proportions of recurrences within 2 or 3 years after surgery were 48.2% and 66.5%, respectively (unpublished data). Previous studies have reported that the incidence of recurrence in stage I NSCLC patients was 14-36%, with the 1-year survival rate ranging from 30% to 68% (details in Table 5).[1-6,8,24]

We examined risk factors for recurrence in stage I NSCLC, and identified 3: pathological vascular invasion, pleural invasion, and poorly-differentiated carcinoma. These standard pathological factors have also been reported to be good predictors of OS for patients with stage I NSCLC.[25-36] In our study, univariate analysis for PRS identified 6 significant risk factors (male gender, smoking, poorly-differentiated carcinoma, non-adenocarcinoma, no PRT, and shorter recurrence-free interval; $\leq$ 24 months), while multivariate analysis revealed that gender, PRT, and differentiation were independent prognostic factors. Only differentiation was a significant predictor of recurrence and poor PRS, and pathological vascular invasion and pleural invasion had no significant impact on PRS. PRS may be associated with recurrent disease characteristics, including the recurrence site, PRT, recurrence-free interval, or PS at time of recurrence, rather than with the biologically aggressive characteristics of lung cancer.

Previous studies have demonstrated the survival benefit of PRT in stage I NSCLC patients. Nakagawa et al. and Hung et al. demonstrated that patients with stage I

NSCLC treated either surgically or non-surgically had a significantly better PRS than those with supportive care alone.[2-4] In our study, PRT provided a more favorable PRS than that of no treatment, similarly to previous reports. However, the results of PRS in the patients who underwent any PRT showed that surgical resection was not related to a favorable outcome. This may have been because the number of patients who received surgery for recurrent disease was too small to provide any supportive data in terms of survival benefit. However, in cases of surgical resection for recurrent lung metastasis, objective evidence supporting the role of surgery is limited because it may be difficult to distinguish second primary tumors from recurrent pulmonary metastasis. Advances in genomic analysis, molecular biological tools, or diagnostic imaging may enable more accurate diagnosis of a solitary pulmonary lesion.

Among the cohort of 118 patients with any PRT, we identified 5 independent favorable prognostic factors of PRS by multivariate analysis: the absence of bone or liver metastasis, chemotherapy, EGFR-TKI therapy, and non-adenocarcinoma. Moreover, the result of the study showed an important aspect of a prognostic-factor based risk stratification. Median PRS times of 42.4 months for the patients lacking all 5 factors and 18.8 months for the patients with one of these risk factors ($p = 0.001$).

Some authors have found that the site of initial recurrence was a prognostic factor

for PRS, which agrees with the current study. Yoshino et al. demonstrated that bone metastasis was a marginally prognostic factor for PRS in stage I-III patients at the first resection.[8] Assessment of bone metastatic type, osteoblastic or osteolytic, may be important as a part of postrecurrence therapeutic strategy because it has been noted that osteoblastic tumors would have lead to both a better prognosis and activating *EGFR* mutation presence.[37]

Major advances in NSCLC management have resulted from the understanding of molecular biology, development of molecule-targeting agents, and identification of biomarkers for targeted treatment. Since 2002, gefitinib has been used in Japan for the treatment of inoperable or recurrent NSCLC, and we started to administer it around the same period. It is now felt that EGFR-TKIs can improve the survival of some previously treated and untreated advanced NSCLC patients, with the overall benefit being driven primarily by the subgroup with *EGFR* mutations.[15-17,38,39] EGFR-TKIs have also improved endurance and health-related quality of life compared with platinum-based doublet chemotherapy.[15-17] EGFR-TKIs are therefore good candidates for first-line PRT in resected adenocarcinoma patients with distant metastases, but only in those with *EGFR* mutations.

There are several limitations in the present study. This study is retrospective, and

bias may exist. First, patient selection bias regarding PRT was unavoidable. Curative intent therapy or systematic treatment is difficult to perform in patients with poor PS. In the current study, PS or comorbidities at the time of recurrence was not accurately evaluated. Second, distinguishing second primary tumors from recurrent pulmonary metastasis was difficult. Even if a pathologic specimen was obtained, definitive diagnosis could be difficult under the current morphology-based diagnostic criteria. Third, complete follow-up was not available for all eligible patients.

There are presently no clinical guidelines for PRT regarding resected NSCLC based on large-scale prospective studies. Molecularly-targeted therapy, chemotherapeutic regimens, and surgical strategies have evolved substantially over the decades. A challenge for the future will be to create systematic treatment strategies for recurrent NSCLC, according to the individual patient's recurrent disease characteristics, including the initial recurrence site, age, gender, PS, or recurrence-free interval, and original tumor characteristics.

Conclusion

This study showed that male gender, the absence of PRT, and poorly-differentiated carcinoma were independent unfavorable prognostic factors of PRS in resected stage I

NSCLC patients. Moreover, in patients who underwent any PRT, receiving EGFR-TKIs and chemotherapy, absence of liver or bone metastasis, and non-adenocarcinoma had a statistically significant association with favorable PRS. Further clinical studies may give more accurate information about the benefits of PRT for survival, and lead to the improvement of clinical assessment and therapeutic strategies in recurrent NSCLC.

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Author contributions

Dr Shimada: contributed to the design and coordination of the study, prepared the manuscript, and read and approved the final manuscript.

Dr Ikeda: contributed to the design and coordination of the study, revised the article for important intellectual content, and read and approved the final manuscript.

Dr Saji: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Yoshida: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Kakihana: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Honda: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Nomura: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Usuda: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Kajiwara: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Ohira: contributed to preparing the manuscript, and read and approved the final manuscript.

Figure legends

Figure 1

Postrecurrence survival curve of patients with recurrence

Figure 2

Postrecurrence survival curves of the patients lacking all 5 unfavorable factors (not receiving EGFR-TKI therapy and chemotherapy, liver or bone metastasis positive, non-adenocarcinoma) (A), and the patients with one of the risk factors (B)

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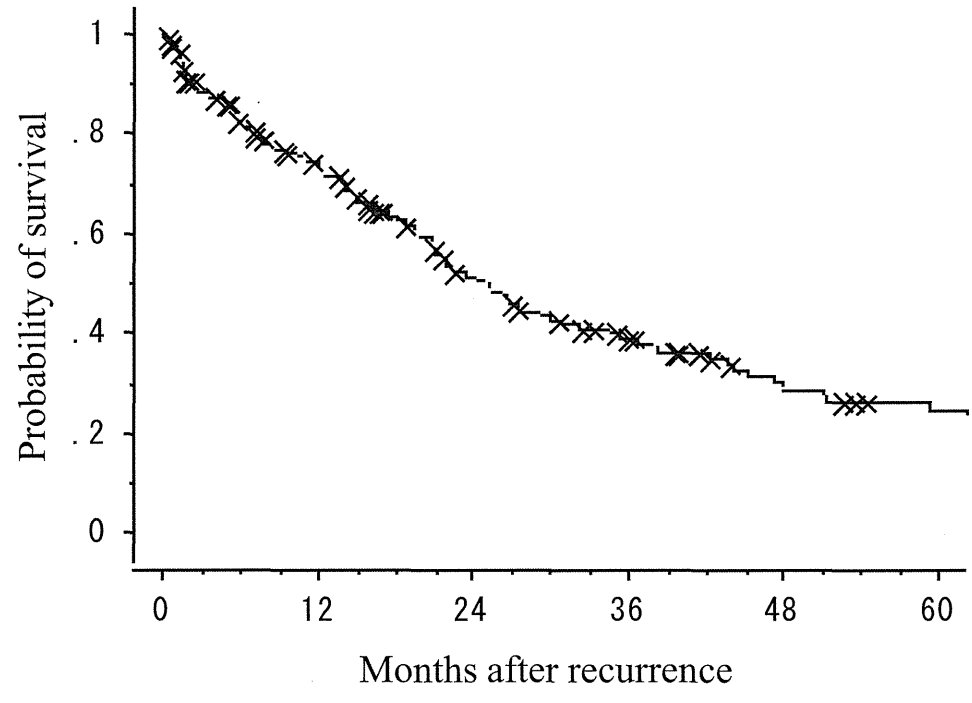
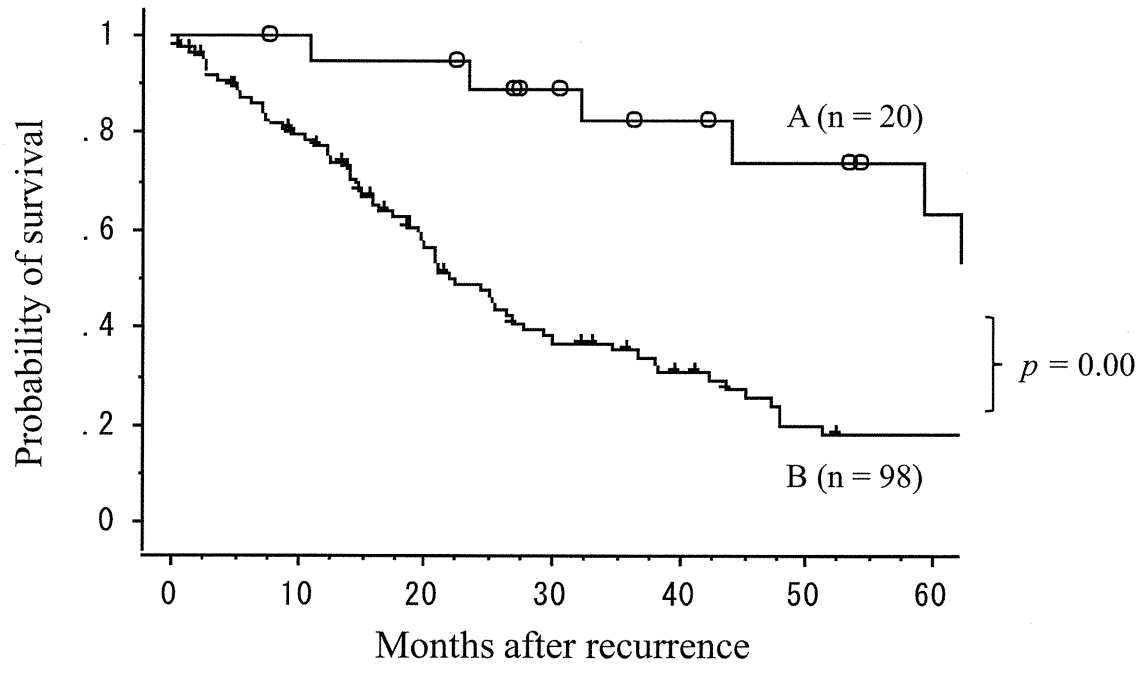
Figure 1



Patients at risk of death (n = 170)

170	109	65	42	25	19

Figure 2



Patients at risk of death (n = 118)

A	20	18	16	12	9	6
B	98	67	37	24	11	9

A: The patients lacking all 5 unfavorable factors (not receiving EGFR-TKIs and chemotherapy, presence of liver or bone metastasis, non-adenocarcinoma)
B: The patients with one of the above mentioned risk factors

Table 1
Patient characteristics, and univariate and multivariate analyses of recurrence

Factors	Univariate analysis			Multivariate analysis		
	Number	5-y RFP (%)	*p*-value	HR	95% CI	*p*-value
Age (years; median 65)						
< 65	439	84.1				
≥ 65	480	80.4	0.129			
Gender						
Male	542	78.0				
Female	377	87.8	< 0.001			
Smoking status						
Never smoker	347	85.2	0.134			
Ever smoker	572	80.2				
T category						
T1	512	84.7				
T2	407	78.9	0.100			
Tumor size						
0-30 mm	663	84.0				
> 30 mm	256	81.5	0.112			
Pathological vascular invasion						
Absent	481	91.0		1		
Present	421	72.1	< 0.001	2.306	1.621-3.280	< 0.001
Pleural invasion						
Absent	719	84.9		1		
Present	191	71.8	< 0.001	1.489	1.048-2.115	0.026
Histology						
Adenocarcinoma	706	83.8				
Nonadenocarcinoma	213	76.3	0.039			
Differentiation						
Well or moderate	656	86.7		1		
Poor	216	67.7	< 0.001	1.842	1.328-2.555	< 0.001
Type of surgery						
Single lobectomy	873	81.9				

Bilobectomy or pneumonectomy	46	87.2	0.942

5y-RFP: 5 year recurrence-free proportion, HR: hazard ratio, CI: confidence interval

Table 2
Initial recurrence site and postrecurrence therapy

	Number	
Overall	170	
Type of recurrence		
Distant	113	
Local	43	
Both	14	
Initial recurrence site		
Ipsilateral lung	23	
Contralateral/Bilateral lung	43	
Regional lymph nodes	37	
Malignant effusion/dissemination	13	
Stump	9	
Brain	30	
Bone	21	
Liver	16	
Adrenal gland	10	
Others	14	
Postrecurrence therapy		
Initial therapy		
Surgery	8	(lung 3, brain 3, adrenal gland 1, lymph nodes 1)
Surgery alone	6	
Surgery + CT	3	
CT	79	
RT	10	
CRT	21	
None	41	
Unknown	11	
Second-line or the subsequent therapy	66	
CT	58	
EGFR-TKIs	27 (gefitinib 22/erlotinib 3/both 2)	
EGFR mutation status/histology	positive	12 (Ad 11/Sq 1)

	wild	4 (Ad 3/LCC 1)
	unknown	11 (Ad 10/LCC 1)
Others		7

CT: chemotherapy, RT: radiation therapy, CRT: chemoradiotherapy, EGFR-TKIs: epidermal growth factor receptor-tyrosine kinase inhibitors, Ad: adenocarcinoma, Sq: squamous cell carcinoma, LCC: large cell carcinoma