomy was made depending on nodule depth relative to the lung surface (ie, feasibility of sufficient resection margin). We added these comments in the Method section.

Change 3.

Methods

Patient work-up for diagnosis, staging, and surgical resection were conducted according to well-established, widely accepted protocols, including full body (brain to pelvis) computed tomography, 18F-fluorodexyglucose positron emission tomography (PET), bronchoscopy, and either endobronchial or CT-guided fine needle biopsy. Although there were no definite criteria, sublobar resection was generally considered for patients with a tumor size of less than or equal to 2 cm and clinical N0 disease. Many patients who had a borderline pulmonary reserve (forced expiratory volume in 1 second <60% and diffusing capacity of the lungs for carbon monoxide <60%) and comorbidities also underwent sublobar resection. The decision to undergo wedge resection or segmentectomy was made depending on nodule depth relative to the lung surface (ie, feasibility of sufficient resection margin). The pathological staging was performed retrospectively, based on the 8th edition of American Joint Committee on Cancer (AJCC) criteria. For the simplicity of the study, adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) was considered stage IA1.

Comment 4. Can you provide a breakdown on adjuvant therapy by pathologic stage?

Response 4. In accordance with your comment, we added a breakdown on adjuvant therapy by pathologic stage in the Supplementary Table 1.

	pStage I (n=3687)	pStage II (n=1194)	pStage III (n=1131)	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	3591 (97.4%)	700 (58.6%)	284 (25.1%)	<0.001

Change 4.

3. Results

3.1. Overall patients

A total of 6012 patients fitting the inclusion criteria were identified (Supplementary Figure 1). The mean follow-up after surgery was 58.5 ± 30.4 months. During the study period, 27.6% (1658/6012) of patients had developed recurrence. In detail, 409 patients had only local recurrence, 1074 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 3687 (61.3%), 1194 (19.9%), 1131 (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 Supplementary Table 1.

Comment 5. The central message of this study is that most NSCLC recurrences will take place within the first 12 months after surgery regardless of pathologic stage. However, I don't think you can make any specific recommendations on surveillance given the inherent selection bias of retrospective study.

Response 5. Thank you for mentioning a critical point. We agree with you that we cannot make any specific recommendations on surveillance given the inherent selection bias of retrospective study.

As described in the text, 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. 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. In addition, the benefit of postoperative surveillance is questioned from the perspectives of efficacy and cost–effectiveness (2,3). 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.

2. Virgo KS, McKirgan LW, Caputo MCA, et al. Post-Treatment Management Options for Patients with Lung Cancer. Annals of Surgery 1995;222.
3. Calman L, Beaver K, Hind D, et al. Survival benefits from follow-up of patients with lung cancer: a systematic review and meta-analysis. J Thorac Oncol 2011;6:1993-2004.

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, 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.

Reviewer C:

Comment 1. The recurrence dynamics of NSCLC patients who undergo curative surgical treatment should be changed by various confounding factors, such as the frequency of the follow-up visits and radiologic examinations, the diagnostic modalities, and the interruption. Your routine follow-up visits and chest CT seems more frequent than those recommended in any guidelines. Did it affect the earlier detection of recurrence? You need to explain and discusses about this possibility.

Response 1. Thank you for your valuable comment. We agree with your comment that the recurrence dynamics of NSCLC patients who undergo curative surgical treatment should be changed by various confounding factors. In our institution, 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. Chest CT was performed concomitantly with clinic visits and PET-CT was additionally performed when disease recurrence was clinically suggested, which seems more frequent than those recommended in any guidelines.

As for postoperative follow-up of lung cancer, many previous studies examined surveillance strategies that potentially contribute to overall survival (4). Williams et al. reported a more than twofold increase in post-recurrence mortality risk associated with the presence of symptoms at recurrence (5). A significant survival advantage has been demonstrated in asymptomatic patients whose recurrences were diagnosed during follow-up, which supports intensive follow-up after complete resection (6). In our current practice, routine brain assessment with imaging at 6 and 12 months postoperatively enabled us early diagnosis of brain metastasis before symptom onset. Aggressive treatment with stereotactic radiosurgery resulted in effective local control of metastatic brain lesion without compromising performance and prolonged recurrence-free states achieved. In addition, since we applied EGFR-TKI in cases of recurrence with EGFR mutation, prolonged post-recurrence survival has been observed. However, the benefit of postoperative surveillance was also questioned from the perspectives of efficacy and cost–effectiveness (2). At present, sufficient

evidence to support intensive surveillance is not available, and it remains unclear whether the early detection of recurrence contributes to improved outcomes. We added these comments in the Discussion section.

2. Mollberg NM, Ferguson MK. Postoperative surveillance for non-small cell lung cancer resected with curative intent: developing a patient-centered approach. Ann Thorac Surg 2013;95:1112-21.
4. Williams BA, Sugimura H, Endo C, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. Ann Thorac Surg 2006;81:1021-7.
5. Westeel V, Choma D, Clement F, et al. Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. Ann Thorac Surg 2000;70:1185-90.
6. Virgo KS, McKirgan LW, Caputo MCA, et al. Post-Treatment Management Options for Patients with Lung Cancer. Annals of Surgery 1995;222.

Change 1.

Discussion

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. Many previous studies examined optimal surveillance strategies that potentially contribute to overall survival. 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 surgery. 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. Accumulated evidence from prospective randomized studies and meta-analysis suggests intensive local therapy for oligo–recurrence may improve outcomes in a meaningful way. Furthermore, the adoption of molecular targeted therapy with an epidermal growth factor receptor (EGFR) gene mutation and an anaplastic lymphoma tyrosine kinase (ALK) gene mutation for recurrent NSCLC has improved post-recurrence survival. However, the benefit of postoperative surveillance was also questioned from

the perspectives of efficacy and cost–effectiveness. 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.

Comment 2. Related to the above comment, data regarding the mode of recurrence detection would be of interest. How many patients discovered recurrence by routinely performed chest CT? How many patients had symptomatic and asymptomatic recurrence? The data of the mode of recurrence detection needs to be showed in tabular form. i.e. routine chest CT, PET-CT, any symptoms, physical examination, etc.

Response 2. Thank you for your valuable comment. Among patients with cancer recurrence (n=1658), 1169 (70.4%) patients were diagnosed by routinely performed chest CT. In addition, 85 (5.1%) patients had symptomatic recurrence. In response to your request, we presented a tabular form of details of the recurrence detection mode in the Supplementary Table 3.

Change 2.

Supplementary Table 3. 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.

Comment 3. You described in the Methods section that "chest CT was performed concomitantly with clinic visits and PET-CT was additionally performed when disease recurrence was clinically suggested". How did you detect the extrathoracic recurrences, such as brain, bone, and liver metastases? Some of the extrathoracic recurrences cannot be detected even by PET-CT. You should describe the method for extrathoracic recurrence evaluation in the Methods section. Moreover, the data of the recurrence sites needs to be showed in tabular form in detail. i.e. bone, brain, lung, mediastinal LNs, etc. This information may also be useful to assess whether your postoperative surveillance strategy, that is based on routine chest CT contributed the detection of recurrence in NSCLC patients who underwent curative resection.

Response 3. Thank you for mentioning a critical point. As mentioned in the Method section, we performed chest CT concomitantly with clinic visits. When cancer recurrence was suspected on chest CT images, patient's symptoms, or physical exam, 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. However, 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.

According to your comment, we described the details of workup for recurrence. In addition, we added the information of recurrence sites according to the recurrence pattern.

Change 3.

2.1. Patients

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 (3). Chest CT was performed concomitantly with clinic visits. When cancer recurrence was suspected on

chest CT images, patient's symptoms, or physical exam, 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.

Supplementary Table 2. Recurrence pattern for overall patients with NSCLC

			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%)

Comment 4. How did you differentiate recurrence from a metachronous primary tumor in newly developed lung nodules? In the Methods section, you described that "when the clinical scenario was more consistent with a new primary tumor than a local recurrence". This should be explained in more detail.

Response 4. To differentiate between recurrence of the primary tumor and second primary pulmonary tumor (SPPT), we used the criteria of Martini and Melamed, with the interval proposed by Detterbeck (7,8), defining second primary tumor as: (1) different histologic type; (b) different lung site, in the absence of mediastinal node involvement; or (c) time to occurrence >4 years (8). We added these comments in the Method section.

7. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
8. Detterbeck FC, Jones DR, Kernstine KH, et al. Lung cancer. Special treatment issues. Chest 2003;123:244.

Change 4.

2.1. Patients

Second primary lung cancers (defined as: (1) different histologic type; (b) different lung site, in the absence of mediastinal node involvement; or (c) time to occurrence >4 years) were excluded in this study. Recurrence-free survival (RFS) was calculated as the interval between the date of resection and the date of recurrence, and patients without recurrence were censored at the latest timepoint known to be recurrence-free. Treatment modalities and chemotherapeutic regimens in relapsed cases were determined at the discretion of the attending physician.

Comment 5. Related to the above comment, how many patients had pathologically confirmed recurrence?

Response 5. Among patients with cancer recurrence (n=1658), 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% (272/1084), and 21.0% (39/186) for local, distant, and mixed recurrence. We added these comments in the Result section.

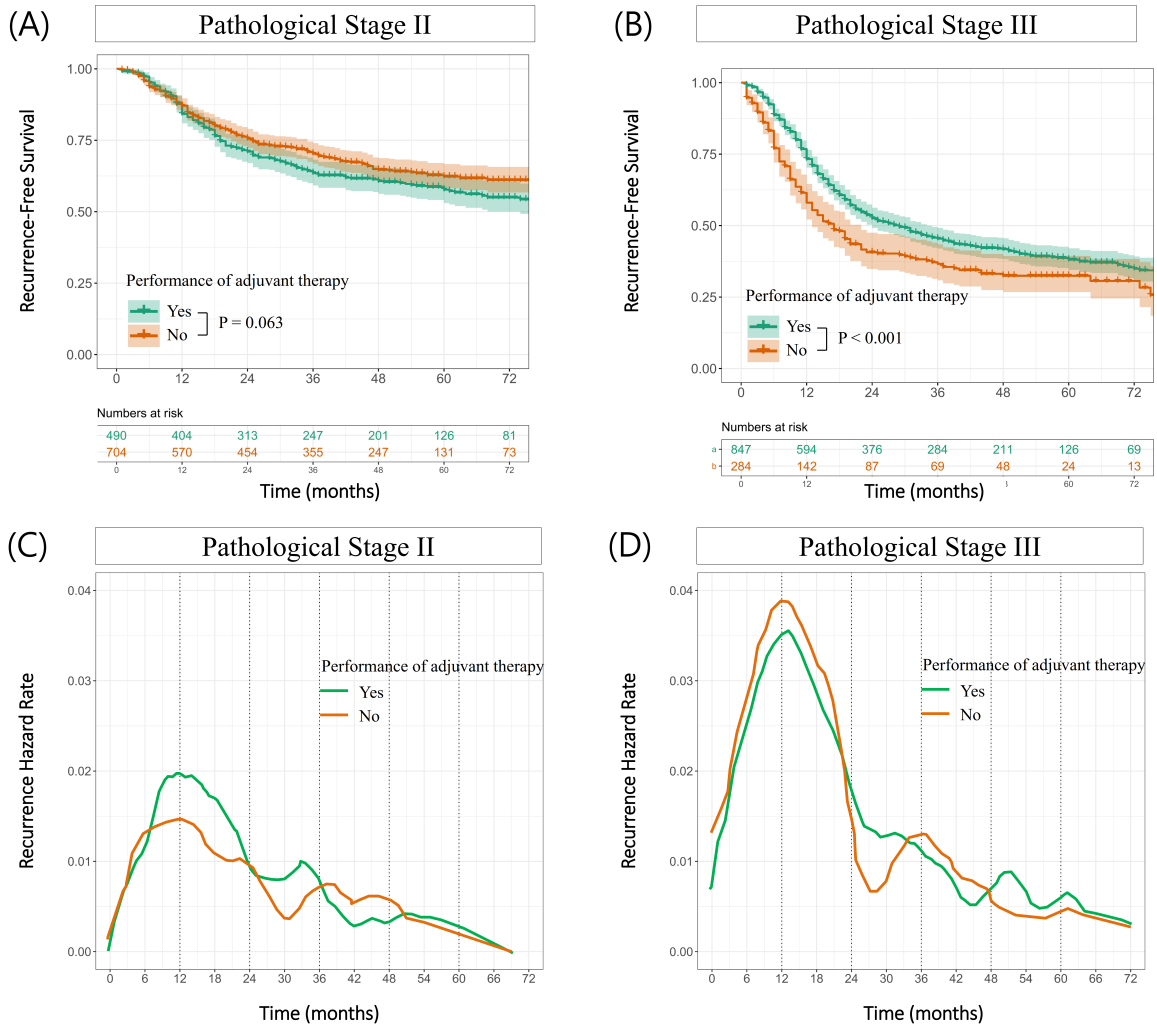
Change 5.

3.1. Overall patients

A total of 6012 patients fitting the inclusion criteria were identified (Supplementary Figure 1). The mean follow-up after surgery was 58.5 ± 30.4 months. During the study period, 27.6% (1658/6012) of patients had developed recurrence. In detail, 409 patients had only local recurrence, 1074 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 3687 (61.3%), 1194 (19.9%), 1131 (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 Supplementary Table 1. The most frequent recurrence site was chest wall (32.3%) in loco-regional metastasis and the contralateral lung in distant metastasis (48.2%) (supplementary Table 2). Among patients with cancer recurrence (n=1658), 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% (272/1084), and 21.0% (39/186) in patients with local, distant, and mixed recurrence.

Comment 6. The inclusion of patients with stage II and III disease who received adjuvant therapies complicates the study and the analyses. These patients would be potentially followed more closely by medical oncology compared to the patients who did not undergo postoperative adjuvant therapies. Recommend separating the analysis who received and did not receive adjuvant therapies.

Response 6. Thank you for mentioning the critical point. We agree with you that patients who performed adjuvant therapy would be potentially followed more closely, which in turn may influence selection bias on the results of this study. According to your recommendation, we divided patients with stage II and III based on whether adjuvant therapy was conducted or not. As a result, all hazard rate curves showed a similar pattern with the highest peak at about 12 months in both stages II and III, although there were slight differences depending on whether adjuvant therapy was administered. We included these results in the Supplementary Figure 2.



Change 6.

3.2. 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 (Supplementary Figure 2).

Comment 7. Finally, what NEW take-home message are you trying to impart? Chest CT surveillance at 6 months x 2 years then yearly to 5 years is already part of most disease management programs. How would this change?

Response 7. Thank you for this comment. 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, 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.