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Adjuvant chemotherapy for completely resected non-small-cell lung cancer

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Abstract

For many years, surgery alone was the standard treatment for patients with stage I-IIIA non-small-cell lung cancer (NSCLC). However, recent studies have demonstrated that adjuvant chemotherapy provides a survival benefit. The first adjuvant chemotherapy for NSCLC was performed in the 1960s using a key drug known as cyclophosphamide. In the 1980s and early 1990s, a new anti-cancer drug, cisplatin, was developed. The first meta-analysis of this drug was conducted by the Non-small Cell Lung Cancer Collaborative Group in 1995. This analysis comparing surgery with surgery plus chemotherapy containing cisplatin produced a hazard ratio of 0.87 and suggested an absolute benefit of chemotherapy of 5% at 5 years;this difference was not statistically significant (p0.08). Several clinical trials of adjuvant chemotherapy were planned after the meta-analysis conducted in 1995, but the efficacy of adjuvant chemotherapy remained a matter of controversy. However, useful evidence was reported after 2003. The International Adjuvant Lung Cancer Collaborative Group Trial (IALT) demonstrated a 4.1% improvement in survival for patients with stage I to III NSCLC. The JBR. 10 trial demonstrated a 15% improvement in 5-year survival for the adjuvant chemotherapy arm in stage IB or II (excluding T3N0) patients. The Adjuvant Navelbine International Trialist Association (ANITA) trial reported that the overall survival at 5 years improved by 8.6% in the chemotherapy arm and that this survival rate was maintained at 7 years (8.4%) in stage II and IIIA patients. A meta-analysis based on collected and pooled individual patient data from the 5 largest randomized trials was conducted by the Lung Adjuvant Cisplatin Evaluation (LACE). This analysis demonstrated that cisplatin-based adjuvant chemotherapy improved survival in patients with stage II or III cancer. Alterna-tively, uracil-tegafur has been developed and tested in Japan. The Japan Lung Cancer Research Group (JLCRG) on Postsurgical Adjuvant Chemotherapy reported a 5-year overall survival advantage of 11% in the uracil-tegafur group patients with stage IB cancer. The efficacy of adjuvant chemotherapy with uracil-tegafur was confirmed in a meta-analysis. In conclusion, the results of phase III trials and a meta-analysis have confirmed the benefit of adjuvant chemotherapy for resected stage IB, II, and IIIA NSCLC.

KEYWORDS: adjuvant chemotherapy, lung cancer, non-small-cell lung cancer, cisplatin, uracil-tegafur

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Review

Adjuvant Chemotherapy for Completely Resected Non-Small-Cell Lung Cancer

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For many years, surgery alone was the standard treatment for patients with stage I-IIIA non-small-cell lung cancer (NSCLC). However, recent studies have demonstrated that adjuvant chemotherapy provides a survival benefit. The first adjuvant chemotherapy for NSCLC was performed in the 1960s using a key drug known as cyclophosphamide. In the 1980s and early 1990s, a new anti-cancer drug, cisplatin, was developed. The first meta-analysis of this drug was conducted by the Non-small Cell Lung Cancer Collaborative Group in 1995. This analysis comparing surgery with surgery plus chemotherapy containing cisplatin produced a hazard ratio of 0.87 and suggested an absolute benefit of chemotherapy of 5% at 5 years; this difference was not statistically significant ($p = 0.08$). Several clinical trials of adjuvant chemotherapy were planned after the meta-analysis conducted in 1995, but the efficacy of adjuvant chemotherapy remained a matter of controversy. However, useful evidence was reported after 2003. The International Adjuvant Lung Cancer Collaborative Group Trial (IALT) demonstrated a 4.1% improvement in survival for patients with stage I to III NSCLC. The JBR. 10 trial demonstrated a 15% improvement in 5-year survival for the adjuvant chemotherapy arm in stage IB or II (excluding T3N0) patients. The Adjuvant Navelbine International Trialist Association (ANITA) trial reported that the overall survival at 5 years improved by 8.6% in the chemotherapy arm and that this survival rate was maintained at 7 years (8.4%) in stage II and IIIA patients. A meta-analysis based on collected and pooled individual patient data from the 5 largest randomized trials was conducted by the Lung Adjuvant Cisplatin Evaluation (LACE). This analysis demonstrated that cisplatin-based adjuvant chemotherapy improved survival in patients with stage II or III cancer. Alternatively, uracil-tegafur has been developed and tested in Japan. The Japan Lung Cancer Research Group (JLCRG) on Postsurgical Adjuvant Chemotherapy reported a 5-year overall survival advantage of 11% in the uracil-tegafur group patients with stage IB cancer. The efficacy of adjuvant chemotherapy with uracil-tegafur was confirmed in a meta-analysis. In conclusion, the results of phase III trials and a meta-analysis have confirmed the benefit of adjuvant chemotherapy for resected stage IB, II, and IIIA NSCLC.

Ker words: adjuvant chemotherapy, lung cancer, non-small-cell lung cancer, cisplatin, uracil-tegafur

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Lung cancer is the most common cause of death from cancer in industrialized countries [1]. Human lung cancers are divided into 2 major types,

small-cell lung cancer and non-small-cell lung cancer (NSCLC) [2]. Despite great efforts to improve the survival of patients with NSCLC, satisfactory outcomes have not been achieved. Even in early-stage NSCLC patients who undergo surgical resections, recurrent disease often impairs the clinical outcome. The postoperative 5-year survival rate for stage IA and IB NSCLC was reported to range from 72% to 46% in America and European countries [3–5]. In Japan, this value reportedly ranged from 83% to 60% (Table 1) [6, 7].

For many years, surgery alone was the standard treatment for patients with stage I-IIIA NSCLC. However, recent studies have demonstrated that adjuvant chemotherapy provides a survival benefit in patients with resected NSCLC.

The purpose of this article was to provide a general overview of the evolution of adjuvant chemotherapy for resected NSCLC, with a special emphasis on recently reported randomized trials that have demonstrated improvements in survival and reductions in cancer recurrence with adjuvant chemotherapy.

Earlier Studies from 1980s to 1995

The first adjuvant chemotherapy for NSCLC was performed in the 1960s. The key drug was cyclophosphamide with or without other drugs. These trials failed to prove the effectiveness of adjuvant chemotherapy for patients with resected NSCLC.

In the 1980s and early 1990s, multiple studies of adjuvant chemotherapy after resection showed conflicting results. In this era, the development of a new anti-cancer drug, cisplatin, was the new hope of chemotherapy. The first report to prove the efficacy of adjuvant chemotherapy for resected NSCLC was performed by the Lung Cancer Study Group (LCSG) in America. The LCSG evaluated cyclophosphamide, doxorubicin, and cisplatin (CAP) chemotherapy. This trial randomized 141 patients and compared Bacillus Calmette-Guerin (BCG) and levamisole immunotherapy with postoperative chemotherapy in patients with stage II and III (any T3 and/or any N2) adenocarcinoma and large cell carcinoma after complete surgical resection. Disease-free survival was significantly prolonged in the group receiving CAP chemotherapy. A 6-month delay in the median time to recurrence and a 15% survival advantage at 1 year in favor of chemotherapy were reported [8]. Of note, the control group in this trial consisted not of patients receiving surgery alone, but of patients administered BCG for cancers in the intrathoracic space or levamisole for cancers in the oral region. Another LCSG trial for CAP did not show significant improvements in overall survival or progression-free survival in NSCLC patients.

In 1992, a randomized trial with CAP chemotherapy was reported in Finland. One hundred ten patients with T1-3N0 (World Health Organization [WHO] staging 1981) NSCLC underwent radical surgery and were randomized to receive adjuvant chemotherapy (n = 54) (CAP for 6 cycles) or no active treatment (n = 56). Seventeen patients (31%) in the CAP group and 27 patients (48%) in the control group developed a recurrence during the follow-up period ($p = 0.01$). The 5-year survival rate was 67% in the chemotherapy group and 56% in the control group ($p = 0.050$). The patients in the chemotherapy group who completed the planned treatment had a slightly better 5-year survival rate than those who did not complete chemotherapy (72.5% vs. 50.3%; $p = 0.15$). Chemotherapy-related gastrointestinal toxicity of grade 3 to 4 (WHO) occurred in 63% and was the main reason why patients refused further planned

Table 1 The pathological 5-year survival rate (%) for resected NSCLC

Stage	Goya [6]	Asamura [7]	Mountain [3]	Van Rens [4]
ⅠA	79.5	83.9	67	63
ⅠB	60.1	66.3	57	46
ⅡA	59.9	61.0	55	52
ⅡB	42.2	47.4	39	33
ⅢA	29.8	32.8	23	19
ⅢB	19.3	29.6	3–7	–
Ⅳ	20.0	23.1	1	–

therapy [9].

Meta-analysis by the Non-small Cell Lung Cancer Collaborative Group in 1995

The inconclusive results of the clinical trials led to the publication of the first meta-analysis, conducted by the Non-small Cell Lung Cancer Collaborative Group, in 1995. This analysis included 9,387 NSCLC patients who had undergone complete resections in 52 randomized clinical trials performed between 1965 and 1991. Among the 4,357 patients who were included in the analysis, trials comparing surgery with surgery plus chemotherapy containing cisplatin yielded a hazard ratio of 0.87, corresponding to a 13% reduction in the risk of death, and suggested an absolute benefit of chemotherapy of 3% at 2 years and 5% at 5 years. The P-value was 0.08 and, therefore, was not statistically significant [10]. Although the results of this meta-analysis had no impact on clinical practice, the statistically non-significant benefit of adjuvant chemotherapy on the 5-year survival rate resulted in several new randomized adjuvant studies to determine the real benefit of adjuvant chemotherapy.

After the above-mentioned meta-analysis by the Non-small Cell Lung Cancer Collaborative Group, several clinical trials examining adjuvant chemotherapy were performed. However, no survival benefit was demonstrated. Two large studies with negative results are described below.

Adjuvant Lung Project Italy (ALPI) Trial

The Adjuvant Lung Project Italy (ALPI) trial randomized 1,209 patients with stage I, II, or IIIA NSCLC between 1994 and 1999. Patients were randomly assigned to receive mitomycin, vindesine, or cisplatin every 3 weeks for 3 cycles or no treatment. After a median follow-up time of 64.5 months, no statistically significant differences in overall survival (hazard ratio (HR) = 0.96, 95% confidence interval (CI) = 0.81 to 1.13; $p = 0.589$) or progression-free survival (HR = 0.89, 95% CI = 0.76 to 1.03; $p = 0.128$) were observed between the 2 patient groups. In the multivariable analysis, only disease stage and sex were associated with survival [11].

Big Lung Trial (BLT)

Another study with negative results was the Big Lung Trial (BLT) from Great Britain, which examined the role of cisplatin-based chemotherapy. A total of 381 patients were randomized to receive chemotherapy (192 patients) or no chemotherapy (189 patients). Chemotherapy consisted of three 3-week cycles of cisplatin/vindesine, mitomycin/ifosfamide/cisplatin, mitomycin/vinblastine/cisplatin or vinorelbine/cisplatin. Chemotherapy was administered before surgery in 3% of the patients while 97% received adjuvant chemotherapy. The median patient age was 61 years, 69% were male, and 48% had a squamous histology. Twenty-seven percent of the patients had stage I cancer, 38% had stage II, and 26% had stage IIIA. A complete resection was achieved in approximately 95% of the patients. After a median follow-up period of 34.6 months, no significant difference between the 2 treatment groups in terms of overall survival (HR = 1.02, 95% CI = 0.77 to 1.35; $p = 0.90$) or progression-free survival (HR = 0.97, 95% CI = 0.74 to 1.26; $p = 0.81$) was observed [12].

On the other hand, reports on adjuvant chemotherapy began to appear after 2003.

The International Adjuvant Lung Cancer Collaborative Group Trial (IALT)

The International Adjuvant Lung Cancer Collaborative Group Trial (IALT) presented their results at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2003. This trial was the largest study of adjuvant chemotherapy that had been conducted to date, and was designed to demonstrate an absolute improvement in survival of 5%, from 50% to 55%, at 5 years with adjuvant chemotherapy, based on the hypothesis generated in 1995 as a result of the meta-analysis. A total of 1,867 patients with pathological stage I, II, or III NSCLC underwent randomization. Adjuvant chemotherapy consisted of cisplatin for 3 to 4 cycles combined with vindesine, vinblastine, vinorelbine, or etoposide. In this trial, $>50\%$ of the patients in the treatment group received the second-generation combination of cisplatin and etoposide. Approximately one-quarter of the patients received postoperative radiotherapy. At the time of publication, the median follow-up time was 56 months.

The survival rate was significantly higher in the chemotherapy group than in the observation group (44.5% vs. 40.4% at 5 years; HR = 0.86; 95% CI = 0.76 to 0.98, $p < 0.03$). The disease-free survival rate was also significantly higher in the chemotherapy group than in the observation group (39.4% vs. 34.3% at 5 years; HR = 0.83; 95% CI = 0.74 to 0.94, $p < 0.003$). Seven patients (0.8%) died of chemotherapy-induced toxic effects [13].

At the Annual Meeting of the ASCO in 2008, the results of a long-term follow-up analysis of the patients enrolled in the IALT were reported. The median follow-up period was 7.5 years as of the cut-off date of September 1, 2005. The survival status of 1,807 patients was known. The results showed no significant effect of adjuvant chemotherapy on overall survival (HR = 0.91; 95% CI = 0.81 to 1.02; $p = 0.10$). Overall survival was significantly different before and after 5 years. These results confirmed the efficacy of chemotherapy for the first 5 years after surgery [14].

At the Annual Meeting of the ASCO in 2004, 2 important presentations were made by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Cancer and Leukemia Group B (CALGB).

JBR. 10 Trial

The NCIC CTG presented the results of an intergroup trial, JBR. 10. This phase III study randomly assigned 482 patients with completely resected stage IB or II (excluding T3N0) cancer to observation or four cycles of cisplatin plus vinorelbine weekly for 16 weeks. Forty-five percent of the patients had pathological stage IB disease and 55% had stage II disease. In both groups, the median age was 61 years, and 53% had adenocarcinomas. Overall survival was significantly prolonged in the chemotherapy group, compared with the observation group (94 vs. 73 months; HR = 0.69; 95% CI = 0.52 to 0.91, $p = 0.04$), as was relapse-free survival (not reached vs. 46.7 months; HR = 0.60; 95% CI = 0.45 to 0.79, $p < 0.001$). A 15% improvement in 5-year survival favoring adjuvant chemotherapy was also observed (69% vs. 54%, $p = 0.03$) [15].

CALGB 9633 Trial

The CALGB 9633 trial had evaluated adjuvant chemotherapy in patients with completely resected stage IB NSCLC. A total of 344 patients were randomized to receive 4 cycles of adjuvant paclitaxel plus carboplatin every 3 weeks versus no further treatment. The overall survival time was significantly longer in the chemotherapy arm ($p = 0.028$) with a 12% improvement in 4-year survival at a median follow-up time of 34 months. But, after a median follow-up period of 74 months, the overall survival rates at 5 years were 60% and 58% for the chemotherapy and observation groups, respectively (HR = 0.83; 90% CI = 0.64 to 1.08, $p = 0.125$). An exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for patients with tumors > 4 cm in diameter (HR = 0.69; 90% CI = 0.48 to 0.99, $p = 0.043$) [16].

The Adjuvant Navelbine International Trialist Association (ANITA) Trial

At the Annual Meeting of the ASCO in 2005, the Adjuvant Navelbine International Trialist Association (ANITA) trial was presented. In this prospective phase III trial, 840 completely resected stage IB, II or IIIA patients were randomly assigned to receive 4 cycles of cisplatin plus vinorelbine versus no further treatment. Postoperative radiotherapy was not mandatory and was given according to the policy at each center. After a median follow-up period of 76 months, the median survival was 65.7 months (95% CI = 0.48 to 0.89) in the chemotherapy group and 43.7 months (95% CI = 0.36 to 0.52) in the observation group. The adjusted risk for death was significantly reduced among the patients assigned to the chemotherapy arm, compared with the controls (HR = 0.80; 95% CI = 0.66 to 0.96, $p = 0.017$). Overall survival at 5 years improved by 8.6% in the chemotherapy arm, and this survival rate was maintained at 7 years (8.4%). In this study, the favorable impact on survival using adjuvant chemotherapy was restricted to stage II and IIIA patients, and no benefit was observed among those with stage IB cancer [17].

The Lung Adjuvant Cisplatin Evaluation (LACE) Meta-Analysis

The Lung Adjuvant Cisplatin Evaluation (LACE) study was presented at the Annual Meeting of the ASCO in 2006. This meta-analysis was based on collected and pooled individual patient data from the 5 largest randomized trials (ALPI, ANITA, BLT, IALT and JBR. 10; 4,584 patients) conducted after the 1995 NSCLC meta-analysis. With a median follow-up period of 5.2 years, the overall HR of death was 0.89 (95% CI = 0.82 to 0.96, $p = 0.005$), corresponding to a 5-year absolute benefit from chemotherapy of 5.4%. The benefit varied with stage (test for trend, $p = 0.04$; HR for stage IA = 1.40; 95% CI = 0.95 to 2.06; HR for stage IB = 0.93; 95% CI = 0.78 to 1.10; HR for stage II = 0.83; 95% CI = 0.73 to 0.95; and HR for stage III = 0.83; 95% CI = 0.72 to 0.94). The effect of chemotherapy did not vary significantly (test for interaction, $p = 0.11$) with the associated drugs, including vinorelbine (HR = 0.80; 95% CI = 0.70 to 0.91), etoposide or vinca alkaloid (HR = 0.92; 95% CI = 0.80 to 1.07) [18]. When subgroups according to age were analyzed (3,269 patients < 65 years old, 71%; 901 patients 65–69 years old, 20%; and 414 patients ≥ 70 years old, 9%), no statistically significant interaction ($p = 0.26$) or test for trends ($p = 0.29$) was observed between age and the treatment effect on overall survival. Similarly, no significant differences in event-free survival were observed ($p = 0.42$) [19].

The Medical Research Council (MRC) Meta-Analysis

The Medical Research Council (MRC) meta-analysis was reported at the Annual Meeting of the ASCO in 2007. Individual patient data were obtained for 8147 patients from 30 randomized clinical trials, of which 22 trials examined a cisplatin-based regimen. An overall survival benefit for chemotherapy was reported (HR = 0.86; 95% CI = 0.81 to 0.93; $p < 0.000001$), with an absolute benefit of 4% (from 60% to 64%) at 5 years. Similar results for recurrence-free survival and time to distant recurrence were obtained [20].

Trials for Uracil-Tegafur in Japan

Since 2003, cisplatin-based adjuvant chemotherapy for resected NSCLC has provided a significant survival benefit for patients with stage II-III cancer. As an alternative to this treatment and in view of its mild toxicity profile, uracil-tegafur has been developed and tested in Japan. Uracil-tegafur, an antimetabolite that combines tegafur (a fluorouracil [FU] prodrug) and uracil in a 1: 4 molar ratio and can be administered orally, has been approved for the treatment of patients with resected NSCLC, and its use in adjuvant settings has been extensively examined since the 1980s.

The West Japan Study Group for Lung Cancer Surgery (WJSG) study II

The second study conducted by the West Japan Study Group for Lung Cancer Surgery (WJSG) was the first trial to confirm a survival benefit of uracil-tegafur in an adjuvant chemotherapy setting. This trial contained three-arms, and 323 patients with resected p-stage I-III NSCLC were randomly assigned to a surgery alone group, a uracil-tegafur (Uft) alone group, or a cisplatin plus vindesine followed by uracil-tegafur (CVUft) group. The overall 5-year survival rates were 60.6% for the CVUft group and 64.1% for the Uft group, versus 49.0% for the control group. The results of statistical testing among the 3 groups yielded a p value of 0.044. The most favorable finding was the significantly better survival obtained in the Uft groups compared with the surgery alone group (HR = 0.55; 95% CI = 0.36 to 0.86; $p = 0.022$) [21].

After this second WJSG study, uracil-tegafur was studied as both a single-agent therapy following surgery [22–26] or following one or more cycles of cisplatin-based chemotherapy. The results from these trials have been mixed, with some demonstrating a survival benefit [23, 26] and others not [22, 24, 25].

The Japan Lung Cancer Research Group (JLCRG) Study

A larger study comparing uracil-tegafur therapy versus observation was performed by the Japan Lung Cancer Research Group (JLCRG) on Postsurgical

Adjuvant Chemotherapy. A total of 979 patients with stage I adenocarcinoma were assigned to receive either oral uracil-tegafur for 2 years or observation. These patients had either T1 disease (72%) or T2 disease (28%). The median follow-up period was 73 months. A grade 3 adverse reaction developed in 10 of the 482 patients (2%), but no grade 4 adverse reactions occurred. The 5-year overall survival rate was 88% in the uracil-tegafur group and 85% in the control group (HR = 0.71; 95% CI = 0.52 to 0.98; p = 0.04). The 5-year overall survival rate among the patients with T2 disease was 85% in the uracil-tegafur group and 74% in the control group (HR = 0.48; 95% CI = 0.29 to 0.81; p = 0.005). Moreover, in the T1 disease subgroup of patients with a tumor that was greater than 2 cm in diameter, treatment with uracil-tegafur provided a definite survival benefit (p = 0.05) [23].

Meta-Analysis for Uracil-Tegafur

The efficacy of adjuvant chemotherapy with uracil-tegafur was confirmed in a meta-analysis of the above-mentioned 6 trials comparing surgery alone with surgery plus uracil-tegafur. A total of 2,003 patients were eligible. The most common histologic type was adenocarcinoma (1,679 patients, 83.8%). Most patients had p-stage I (1,982 patients, 99.0%). The median follow-up period was 6.44 years. The survival rates at 5 and 7 years were significantly higher in the surgery plus uracil-tegafur group (81.5% and 76.5%, respectively) than in the surgery alone group (77.2% and 69.5%, respectively; p = 0.011 and 0.001, respectively). The overall pooled hazard ratio was 0.74, and its 95% CI was 0.61 to 0.88 (p = 0.001) [27].

New Strategies Based on Molecular Markers

Accumulating knowledge of molecular oncology is enabling us not only to understand the pathogenesis of NSCLC but also to predict the sensitivity of tumors to anticancer drugs. In adjuvant settings, patients with excision of repair cross-complementation group 1 (ERCC1)-negative tumors showed prolonged survival compared with patients with *ERCC1*-positive tumors [28].

In addition, epidermal growth factor receptor (*EGFR*) gene mutations have been identified in NSCLC and are significantly related to a favorable clinical outcome among patients treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) [29–31]. Moreover, *EGFR* status influenced the effect of adjuvant chemotherapy with uracil-tegafur [32]. It would be of great interest to further examine the efficacy of

Table 2 Randomized trials and meta-analyses of adjuvant chemotherapy for NSCLC after the 1995 meta-analysis

Trials and meta-analyses	No. of patients	Stage	Agents	Hazard Ratio (95% C.I.)	*P*-value	Advantage of 5-year survival
1995 meta-analysis [10]	1394	I-IIIA	CDDP based	0.87 (0.74–1.02)	NS	5
ALPI [11]	1209	I-IIIA	MVP	0.96 (0.81–1.13)	NS	1
BLT [12]	481	I-IIIA	CDDP based	1.02 (0.77–1.35)	NS	−
IALT [13]	1867	I-III	CDDP+Vin	0.86 (0.76–0.98)	<0.03	4.1
JBR. 10 [15]	482	IB-II	CDDP+VNB	0.69 (0.52–0.91)	0.04	15
CALGB9633 [16]	344	IB	CBDCA+PTX	0.83 (0.64–1.08)*	NS	2
ANITA [17]	840	IB-IIIA	CDDP+VNB	0.80 (0.66–0.96)	0.017	8.6
LACE meta-analysis [18]	4584	I-III	CDDP based	0.89 (0.82–0.96)	0.005	5.8
MRC meta-analysis [20]	8147	I-IIIA	CDDP based, uft	0.86 (0.81–0.93)	<0.000001	4
WJSG(II) [21]	323	I-III	uft	0.55 (0.36–0.86)	0.022	15.1
JLCRG [23]	979	I (Ad)	uft	0.71 (0.52–0.98)	0.04	3
Uft meta-analysis [27]	2003	I	uft	0.74 (0.61–0.88)	0.001	4.6

Abbreviations: NSCLC, non-small-cell lung cancer; C.I., confidence interval; CDDP, Cisplatin; NS, Not Significant; ALPI, Adjuvant Lung Project Italy; MVP, mitomycin + vindesin + cisplatin; BLT, Big Lung Trial; IALT, International Adjuvant Lung Cancer Collaborative Group Trial; Vin, vinca alkaloid; VNB, vinorelbine; CALGB, Cancer and Leukemia Group B; CBDCA, carboplatin; PTX, paclitaxel; ANITA, Adjuvant Navelbine International Trialist Association; LACE, Lung Adjuvant Cisplatin Evaluation; MRC, Medical Research Council; WJSG, West Japan Study Group for Lung Cancer Surgery; uft, uracil-tegafur; JLCRG, Japan Lung Cancer Research Group; Ad, Adenocarcinoma *90% C.I.

adjuvant chemotherapy according to the status of *EGFR* mutation.

Concluding Remarks

The benefit of adjuvant chemotherapy for resected stage IB, II, or IIIA NSCLC has been shown based on the results of phase III trials, such as the IALT, JBR10, ANITA and JLCRG studies, and the meta-analysis Table 2. In clinical practice, however, the 5-year survival benefit was only 5% to 10%, and severe adverse reactions were seen in patients receiving cisplatin. Further studies examining the value of biomarkers for predicting the clinical outcome of adjuvant chemotherapy are now being planned.

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