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ORIGINAL ARTICLE

Impact of pathological stage and histological subtype on clinical outcome of adjuvant chemotherapy of paclitaxel plus carboplatin versus oral uracil–tegafur for non-small cell lung cancer: subanalysis of SLCG0401 trial

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Abstract

Background Pathological stage (pStage) and histological subtype are strong determinants of the treatment strategy for non-small cell lung cancer (NSCLC). Setouchi Lung Cancer study Group (SLCG) recently reported the results of a multicenter trial (SLCG0401) indicating that paclitaxel plus carboplatin (CBDCA/PTX) as adjuvant chemotherapy does not yield better survival than uracil–tegafur (UFT) in NSCLC patients with pStage IB–IIIA disease, while stratified analyses considering the pStage and histological subtype have not been performed.

Methods We reanalyzed the overall survival (OS) and relapse-free survival (RFS) in 402 patients who had been randomly assigned to receive CBDCA/PTX or UFT by multivariate analysis with adjustments for the pStage and histological subtype.

Results There were no significant differences in the OS or RFS between the two treatment settings either in the entire cohort ($n=402$) and in some of subsets: pStage IB ($n=228$), pStage II ($n=117$), adenocarcinoma (AD, $n=265$), and squamous cell carcinoma (SQ, $n=101$). In pStage IIIA patients ($n=57$), CBDCA/PTX yielded superior RFS to UFT [hazard ratio (HR) 0.44; $P=0.016$]. Among the patients with non-AD and non-SQ histology ($n=36$), UFT yielded both superior OS and RFS to CBDCA/PTX (HRs 0.16 and 0.23; $P=0.046$ and 0.011, respectively).

Conclusions There are subsets of patients in which one or the other between UFT and CBDCA/PTX is significantly more effective. Selection of adjuvant therapy for NSCLC patients needs to be made taking into consideration the pStage and histological subtype.

Keywords Non-small cell lung cancer · Paclitaxel · Carboplatin · Uracil–tegafur · Adjuvant chemotherapy

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1] as well as in Japan. For patients with non-small cell lung cancer (NSCLC), primary surgery is usually selected for the limited disease, but adjuvant chemotherapy is needed for the patients with advanced stage disease, even if complete resection has been performed.

The Setouchi Lung Cancer study Group (SLCG) has launched an open-label multi-institutional, prospective randomized controlled trial (SLCG0401) to investigate the survival benefit of four cycles of intravenous administration of paclitaxel plus carboplatin versus 2 year daily oral administration of uracil–tegafur (UFT), a combination of the antimetabolite tegafur (a fluorouracil prodrug) with uracil at a 1:4 molar ratio, administered as adjuvant chemotherapy in patients with resected pathological stage (pStage) IB–IIIA NSCLC [2]. This study was started in 2004, before the publication of an important meta-analysis of adjuvant therapy [3] that deeply influenced several current guidelines on adjuvant therapy for NSCLC. The final results of SLCG0401 published recently indicate that four cycles of paclitaxel plus carboplatin do not yield better survival than UFT monotherapy, and that the toxicity of UFT is milder as compared to that of paclitaxel plus carboplatin treatment, even though both treatments are feasible [2].

Pathological stage and histological subtype are significant determinants of the treatment strategy in patients with NSCLC. The combination of platinum and a 3rd-generation anticancer agent is, in general, considered to have a stronger anticancer effect than UFT in patients with advanced stage NSCLC [4, 5]. On the other hand, cisplatin-based regimens are not recommended as adjuvant therapy for patients with early-stage (pStage I) NSCLC, except the subset of patients with pStage IB disease with high-risk factors, because postoperative chemotherapy in this population was associated with a worse clinical outcome [6, 7]. By contrast, UFT treatment is recommended as adjuvant therapy for early-stage [stage IB or stage IA (maximum tumor diameter 2 cm or greater)] adenocarcinoma (AD), but not non-AD, patients in Japan [8-10]. Furthermore, clinical practice guidelines for NSCLC in western countries [11], including the NCCN guideline (https://www.nccn.org/professionals/), recommends selecting the chemotherapy regimen for metastatic disease based on the histological subtype. However, the clinical practice guidelines mentioned above do not yet recommend selection of the adjuvant chemotherapy regimen based on the pStage or histological subtype.

Under the aforementioned circumstances, we conducted a stratified multivariate analysis of the SLCG0401 data to identify the determinations of survival, focusing on the pStage and histological subtype in the NSCLC patients with resected pStage IB–IIIA disease who received either paclitaxel plus carboplatin or UFT.

Patients and methods

Patients

In this subanalysis, we evaluated the survival benefit in the entire cohort ($n = 402$) of the previous study entitled SLCG0401 (UMIN000000810) [2], considering adjustment factors such as the pStage and histological subtype. The pStage that had been registered for this study was used for the intention-to-treat (ITT) analysis, even though the edition of the UICC TNM staging system had been updated from the 6th edition [12] to the 7th edition [13] during the study period in 2009. The details of the main inclusion and exclusion criteria have been described previously [2].

Study design and treatment

In this open-label multi-institutional, prospective randomized controlled trial, eligible patients from 40 hospitals and institutes have been randomly assigned to receive either paclitaxel plus carboplatin (Arm A) or UFT (Arm B) at a 1:1 ratio with computer-generated random numbers using the following stratification factors: institution, histological subtype [adenocarcinoma (AD) versus others], and pStage (IB/II/IIIA). Adjuvant treatments in both Arms had been started within 6 weeks after surgery. In Arm A, the patients had received four cycles of a 3-h infusion of paclitaxel (175 mg/m^2) followed by a 1-h infusion of carboplatin (AUC 5) on day 1 of every 3-week cycle. In Arm B, the patients received oral UFT twice or thrice daily every day for 2 years. The dose of UFT was 300 mg/body/day in subjects with a body surface area of < 1.40 m^2, 400 mg/body/day in subjects with a body surface area of 1.40–1.80 m^2, and 500 mg/body/day in subjects with a body surface area of > 1.80. Details of the criteria for discontinuation, entry, and dose modification method of the protocol treatments have been described previously [2].

Follow-up

Patient's evaluations during and after the protocol treatments have been described previously [2]. Additional examinations such as CT, MRI, bone scintigraphy, and abdominal ultrasonography, had been performed whenever the disease relapse had been suspected.

Ethics

The protocol of the original study had been approved by the institutional review boards of every participating institution. Written informed consent had been obtained prior to enrollment in the original study from all patients by each investigator at each participating institute. The protocol of this subanalysis was also approved by the Ethics Committee of Okayama University (Ken 1807–034).

Outcome

The 5-year overall survival (OS) and relapse-free survival (RFS) rates were investigated by ITT analysis in this study. Disease relapse was defined as the presence of new lesions detected by image inspections or by palpitation of enlarged lymph nodes. Elevation of the levels of any blood tumor markers alone or subjective complaints by the patient himself was not regarded as disease relapse.

Statistical analysis

For survival analysis, we applied the Kaplan–Meier method, with comparison by the log-rank test and analysis using the Cox proportional hazards model.

Statistical significance was defined as $P < 0.05$. All the statistical analyses were performed using JMP 9.0.2 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA) and GraphPad Prism 5 (La Jolla, CA, USA).

Results

Patient characteristics

Between November 2004 and November 2010, 402 patients had been enrolled in the original study in Japan. The basic characteristics of all 402 patients are shown in Table 1. The median age of the 402 participants was 67 years (range 44–82). Of the 402, 260 patients were male, and 300 patients had a performance status (PS) of 0. The histological subtype was classified as AD ($n = 265$), squamous cell carcinoma

Table 1 Clinicopathological factors

Variables		Total		CBDCA/PTX		UFT	
		n	%	*n*	%	*n*	%
Arm	CBDCA/PTX (Arm A)	201	50.0	201	100.0	–	–
	UFT (Arm B)	201	50.0	–	–	201	100.0
Age (y.o.)	>67	200	49.8	109	54.2	91	45.3
	≤67	202	50.2	92	45.8	110	54.7
Sex	Male	260	64.7	131	65.2	129	64.2
	Female	142	35.3	70	34.8	72	35.8
Smoking*	Never	125	31.1	60	30.0	65	32.3
	Ever	276	68.7	140	70.0	136	67.7
Performance status	0	300	74.6	149	74.1	151	75.1
	1/2	102	25.4	52	25.9	50	24.9
Histology	AD	265	65.9	132	65.7	133	66.2
	SQ	101	25.1	46	22.9	55	27.4
	Non-AD/SQ						
	All	36	9.0	23	11.4	13	6.5
	ADSQ	18	4.5	13	6.5	5	2.5
	LCC	7	1.7	3	1.5	4	2.0
	LCNEC	3	0.7	3	1.5	0	0.0
	Pleomorphic	6	1.5	4	2.0	2	1.0
	Giant	2	0.5	0	0.0	2	1.0
pStage	IB	228	56.7	114	56.7	114	56.7
	II	117	29.1	58	28.9	59	29.4
	IIIA	57	14.2	29	14.4	28	13.9

CBDCA/PTX paclitaxel plus carboplatin, *UFT* uracil–tegafur, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *ADSQ* adenosquamous carcinoma, *LCC* large cell carcinoma, *LCNEC* large cell neuroendocrine carcinoma, *Pleomorphic* pleomorphic carcinoma, *Giant* giant cell carcinoma, *pStage* pathological stage, * including a patient without information

(SQ, $n=101$), or other histological subtype (non-AD/SQ, $n=36$). There were 228 subjects with pStage IB disease, 117 with pStage II disease, and 57 with pStage IIIA disease.

Univariate and multivariate analyses of survival without stratification

In the overall study cohort, younger patients, patients with PS 0, and patients with pStage IB disease showed superior OS as compared to older patients, patients with PS 1/2, and patients with each pStage II or IIIA disease, respectively (Fig. 1 and Supplemental Table 1). The RFS in younger patients and pStage IB patients was also superior to that in older patients and patients with pStage II or IIIA disease, respectively. However, there was no significant difference in either the OS or RFS between the two treatment settings, as we have previously reported [2].

Impact of two treatment arms on survival stratified by each clinicopathological factor

Subgroup analyses of survival were performed after stratification by each clinicopathological factor between two treatment arms (Fig. 2). Among patients with non-AD/SQ, UFT treatment showed superior OS and RFS as compared to CBDCA/PTX treatment ($P=0.0036$ and 0.015, respectively). Among pStage IIIA patients, CBDCA/PTX treatment showed superior RFS to UFT treatment ($P=0.018$).

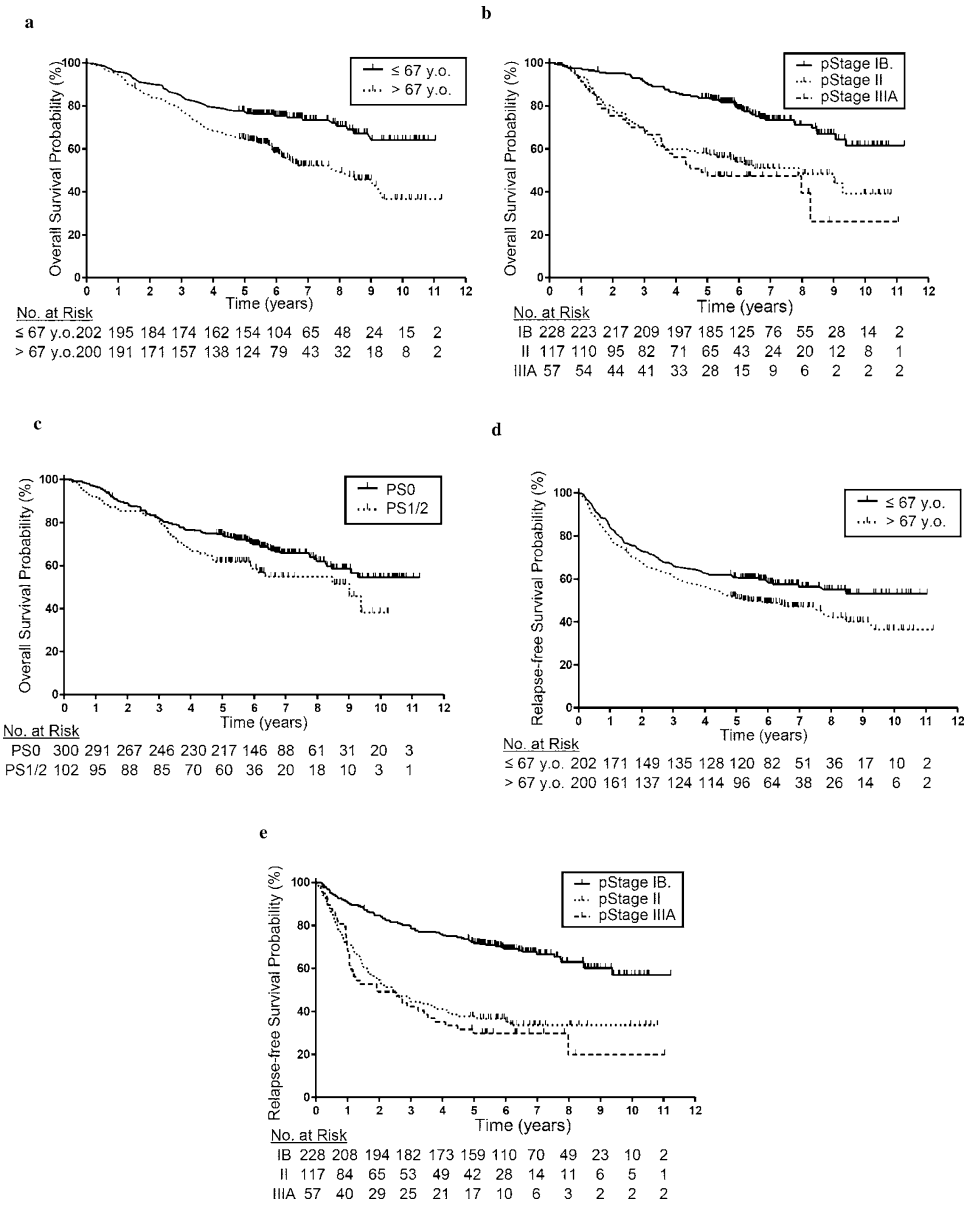

Fig. 1 Kaplan–Meier curves in the overall study cohort. The Kaplan–Meier curves in the overall study cohort are shown. Statistically significant differences are observed in all presented curves: overall survival (**a**–**c**) and relapse-free survival (**d**, **e**)

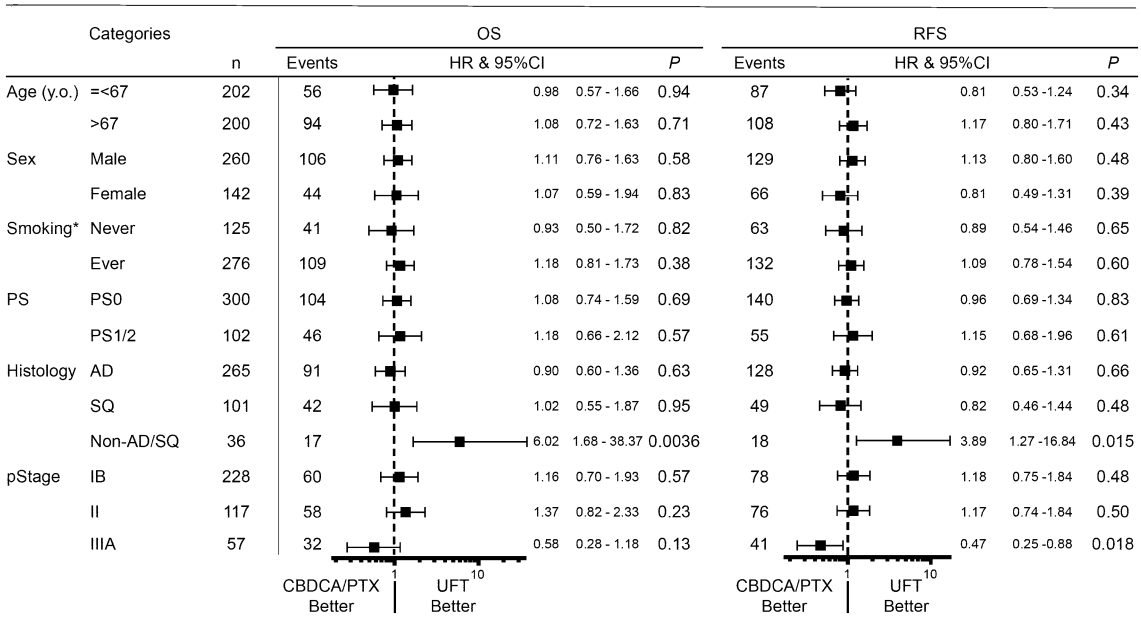

Fig. 2 Hazard ratios of overall survival and relapse-free survival with two treatment arms by baseline patient characteristic. *OS* overall survival, *RFS* relapse-free survival, *HR* hazard ratio, *95% CI* 95% confidential interval, *PS* performance status, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *pStage* pathological stage, *CBDCA/PTX* paclitaxel plus carboplatin, *UFT* uracil–tegafur, * including a patient without information

Based on these findings, we performed multivariate analysis stratified by the pStage or the histological subtype.

Multivariate analysis of survival stratified by the pStage

Multivariate analyses using the Cox proportional hazards model was performed after stratification of the patients by the pStage (Table 2). Among the pStage IB patients, patients with AD, younger patients, and females showed superior OS to patients with non-AD/SQ histology [hazard ratio (HR) 0.38, $P=0.0077$], older patients (HR 0.40, $P=0.0008$), and males (HR 0.47, $P=0.022$), respectively, and younger patients showed superior RFS to older patients (HR 0.57, $P=0.018$). Among the pStage II patients, only younger patients showed superior OS to older patients (HR 0.52, $P=0.022$). Importantly, among the pStage IIIA patients, patients who had received paclitaxel plus carboplatin treatment and those with a non-AD/SQ histology showed superior RFS than those who had received UFT treatment (HR 0.44, $P=0.016$) and had AD histology (HR 0.15, $P=0.021$), respectively (Figs. 3a/b).

Multivariate analysis of survival stratified by the histological subtype

We also performed multivariate analyses after stratification of the subjects by the histological subtypes (Table 3). Among the patients with AD histology, patients who were younger, had PS 0, and pStage IB disease showed superior OS to patients who were older (HR 0.51, $P=0.0023$), had PS 1/2 (HR 0.63, $P=0.048$), and pStage II (HR 0.24, $P<0.0001$) or IIIA (HR 0.19, $P<0.0001$) disease, respectively. Only patients with pStage IB disease showed superior RFS to those with pStage of II (HR 0.27, $P<0.0001$) or IIIA (HR 0.20, $P<0.0001$) disease. Among the patients with SQ histology, patients who were younger and had pStage IB disease showed superior OS to patients who were older (HR 0.43, $P=0.0097$) and had pStage IIIA disease (HR 0.27, $P=0.0034$), respectively, and only patients with pStage IB disease showed superior RFS to those with pStage II (HR 0.44, $P=0.015$) or IIIA (HR 0.32, $P=0.0059$) disease. Of particular interest, among the patients with non-AD/SQ histological subtypes, only the UFT treatment showed both superior OS (HR 0.16, $P=0.0046$) and RFS (HR 0.23, $P=0.011$) as compared to the paclitaxel plus carboplatin treatment (Figs. 3c, d).

Delivery of chemotherapy and toxicity stratified by the pStage and the histological subtype

As we previously reported, 386 patients (190 in the CBDCA/PTX group and 196 in the UFT group) have been investigated for the delivery of chemotherapy and toxicity (Supplemental Table 2). There were no statistical difference of drug delivery and toxicity among each group stratified by the

Table 2 Multivariate analysis stratified by pathological stage

	Variables	pStage IB			pStage II			pStage IIIA		
		HR	*P*	95% CI	HR	*P*	95% CI	HR	*P*	95% CI
a) Overall survival										
Arm	CBDCA/PTX vs UFT	1.15	0.59	0.69–1.92	1.19	0.53	0.69–2.09	0.61	0.20	0.28–1.30
Histology	AD vs SQ	0.70	0.27	0.38–1.33	1.40	0.31	0.38–2.77	1.11	0.82	0.46–2.72
	AD vs non-AD/SQ	0.38	0.008	0.20–0.76	0.78	0.70	0.20–3.35	2.81	0.27	0.50–52.73
	SQ vs non-AD/SQ	0.54	0.11	0.26–1.14	0.56	0.41	0.26–2.52	2.54	0.34	0.43–48.18
Age	> 67 vs = < 67	2.47	0.001	1.43–4.48	1.84	0.032	1.43–3.24	1.62	0.20	0.77–3.45
Sex	M vs F	2.30	0.07	0.93–6.00	2.56	0.14	0.93–10.20	0.95	0.93	0.34–3.17
PS	0 vs 1–2	0.71	0.24	0.42–1.26	0.74	0.33	0.42–1.37	0.54	0.15	0.25–1.26
Smoking	Never vs ever	1.13	0.80	0.43–2.71	2.96	0.10	0.43–11.85	0.74	0.64	0.22–2.69
b) Relapse-free survival										
Arm	CBDCA/PTX vs UFT	1.18	0.46	0.76–1.86	1.26	0.35	0.78–2.04	0.43	0.014	0.21–0.85
Histology	AD vs SQ	0.90	0.70	0.51–1.61	1.15	0.63	0.66–2.08	1.85	0.13	0.83–4.31
	AD vs non-AD/SQ	0.53	0.054	0.29–1.01	1.05	0.94	0.36–4.47	6.76	0.020	1.28–124.86
	SQ vs non-AD/SQ	0.59	0.14	0.29–1.21	0.91	0.89	0.29–4.08	3.65	0.16	0.66–68.33
Age	> 67 vs = < 67	1.72	0.020	1.09–2.79	1.29	0.30	0.79–2.10	1.07	0.83	0.56–2.05
Sex	M vs F	1.92	0.08	0.93–4.07	2.47	0.11	0.84–8.02	1.02	0.98	0.36–3.59
PS	0 vs 1–2	0.83	0.45	0.51–1.37	0.95	0.86	0.57–1.67	0.68	0.31	0.34–1.45
Smoking	Never vs ever	1.38	0.40	0.65–2.85	4.26	0.009	1.40–13.94	0.79	0.70	0.25–2.91

CBDCA/PTX paclitaxel plus carboplatin (Arm A), *pStage* pathological stage, *HR*, hazard ratio, *95% CI* 95% confidential interval, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *non-AD/SQ* histology of non-AD and non-SQ, *M* male, *F* female, *PS* performance status

pStage and the histological subtype. However, UFT administration period tended to be short in pStage IIIA patients (14.3% for 2 years) compared with pStage IB (40.2%) or II (35.7%) patients, and 17 pStage IIIA (60.7%) patients experienced discontinuation of UFT treatment by relapse of disease while 19 pStage II (33.9%) patients and 13 pStage IB (11.6%) patients discontinued the UFT treatment by relapse of disease. In contrast, CBDCA/PTX administration was done similarly regardless of the stratification group.

Discussion

As a subanalysis of the SLCG0401 study, we performed multivariate analyses to evaluate the impact of the pStage and histological subtype on the survival. We found that (1) among patients with pStage IIIA disease, paclitaxel plus carboplatin treatment yielded superior RFS to UFT treatment, and (2) among patients with the non-AD/SQ histological subtypes, UFT treatment yielded both superior OS and RFS to paclitaxel plus carboplatin treatment. There was no significant difference in the OS and RFS between the two treatments in patients with any of the other disease stages or histology, except those mentioned above.

Cisplatin-based chemotherapy is a standard regimen for adjuvant chemotherapy in patients with completely resected stage II–IIIA NSCLC according to the clinical practice guidelines of western countries [7] and the Japanese Lung Cancer Society (JLCS) (https://www.haigan.gr.jp). In our study, the multivariate analysis showed that paclitaxel plus carboplatin treatment yielded superior RFS to UFT treatment in patients with pStage IIIA disease. Although paclitaxel plus carboplatin treatment is not cisplatin-based, our findings suggest that a more powerful approach for adjuvant treatment than UFT treatment may be required in patients with advanced pStage disease.

Two prospective trials of UFT have shown survival benefit of UFT treatment in NSCLC patients with stage I–III disease [8, 9]. Based on these findings and other evidences [10, 14], the clinical practice guideline of the JLCS promotes UFT treatment as an adjuvant chemotherapy for NSCLC patients with pStage IA (maximum tumor diameter size ≥ 2 cm)/IB patients with AD histology (Grade 1A recommendation). With regard to patients with non-AD histology, a meta-analysis by Hamada et al. [14] reported that the efficacy of UFT treatment was equivocal (HR 0.82 with 95% CI 0.57–1.19 for SQ; HR could not be defined for non-AD/SQ) in both patients with SQ ($n = 199$, 9.9%) and non-AD/SQ ($n = 21$, 1.0%) histology, resulting in UFT treatment for early pStage patients with non-AD histology being included as a grade 2C recommendation. Similarly, our study indicated that pStage IB patients with AD histology showed superior OS to those with a non-AD/SQ histology (HR 0.38, $P = 0.0077$), even though the pStage IB patients with AD

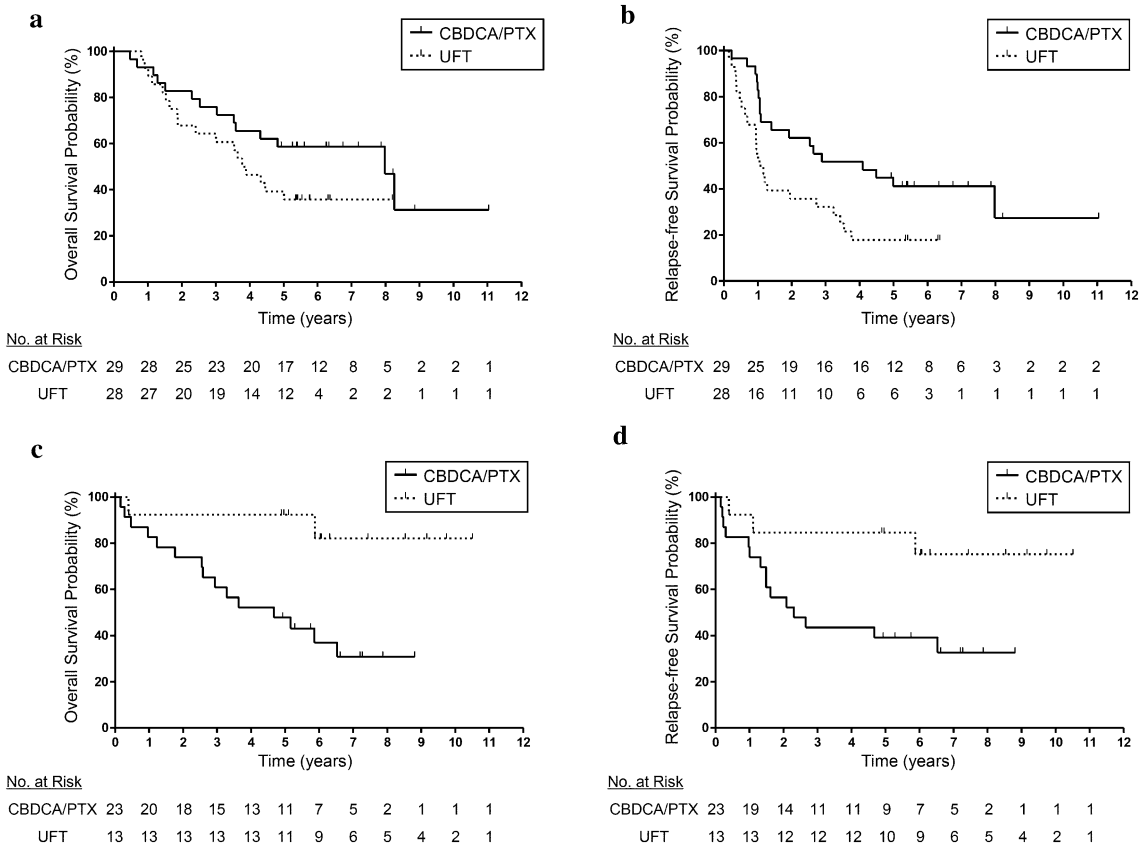

Fig. 3 Kaplan–Meier curves in patients with pathological stage IIIA disease and those with non-adenocarcinoma and non-squamous cell carcinoma histology. The Kaplan–Meier curves in patients with pathological stage IIIA disease are shown: overall survival (**a**) and relapse-free survival (**b**). The Kaplan–Meier curves in patients with non-adenocarcinoma and non-squamous cell carcinoma histology are also shown: overall survival (**c**) and relapse-free survival (**d**). CBDCA/PTX, paclitaxel plus carboplatin

histology showed no significant superiority, in terms of the OS, to those with SQ histology (HR 0.71, $P = 0.28$).

Our study also revealed that UFT treatment yielded superior OS and RFS to paclitaxel plus carboplatin in non-AD/SQ patients. To the best of our knowledge, there are no reports of trials conducted to investigate the efficacy of UFT treatment in non-AD/SQ patients. However, several case reports have shown a favorable clinical outcome of S-1 therapy, the composition of which is similar to UFT (which consists of a mixture of tegafur, gimeracil and oteracil), in patients with adenosquamous carcinoma [15, 16] and pleomorphic carcinoma [17]. Furthermore, the efficacy of fluoropyrimidine-based chemotherapy was recently demonstrated in patients with neuroendocrine tumors [18]. In addition, we compared the drug sensitivities (IC50) of 5-fluorouracil, cisplatin (one of the platinum-based drugs as carboplatin), and paclitaxel among the lung cancer cell lines with AD, SQ, and non-AD/SQ histology by download from the Genomics of Drug Sensitivity in Cancer (https://www.cancerrxgene.org), which is a public database for examining the drug sensitivity of cancer cell lines to various drugs (Supplemental Table 3). Although there were no significant differences in IC50 values between CDDP and PTX among AD, SQ and non-AD/SQ cell lines, non-AD/SQ cell lines showed significantly better sensitivity for 5-fluorouracil than AD cell lines. These lines of evidence may support the efficacy of adjuvant therapy with UFT for NSCLC patents with non-AD/SQ histology.

Recently, various novel treatment strategies have been developed, including treatment with immune checkpoint inhibitors (ICIs) and targeted therapies against specific genes. Combined use of ICIs with other treatment modalities, such as conventional chemotherapy, radiation therapy and targeted therapy, has also received attention [19, 20], because these other modalities also have immunomodulatory effects in addition to exerting direct cancer cell-killing activity [21]. In fact, the efficacy of combined use of ICIs with platinum-based regimens has recently been demonstrated in advanced SQ patients [19]. Furthermore, with regard to fluoropyrimidine antitumor drugs like UFT, pembrolizumab combined with 5-fluorouracil, whose prodrug is a part of UFT (tegafur), cisplatin, or capecitabine is being

Table 3 Multivariate analysis stratified by histological subtype

	Variables	AD			SQ			Non-AD/SQ		
		HR	*P*	95% CI	HR	*P*	95% CI	HR	*P*	95% CI
a) Overall survival										
Arm	CBDCA/PTX vs UFT	0.71	0.12	0.47–1.09	1.07	0.83	0.57–2.02	7.13	0.003	1.81–49.02
pStage	IB vs II	0.24	< .0001	0.15–0.39	0.57	0.13	0.28–1.19	0.62	0.53	0.16–3.05
	IB vs IIIA	0.19	< .0001	0.11–0.34	0.27	0.003	0.12–0.62	2.22	0.45	0.33–44.30
	II vs IIIA	0.78	0.38	0.47–1.36	0.47	0.08	0.21–1.10	3.56	0.32	0.31–90.39
Age	> 67 vs = < 67	1.94	0.0025	1.26–3.01	2.24	0.012	1.19–4.42	1.89	0.32	0.56–8.02
Sex	M vs F	1.43	0.36	0.68–3.16	1.24	0.72	0.42–4.52	2.13	0.29	0.54–11.29
PS	0 vs 1–2	0.63	0.0503	0.40–1.00	0.71	0.37	0.35–1.55	0.62	0.40	0.21–1.93
Smoking	Never vs ever	1.01	0.97	0.47–2.24	2.73	0.17	0.63–10.45	2.95	0.13	0.71–10.74
b) Relapse-free survival										
Arm	CBDCA/PTX vs UFT	0.81	0.25	0.57–1.16	0.82	0.50	0.45–1.46	5.32	0.005	1.59–25.27
pStage	IB vs II	0.27	< .0001	0.18–0.40	0.43	0.012	0.22–0.83	0.57	0.46	0.15–2.80
	IB vs IIIA	0.20	< .0001	0.12–0.32	0.32	0.006	0.15–0.70	2.39	0.40	0.36–47.17
	II vs IIIA	0.75	0.22	0.47–1.20	0.74	0.44	0.36–1.62	4.20	0.26	0.36–105.71
Age	> 67 vs = < 67	1.33	0.12	0.92–1.90	1.60	0.11	0.90–2.90	1.47	0.51	0.48–5.28
Sex	M vs F	1.40	0.31	0.74–2.70	1.65	0.35	0.60–5.61	2.11	0.30	0.54–10.24
PS	0 vs 1–2	0.79	0.26	0.54–1.20	0.88	0.72	0.47–1.80	0.54	0.25	0.19–1.56
Smoking	Never vs ever	1.37	0.35	0.71–2.65	2.84	0.14	0.69–10.00	4.19	0.044	1.04–16.03

CBDCA/PTX paclitaxel plus carboplatin (Arm A), *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *non-AD/SQ* histology of non-AD and non-SQ, *HR* hazard ratio, *95% CI* 95% confidential interval, *pStage* pathological stage, *M* male, *F* female, *PS* performance status

investigated in the KEYNOTE-062 study (NCT02494583) for patients with advanced gastric cancer. However, combined therapy is associated with an elevated risk of adverse effects [22], and postoperative patients are also more likely to suffer from adverse effects, because they usually receive the adjuvant therapy before sufficient postoperative recovery of strength (within approximately 6 weeks after the operation). UFT treatment may be a good candidate for combination adjuvant therapy in NSCLC patients with resected pStage IB–IIIA disease, because it was demonstrated in our previous study [2] and other studies [8, 9] as having a mild adverse effect profile.

Since the original study has used the 6th or 7th editions of UICC TNM-staging system, AD patients with a lepidic pattern whose prognosis is favorable compared with those without have also registered as pStage IB to some extent. This is one of the reasons why AD patients with pStage IB disease showed significantly better OS and RFS than the non-AD/SQ or non-AD patients with pStage IB disease (Table 2 and Supplemental Table 4). There were only five non-AD/SQ patients with pStage IIIA disease (Supplemental Table 5), but they showed statistically significantly better prognosis than AD patients with pStage IIIA disease. Although their clinical significance is unknown, it is important to integrate the clinical results of individual cases with rare histological type to establish novel treatment strategies and to conduct large-scale analysis in the future.

In the original study, the enrolled patients were stratified according to histological subtypes: AD or non-AD. Treatment strategies have dramatically changed in recent decade and the NCCN guidelines recommend that the chemotherapy regimens for advanced lung cancer should be determined according to SQ histology or non-SQ histology. As for non-SQ patients, the regimens should be determined considering presence of mutation of genes such as *EGFR*, *ALK*, *ROS1*, and *BRAF*. However, these genetic alterations are mainly present in AD but rarely found in non-AD/SQ. Given these facts above, we attempted to analyze separately the remaining histological subtypes other than AD and SQ by defining as non-AD/SQ. We also analyzed the impact of histological subtypes on OS or RFS by univariate and multivariate analyses to find the comparable results (Supplemental Tables 4 and 6).

One of the limitations of this study was that the number of patients in each subset after stratification was relatively small. Since quality control of lymph node dissection and pathological assessment has not been planned by central review in the original study as well as the current study, it is inevitable that inter-institutional differences may exist in our study. In addition, non-AD/SQ histology itself was not considered as a stratification factor at the time of the original study. A prospective study is necessary to obtain a clear conclusion, even though completion of enrollment

of patients with rare histological subtypes of NSCLC takes much time to complete.

In conclusion, the pStage and histological subtype significantly affect the survival benefit of adjuvant chemotherapy in some subsets of patients with pStage IB-IIIA NSCLC treated with paclitaxel plus carboplatin or UFT. Our study suggests that there are some subsets of patients in which one or the other treatment is significantly more effective. Selection of adjuvant therapy for patients with NSCLC needs to be made taking into consideration both the pStage and the histological subtype.

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Compliance with ethical standards

Conflict of interest The following authors received research grants from companies: AstraZeneca (KH), Ono Pharmaceutical (KH), Chugai Pharmaceutical (ST and KH), Boehringer-Ingelheim (ST and KH), Astellas (KH), Novartis (KH), Bristol-Myers Squibb (KH), Eli Lilly Japan (KH) and MSD (KH). The following authors received personal fees from companies: Taiho Pharmaceutical (ST, NO, KH, SM and HD), Tsumura & CO (J. Sakamoto), Takeda Pharmaceutical (J. Sakamoto), Chugai Pharmaceutical (J. Sakamoto and KH), AstraZeneca (KH), Ono Pharmaceutical (KH), Boehringer-Ingelheim (KH), Nihon Kayaku (KH and J. Sakamoto), Novartis (KH), Bristol-Myers Squibb (KH and SM), Eli Lilly Japan (KH) and MSD (KH). All the other authors declared no conflicts of interest regarding this study.

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