The adjuvant chemotherapy can be omitted for lepidic predominant lung adenocarcinoma in stage IB of the 8th TNM staging system.

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Research article

Keywords: lung cancer, Adenocarcinoma predominant, adjuvant chemotherapy, stage IB, 8th UICC

Posted Date: January 27th, 2020

DOI: https://doi.org/10.21203/rs.2.21919/v1

Abstract

Objectives

This study was designed to investigate whether the outcomes of adjuvant chemotherapy are affected by the lung adenocarcinoma predominant (AP) in stage IB according to the 8th UICC staging system.

Methods

From 2008 through 2015, 293 patients with pathological stage IB who were ≤ 75-year-old and underwent lobectomy were studied. The relations of clinicopathological factors were investigated by propensity score matching.

Results

The median follow-up period was 66.0 months. The cases of AP were followed: lepidic 96, acinar 71, papillary 54, solid 45, micropapillary 3 and others 17. Adjuvant chemotherapy with UFT was performed in 70 cases (23.9%). Recurrence-free survival at 5 years (RFS) was 72.2%. Lymph vessel invasion (ly+), vascular vessel invasion (v+), pleural invasion (pl+) and non-lepidic statistically affected RFS. Multivariate analysis showed that only AP (non-lepidic) was significant (hazard ratio; HR=2.006 (1.104-3.644)). Overall survival (OS) rate at 5 years was 83.5%. ly+, v+, pl+, EGFR mutation status and AP affected OS. In multivariate analysis, only non-lepidic was left (HR=2.888 (1.231 - 6.774)). After matching AP, adjuvant chemotherapy did not have an impact on RFS or OS (p=0.992, 0.616). In lepidic, both adjuvant and non-adjuvant had excellent outcomes in RFS (84.8% and 92.9%, p=0.574) and OS (100% vs 100%, p=0.361). In non-lepidic group, adjuvant therapy tended to show slightly, but not significantly better RFS (71.5% vs, 60.6%, p=0.177).

Conclusion

Lepidic predominant showed excellent outcomes, adjuvant chemotherapy is not necessary. For non-lepidic predominant, UFT remains standard adjuvant chemotherapy in Japan.

Introduction

Several prospective clinical trials have reported that adjuvant chemotherapy is effective in patients with locally advanced ≥ stage II non-small cell lung cancer (NSCLC) [1–5]. Basically, a combination of two agents including a platinum-based drug is standard treatment and can be expected to improve the 5-year survival rate by approximately 5% [1–5]. However, in earlier stage NSCLC, the role of adjuvant chemotherapy remains unclear. The Cancer and Leukemia Group B (CALGB) 9633 trial initially showed a survival advantage in patients with T2N0 NSCLC, but this advantage disappeared after prolonged follow-up [6–8]. While other prospective clinical trials did not support the effect of adjuvant chemotherapy in patients with stage I NSCLC [2–4] in Japan, treatment with oral UFT (a combination of uracil and tegafur) improved the overall survival rate, especially in patients who had stage IB adenocarcinoma [9, 10].

Improvement of the survival rate by 10% at 5 years postoperatively was reported, and a meta-analysis assessing treatment with adjuvant UFT supported this result [11]. Consequently, in Japan, adjuvant chemotherapy with UFT became a standard treatment for IB stage lung adenocarcinoma after complete resection. However, these clinical trials were performed 20 years ago, and the 1986 classification of the American Joint Committee on Cancer was used [9–11]. Now, the Union for International Cancer Control (UICC) staging system has been updated to the 8th edition. The newer staging system more accurately reflects outcomes than the previous system. However, changing the definition of staging has caused much confusion, and the question arose whether we should use guidelines established on the basis of clinical trials using the old staging system. The usefulness of adjuvant chemotherapy with UFT has not been verified in clinical trials using the current staging system.

On the other hand, a new classification of lung adenocarcinoma has been proposed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) [12]. Adenocarcinoma is classified into seven categories according to the predominant histology. Even when the study group was limited to patients with stage IB disease, the adenocarcinoma subtype was reported to be an independent prognostic factor [13]. However, few studies have investigated the relation between adenocarcinoma predominant and the response to adjuvant therapy in patients with stage IB disease [14]. The impact of adjuvant treatment on each subtype remains unclear. In these prospective trials, the age of patients was limited to ≤ 75 years [2, 3, 9, 10]. Therefore, from these backgrounds, we used propensity-score matching to assemble a cohort of patients who were ≤ 75 years of age and had completely resected stage IB adenocarcinoma predominant of the lung according to the current staging system to evaluate the effect of adjuvant chemotherapy in such patients.

Material And Methods

The institutional review boards at Kanagawa Cancer Center approved this retrospective study and waived the requirement for obtaining informed consent from individual patients. From 2008 through 2015, a total of 293 patients underwent lobectomy with mediastinal lymph node dissection and had a diagnosis of p-stage IB lung adenocarcinoma according to the 8th UICC staging system. At the time of surgery, their age was 75 or less. We examined the relations of recurrence and outcomes to clinical pathologic factors including postoperative adjuvant therapy (UFT for at least 6 months). Histological subtyping was performed to evaluate the proportion of each histological subtype in 5% increments and to identify the predominant subtype according to the new IASLC/ATS/ERS adenocarcinoma classification [12]. We excluded patients who underwent incomplete resection, had postoperative complications above grade IIIb according to the JCOG-Clavien-Dindo classification, or who received induction therapy with unknown or adjuvant regimens other than UFT.

Patient follow-up

All patients were followed up during 5 years after surgery. Physical examinations and chest radiography were done every 3 months, and chest and abdominal computed tomographic (CT) scanning was done

every 6 months. Subsequently after initial 2 years, physical examinations and chest radiography were done every 6 months, with annual chest and abdominal CT scanning. If recurrence was suspected on the basis of symptoms, additional MRI or PET scanning was performed. Detection of an apparent site of recurrence was designated as the time of recurrence.

Statistical analysis

Overall survival was defined as the interval from surgery to death from any cause. All alive patients were censored at last visit. Recurrence-free survival was defined as the interval from surgery to the time of first recurrence or death. For the patients who were alive, data on recurrence-free survival were censored at the last visit.

The data were analyzed by the Kaplan-Meier method and compared by the log-rank test. Clinicopathological data were evaluated by univariate analysis. Frequencies were compared using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Multivariate analysis was performed with a Cox proportional-hazards regression model. Results are summarized as hazard ratios (instantaneous relative risk) with 95% confidence intervals (C.I.). The hazard ratio represents the relative increase (or decrease if <1) in the risk of recurrence. After variables were identified to be prognostic factors, propensity score matching was done with a match tolerance of 0.3 to examine the effect of adjuvant chemotherapy.

All statistical analyses were performed with the use of IBM SPSS Statistics 23 software (IBM, New York, USA). P values of less than 0.05 were considered to indicate statistical significance.

Results

The background characteristics of the 293 patients are shown in Table 1. The median postoperative follow-up period was 66.0 months. About the half of the patients were women (46.1%), and about 60% were smokers. The median age at the time of surgery was 64.9 years. As for the adenocarcinoma subtype, lepidic predominant was most common (103 patients, 35.2%). Acinar subtype (71 patients, 24.2%) and papillary predominant subtype (54 patients, 18.4%) were less frequent than lepidic subtype. Solid predominant subtype was scarce, (45 patients, 15.4%) and micropapillary predominant subtype was very rare (3 patients, 1.0%). Epidermal growth factor receptor (EGFR) mutation status was analyzed in 84 patients (28.7%), and 39 patients (46.4%) were mutation positive. Treatment with UFT was started in 100 patients (34.1%). However, 30 patients discontinued treatment because of adverse effects. A total of 70 patients (23.9%) received UFT for 6 months or longer.

The recurrence-free survival rate at 5 years in the study group as a whole was 72.2%. Table 1 shows clinicopathological factors that may affect recurrence. The presence of lymphatic vessel invasion, vascular invasion and pleural invasion had influence on recurrence. Figure 1 shows the recurrence-free survival curves according to the adenocarcinoma predominant subgroups. The subgroups seemed to be clearly separated according to the degree of malignancy ($p<0.001$). Hazard ratio for recurrence in each of

non-lepidic predominant group (papillary + acinar, solid + micropapillary and others) was statistically inferior than lepidic predominant (Table 2). The 103 cases of lepidic predominant had a recurrence-free survival rate of 88.0% at 5 years, which was significantly higher than the rate at 5years in the non-lepidic predominant group (62.9%, p<0.001). Among them, only 15 cases (14.6%) underwent adjuvant chemotherapy, each of RFS rate at 5 years were excellent and not statistically different (84.8% in adjuvant and 88.4% in no-adjuvant, p=0.841). In multivariate analysis the subjects which showed significance in RFS, only adenocarcinoma predominant was significantly related to recurrence-free survival (Hazard ratio 2.006 (95% confidential interval 1.104 – 3.644, p=0.022).

To examine the role of adjuvant chemotherapy, adenocarcinoma predominant was matched using propensity score matching. Seventy patients were extracted from each group (adjuvant therapy vs. no adjuvant therapy). Table 3 shows a comparison of each group after matching of the adenocarcinoma predominant subtype. There was no significant difference between the two groups. After matching, the adjuvant therapy showed no significant difference in RFS at 5 years (adjuvant 74.7% vs. no adjuvant 67.6%, p=0.247). In the lepidic predominant subgroup, the survival curves of adjuvant and no adjuvant therapy were 84.8 % and 92.9% at 5 years postoperatively (Figure 2A); they were almost overlapped. In the non-lepidic predominant subgroup, the difference was not significant: no adjuvant therapy tended to be associated with a higher recurrence rate; the difference at 5 years was nearly 10 percentage points (Figure 2B, 71.5% vs, 60.6%, p=0.177), but was not significant. This trend was similar in each non-lepidic predominant subgroup.

The overall survival rate at 5 years in the study group as a whole was 83.5%. Table 1 shows clinicopathological factors that may influence overall survival. The presence of lymphatic vessel invasion, vascular vessel invasion, pleural invasion, adenocarcinoma predominant, and EGFR mutation status were significant factors that influenced overall survival. Adjuvant chemotherapy again had no impact on overall survival. Figure 3 shows the overall survival curves in the adenocarcinoma predominant subgroups. Lepidic predominant showed excellent outcomes; the overall survival rate at 5 years was 96.9%, which was significantly better than that in non-lepidic predominant (75.4%, p=0.001). The survival curves of non-lepidic predominant nearly overlapped. In multivariate analysis, only adenocarcinoma predominant showed significance (hazard ratio 2.888; 95% C.I.: 1.231 - 6.774, p=0.015).

After matching adenocarcinoma predominant, adjuvant chemotherapy showed no significant difference in OS at 5 years (adjuvant chemotherapy 80.3% vs. no adjuvant chemotherapy 82.6%, p=0.843). The adenocarcinoma predominant group was divided in two subgroups: lepidic predominant and non-lepidic predominant. In lepidic predominant, the survival curves of adjuvant chemotherapy and no adjuvant chemotherapy were excellent (Figure 4A). In non-lepidic predominant, the survival curves nearly overlapped (Figure 4B, 74.7 % of adjuvant vs. 77.8 % of no adjuvant, p=0.177). This trend was similar in each non-lepidic predominant subgroup.

On the other hand, when focusing on survival in 35 patients with recurrence, EGRF mutation status was analyzed in 29 patients. The 5-year OS was 38.1% in wild type (N=15) and 85.7% in mutant (N=14); this

difference was statistically significant (p = 0.001). The hazard ratio of mutant type vs. wild type was 0.115 (95% C.I.: 0.025 - 0.535). Thirteen of 14 patients who had recurrence with EGFR mutations started to receive EGFR-tyrosine kinase inhibitors (EGFFR-TKI).

Discussion

This study was a retrospective analysis of 293 patients who had a histopathological diagnosis of stage IB lung adenocarcinoma predominant according to the 8th UICC staging system and underwent lobectomy. After a sufficient follow-up period of 66 months, the 5-year RFS was 78.0% and the 5-year OS was 83.5%. These outcomes were better than the results obtained by the Japanese Joint Committee of Lung Cancer Registry in 2004 (OS 73.9%) and 2010 (OS 76.7%) [15,16]. The outcomes of lung cancer treatment have been improving, but the main reason for the good results may be the selection of patients; the subjects were limited to patients who were ≤75 years of age at the time of surgery, and the procedure was limited to lobectomy. In this study, adenocarcinoma predominant of stage IB according to the latest edition of the staging system was an independent prognostic factor not only for RFS, but also for OS. To examine the role of adjuvant chemotherapy, adenocarcinoma predominant was matched using the propensity score-matching test. Overall, adjuvant chemotherapy was not associated with an effect on OS or RFS. However, when focusing on adenocarcinoma predominant, lepidic predominant showed excellent RFS and OS regardless of the presence or absence of adjuvant chemotherapy. Adjuvant chemotherapy is not necessary for this subgroup of patients. In other non-lepidic predominant subgroups, adjuvant chemotherapy tended to show slightly, but not significantly better RFS. A difference may not have been detected owing to the small number of patients. On the other hand, the OS curves overlapped in non-lepidic predominant, and there was no apparent difference. This may be related to the remarkable progress in systemic treatment including EGFR-TKI for EGFR mutant disease. When focusing on the outcomes of 35 patients with recurrence, the 5-year OS was significantly better in mutant disease mainly treated by EGFR-TKI. In advanced lung cancer, EGFFR-TKI showed a positive effect in improving survival in patients with EGFR-mutant disease [17,18]. Even after recurrence, patients can survive for a long period with effective treatment. Evidence showing that EGFR-TKI decreases the postoperative recurrence rate is still not available, and no other study has shown that adjuvant chemotherapy other than UFT is effective in stage IB lung cancer. Although the present study did not show a statistically significant decrease in recurrence, the tendency may be beneficial for patients even if it does not affect OS. UFT is relatively inexpensive (treatment with 400 mg/day of UFT costs 300 US dollars per month), and adverse reactions of grade ≥3 were reported in a few percent of patients [10]. Although the present study could not demonstrate a statistically significant advantage of adjuvant chemotherapy in patients with stage IB disease according to the current TNM staging system, the results of previous randomized clinical trials suggest that UFT administration cannot be omitted [9,10]. Thus, for non-lepidic predominant cases of stage IB lung cancer, adjuvant chemotherapy with UFT after complete resection remains a standard treatment in Japan.

On high resolution CT, lung adenocarcinoma is sometimes accompanied by ground glass opacity (GGO) around the tumor. GGO pathologically shows alveolar replacement growth, which corresponds to the lepidic component; it was considered a non-invasive part of lung cancer. The new, 8th UICC staging system was introduced in 2017 [19-21]. Lepidic component was omitted when the pathological tumor size was measured; only invasive size was set as the tumor size. This made it possible to predict outcomes more precisely than the previous edition of the staging system [19,21]Moreover, tumors with an invasion size of greater than 4 cm was was set at T2b, which is a higher stage than IB. These were large changes, and the population of stage IB in the 7^{th} staging system differed from that in the 8^{th} edition. When the 7^{th} edition of the staging system was launched in 2010, pleural invasion became a factor to upstage to IB. Before then, a small size tumor of ≤3 cm with pleural invasion was staged as IA. Of course, accurate prognostic information is an extremely important factor for developing a more appropriate treatment strategy. In this study, patients with pathological stage IB disease according to the 8th staging system were examined, and the most important prognostic factor was the adenocarcinoma predominance. In particular, lepidic predominant showed excellent outcomes. However, when adenocarcinoma predominant was grouped according to the malignant degree, the intermediate-grade group (lepidic + acinar + papillary) was reported to show fair outcomes [12,22]. However, the lepidic predominant group has also been reported to have better outcomes than other predominant groups in the intermediate-grade group [23-25]. A solid appearance tumor without GGO on high resolution computed tomography has been reported to have higher malignant potential than tumors with GGO [26]. Another study showed that the presence of small micropapillary components had a greater negative effect on outcomes than the absence of such components [27]. Tumors with high-grade fatal adenocarcinoma component, which is a rare subtype, have also been reported to have poor outcomes [28]. Further studies are needed to evaluate the impacts of adenocarcinoma predominant and subtype components on outcomes.

Clinical trials are conducted to develop better treatment strategies. The TNM staging system is fundamental to deciding a patient's treatment plans and predicting outcomes. However, when the TNM staging system is greatly updated, several problems may occur clinically. Especially, if it is difficult to interpret the results of past clinical trials using the new TNM staging system, serious problems might occur because the current standard therapy becomes unknown. In Japanese guidelines for lung cancer, adjuvant chemotherapy with UFT is standard treatment for pathological stage IB lung cancer. This is based on the results of clinical trials reported in the early 2000s. The staging system has been revised several times since these results were published. Of course, if new prognostic information becomes available or very effective new drugs are developed, standard therapy has to be updated. However, costly and laborious prospective clinical trials cannot be performed every time the staging system is updated. A retrospective analysis may be inferior to prospective trials in terms of the reliability and interpretation of the results because potential selection bias cannot be excluded. The propensity score-matching test is one effective statistical analysis technique that increases the accuracy of comparisons based on data gathered in the past [29]. By further developing statistical analysis techniques, more precise results are

likely to be obtained from randomized control trials. It will be important to gather wider and more detailed information when clinical trials are performed.

Limitations

This was a retrospective study, and potential bias can occur, even when propensity score matching is performed. The most common reasons why patients did not receive adjuvant chemotherapy were the TNM update and the patients' will. Before 2010, a small tumor size of ≤3.0 cm was staged as IA, regardless of pleural invasion status. In addition, adverse effects of UFT were the second reason to terminate treatment soon after it began, but there may be unclear reasons why many patients did not receive adjuvant therapy.

Conclusion

Even in 8th UICC staging system, lepidic predominant in stage IB adenocarcinoma showed excellent outcomes. Adjuvant therapy is not necessary for such cases. In patients with non-lepidic predominant disease, UFT remains the standard adjuvant treatment in Japan.

Declarations

Disclosure

The authors have declared no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

Table 1. Patients' characteristics and clinicopathological factors that may influence recurrence and overall survival.

	All cases	Recurrence			Overall survival		
		Recurrence	No recurrence	p value	Death (N=67)	Alive (N=226)	p value
Age (mean±SD)	64.9 years old	63.46±7.69	65.31±7.15	0.073	65.10±7.42	64.82±7.29	0.785
Sex	Male 158 / Female 135	M32/F32	M126/F100	0.457	M41/F26	M117/F109	0.073
Smoking history	155 (59.2%)	Yes 36 / No119	Yes 31 / No 104	0.558	Yes 40 / No26	Yes 115 / No109	0.070
Operation time (min,mean±SD)	195 minutes	186.4±72.50	198.1±131.4	0.293	200.2±76.89	194.0±130.8	0.629
Blood loss (g, mean±SD)	57.6 g	51.73±71.63	59.27±64.47	0.215	64.28±83.51	55.55±60.10	0.428
Lymphatic vessel invasion	59 (20.1%)	Yes 21 / No 46	Yes 38 / No 188	0.003	Yes 21 / No46	Yes 38 / No188	0.008
Vascular vessel invasion	123 (42.0%)	Yes 41 / No 26	Yes 82 / No 144	<0.001	Yes 41 / No26	Yes 82 / No144	<0.001
Pleural invasion	166 (56.7%)	Yes 48 / No19	Yes 118 / No 108	0.001	Yes 48 / No19	Yes 118 / No108	<0.001
Adenocarcinoma predominant	Lepid 103	11/35/15/6	92/90/33/11	<0.001	13/33/16/5		
	Aci 71 and Pap 54					90/92/32/12	0.003
	Solid 45 and MP 3						
	Others 17						
EGFR mutation	39 / 84 (46.4%)	Yes14 / No 15	Yes 25 / No 30	0.640	Yes 14 / No 5	Yes 31 / No 34	0.010
Adjuvant therapy	70 (23.8%)	Yes 16 / No 51	Yes 54 / No172	0.754	Yes 13 / No54	Yes 57 / No169	0.944

Lepid = lepidic predominant, Pap = papillary predominant, Aci = acinar predominant, MP = micropapillary predominant, Solid = solid predominant, SD = standard deviation

Table 2: Hazard ratio for recurrence in adenocarcinoma predominant

	Lepidic	Acinar + Papillary	Solid +Micropap	Others
Lepidic	1	2.739 (1.569-4.781, p<0.001)	1.878 (1.351-2.611, p<0.001)	1.636 (1.216-2.200, p=0.001)
Acinar + Papillary		1	1.307 (0.765-2.233), p=0.328	1.261 (0.846-1.879, p=0.254)
Solid +Micropap			1	1.132 (0.475-2.696, p=0.780)

Table 3. Comparison of each group after matching of adenocarcinoma subtypes

Variables	Adjuvant (N=70)	No adjuvant (N=70)	p value
Age (mean±SD)	63.70±7.71	61.36±7.08	0.063
Sex	M43/F27	M38/F32	0.494
Operation time (min, mean±SD)	178.0±61.51	217.0±226.0	0.178
Blood loss (g, mean±SD)	44.96±59.89	54.44±62.54	0.361
Lymphatic vessel invasion	Yes 18 / No 52	Yes 15 / No 55	0.691
Vascular vessel invasion	Yes 36 / No 34	Yes 32 / No 38	0.612
Pleural invasion	Yes 45 / No 25	Yes 51 / No19	0.363
Histological predominant Lepid vs. Pap + Aci + MP + Solid + Others	15 / 36+16+3	15/ 36+16+3	1.000
EGFR mutation	Yes 15 / No 18	Yes 11 / No 9	0.577

Lepid = lepidic predominant, Pap = papillary predominant, Aci = acinar predominant, MP = Micropapillary predominant, Solid = solid predominant, SD = standard deviation

Figures

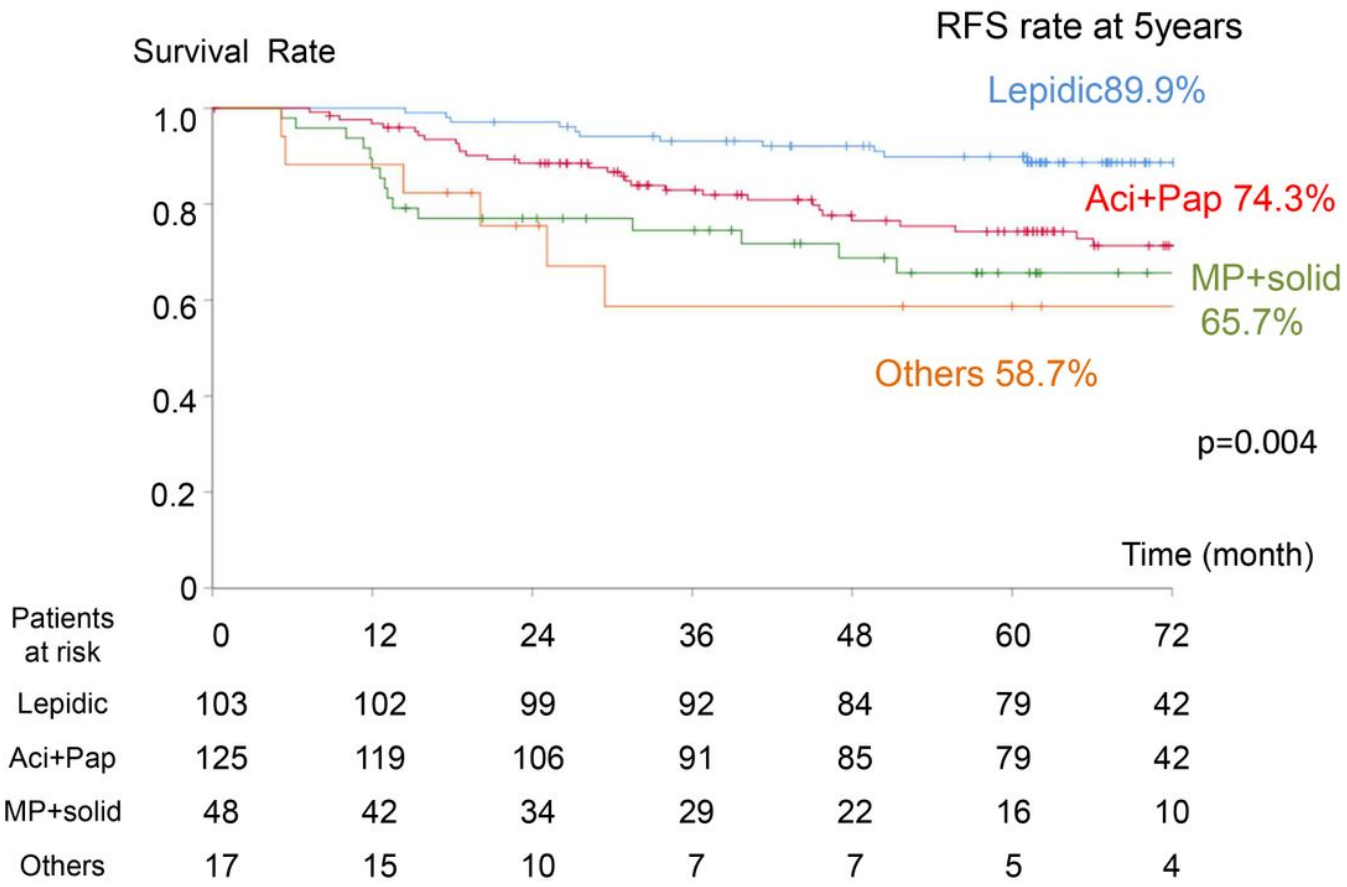


Figure 2

Recurrence-free survival curves of each adenocarcinoma predominant group

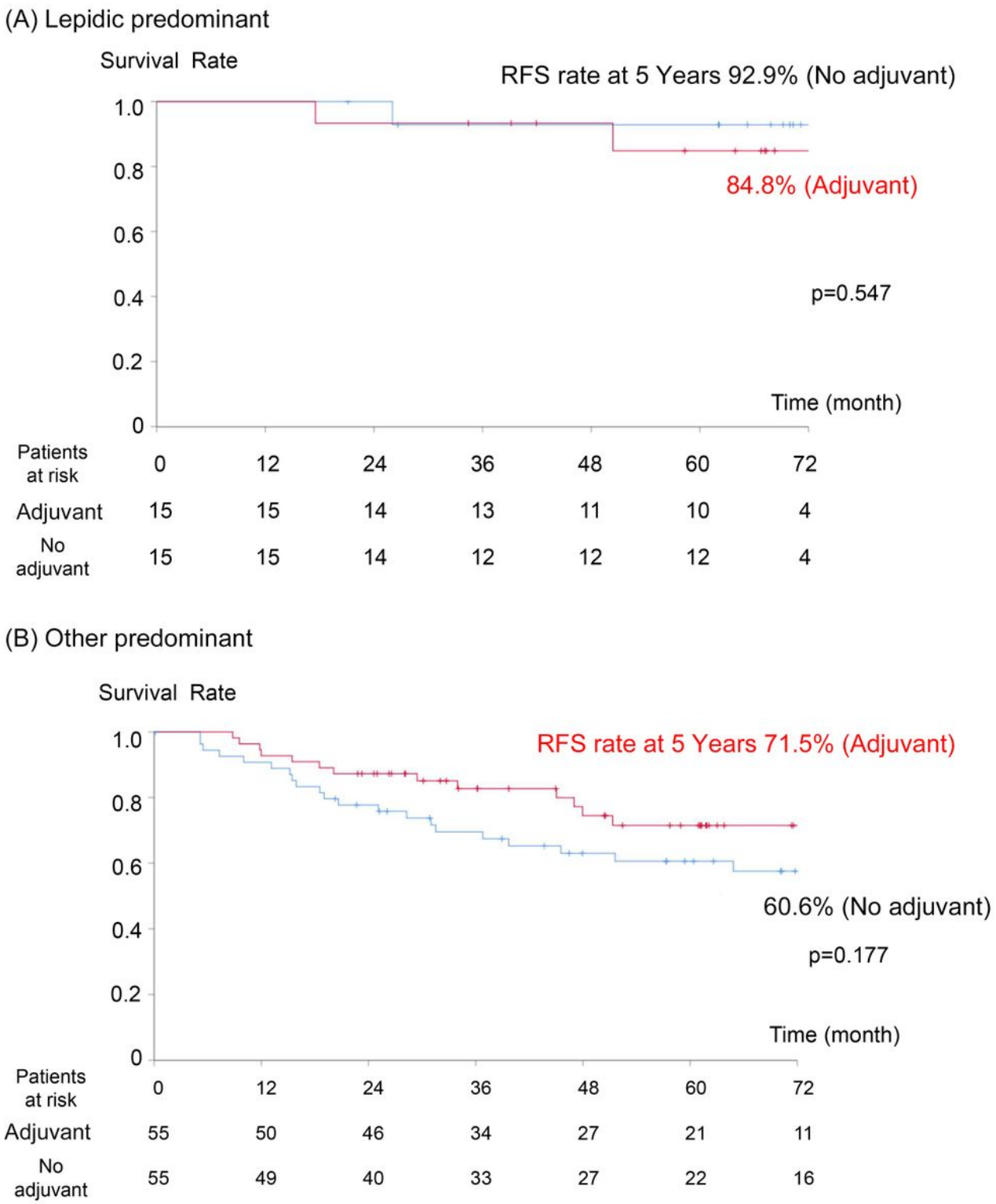
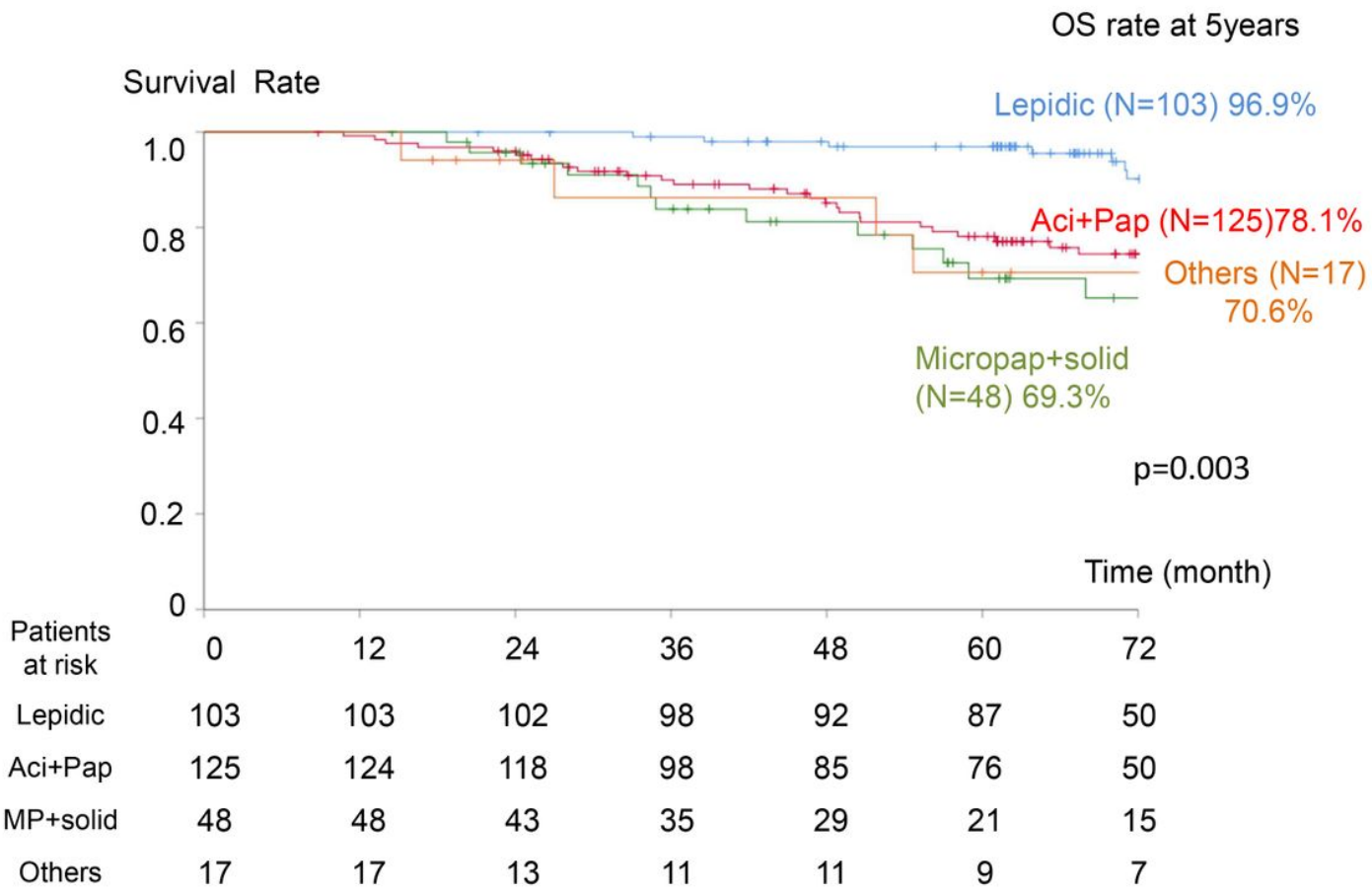


Figure 3

Among matched cases, recurrence-free survival curves in lepidic predominant (A) and other predominant (B)



Patients at risk	0	12	24	36	48	60	72
Lepidic	103	103	102	98	92	87	50
Aci+Pap	125	124	118	98	85	76	50
MP+solid	48	48	43	35	29	21	15
Others	17	17	13	11	11	9	7

Figure 5

Overall survival curves of each adenocarcinoma predominant group.

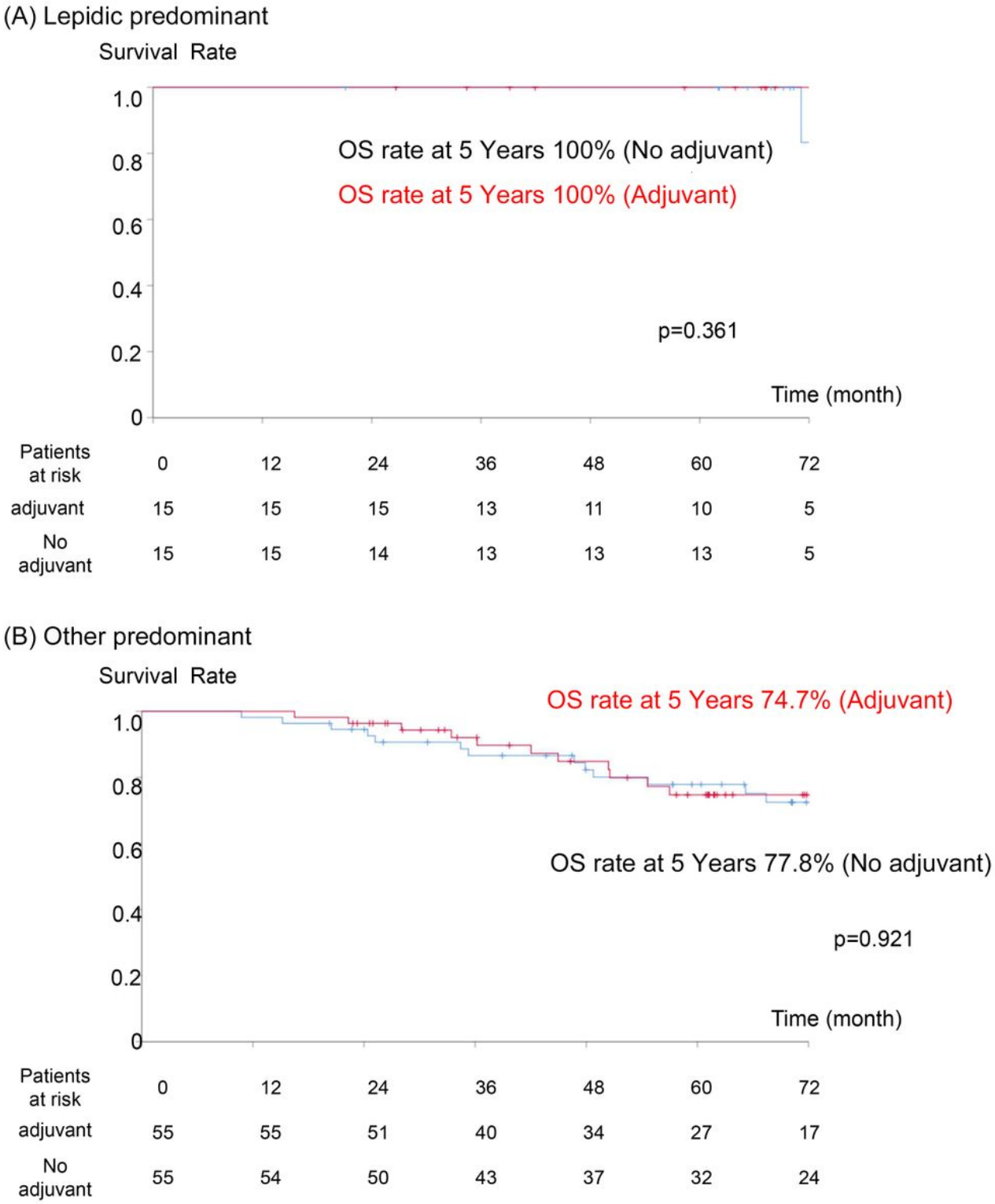


Figure 7

Overall survival curves in lepidic predominant (A) and other predominant (B).