Surg Today (2016) 46:25–37
DOI 10.1007/s00595-015-1174-7

REVIEW ARTICLE

Adjuvant therapy following surgery in non-small cell lung cancer (NSCLC)

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Received: 19 January 2015 / Accepted: 19 February 2015 / Published online: 30 April 2015

Abstract Non-small cell lung cancer (NSCLC) accounts for 80–90 % of cases of primary lung cancer. Although surgery is recommended as the primary treatment for early-stage NSCLC, the prognosis is unsatisfactory even when complete resection is achieved. Recent clinical trials have shown that postoperative adjuvant chemotherapy with cytotoxic agents, namely uracil-tegafur (UFT) for stage IA (>2 cm in diameter)-IB patients or cisplatin-based regimens for stage II-IIIA patients, improves the prognosis, and adjuvant chemotherapy is recommended as the "standard treatment of care." However, adjuvant chemotherapy provides only a modest 5-year survival benefit of 4 % and may sometimes be fatal. To improve the risk–benefit balance of adjuvant chemotherapy, targeting agents such as antibodies against vascular endothelial growth factor (VEGF) and tyrosine-kinase inhibitors of epidermal growth factor receptor (EGFR-TKIs) are being evaluated in ongoing adjuvant trials. Another promising approach may be the individualization of adjuvant chemotherapy based on biomarkers that may predict the prognosis or benefits associated with adjuvant chemotherapy. The current status and future perspectives of adjuvant chemotherapy for NSCLC are reviewed and discussed.

Keywords Non-small cell lung cancer · Surgery · Adjuvant therapy · Biomarker · Circulating tumor cell

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80–90 % of cases of primary lung cancer [1, 2], which is the leading cause of cancer deaths in most industrialized countries, including Japan. Although surgery is the optimal therapeutic modality for the cure of NSCLC, the prognosis following complete resection remains unsatisfactory [2, 3] (Table 1). Accordingly, a number of clinical trials of adjuvant therapy after surgery have been conducted to improve the prognosis. A meta-analysis, reported in 1995, showed the potential benefit of cisplatin-based adjuvant chemotherapy (a 13 % reduction in the risk of death, equivalent to an absolute benefit of 5 % at 5 years); however, the survival benefit was not statistically significant ($p = 0.08$), with a hazard ratio (HR) of 0.87 [95 % confidence interval (CI), 0.74–1.02] [4]. Recently, randomized controlled trials (RCTs) have revealed a significant survival benefit from adjuvant chemotherapy [5], and adjuvant chemotherapy following surgery has been established as the "standard treatment of care" [6]. In this article, we review the recent clinical evidence and discuss the current issues and future perspectives of adjuvant therapy in the treatment of NSCLC.

Adjuvant chemotherapy with cytotoxic agents

Platinum-based chemotherapy

Since the 1995 meta-analysis [5], many large-scale RCTs of adjuvant chemotherapy using cisplatin-based regimens have been conducted [7] (Table 2). Among them, an international trial conducted by the International Adjuvant Lung Cancer Trial Collaborative Group (IALT) was the first trial

Table 1 Postoperative survival of primary lung cancer patients according to pathologic (p-) stage (UICC version 7 classification [2])

Pathologic (p-) stage	IASLC Lung Cancer Staging Project (1999–2000) [2]	Japan Lung Cancer Registry (2004) [3]
IA	73 % ($n = 3666$)	86.8 % ($n = 4978$)
IB	58 % ($n = 2579$)	73.9 % ($n = 2552$)
IIA	46 % ($n = 2579$)	61.6 % ($n = 941$)
IIB	36 % ($n = 2252$)	49.8 % ($n = 848$)
IIIA	24 % ($n = 3792$)	40.9 % ($n = 1804$)

Table 2 Randomized controlled trials of adjuvant cisplatin-based chemotherapy for non-small cell lung cancer (NSCLC) included in the LACE meta-analysis [7]

Trial (year of publication)	Inclusion criteria	No of pts	Chemotherapy	Radiotherapy	Overall survival		HR (95 % CI); *P* value	TRD (%)
					Rate at 5-years after surgery	Median time (m)		
ALPI [2003]	Stage I, II, IIIA	540	No	Optional after chemotherapy		48.0	0.96 (0.81–1.13); $P = 0.589$	1.3
		548	CDDP + MMC + VDS			55.2		0.5
BLT (2004)	Stage I, II, III	189	No	Optional after chemotherapy	74 % (at 2-years after surgery)	33.9	1.02 (0.77–1.35); $P = 0.90$	
		192	CDDP-based*		60 % (at 2-years after surgery)	32.6		3.1
IALT (2004)	Stage I, II, III	935	No	Optional according to pN-status after chemotherapy	40.4 %	44.8	0.86 (0.76–0.98); $P < 0.03$	
		932	CDDP-based**		44.5 %	50.8		0.8
JBR10 (2005)	Stage IB, II(N1)	240	No	No	54 %	73	0.69 (0.52–0.91); $P = 0.04$	
		242	CDDP + VNB		69 %	94		0.8
ANITA01 (2006)	Stage I, II, IIIA	407	No	Optional for pN positive	42.6 %	43.7	0.80 (0.66–0.96); $P = 0.017$	0.2
		407	CDDP + VNB		51.2 %	65.7		1.0

LACE lung adjuvant cisplatin evaluation, *HR* hazard ratio, *CI* confidence interval, *TRD* treatment-related death, *ALPI* Adjuvant Lung Cancer Project Italy, *BLT* Big Lung Trial, *IALT* International Adjuvant Lung Trial, *JBR10* National Cancer Institute of Canada Clinical Trial Group trial JBR10, *ANITA* Adjuvant Navelbine International Trialist Association, *CDDP* cisplatin, *MMC* mitomycin C, *VDS* vindesine, *VNB* vinorelbine, *IFO* ifosfamide, *VBL* vinblastine, *pN* pathological nodal stage

* Choice from MIC(MMC + IFO + CDDP), MVP(MMC + VBL + CDDP), CV(CDDP + VDS), or NP(VNB + CDDP)

** Choice from CV(CDDP + VDS), CDDP + VBL, NP(VNB + CDDP), or PE(CDDP + Etoposide)

to show that cisplatin-based adjuvant chemotherapy significantly improved overall survival (OS) [8]. In this trial, a chemotherapy regimen was selected from four cisplatin-based regimens by each participating center, and postoperative radiotherapy was allowed after the completion of chemotherapy according to each center's policy. The JBR 10 trial [9] and the ANITA01 trial [10] were subsequent "positive" trials, in which cisplatin plus vinorelbine was employed as an adjuvant chemotherapy regimen.

The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group conducted a pooled analysis of 5 adjuvant trials, 3 positive trials (IALT, JBR10, ANITA01), and 2 negative trials (ALPI, BLT), and showed that cisplatin-based chemotherapy significantly improved postoperative OS [HR, 0.89 (95 % CI, 0.82–0.96); $p = 0.005$) with an absolute benefit of 5.4 % at 5 years after surgery. The benefit varied according to stage [HR for stage IA, 1.40 (95 % CI, 0.95–2.06); HR for stage IB, 0.93 (95 % CI, 0.78–1.10); HR for stage II, 0.83 (95 % CI, 0.73–0.95), HR for stage III, 0.83 (95 % CI, 0.72–0.94)], suggesting that postoperative adjuvant cisplatin-based chemotherapy only provided a survival benefit for advanced-stage (stages II–III) NSCLC patients. Regarding toxicity, 19 treatment-related deaths (0.9 %) have been reported to be associated with cisplatin-based adjuvant chemotherapy [7].

As a less toxic chemotherapy, carboplatin plus paclitaxel was employed in some adjuvant trials. In the Cancer and Leukemia Group B (CALGB) 9633 trial, 344 patients with completely resected pathologic (p-) stage IB (T2N0M0) NSCLC were randomly assigned to receive no chemotherapy (observation group) or adjuvant chemotherapy with carboplatin plus paclitaxel (chemotherapy group).

Although the preliminary results indicated that postoperative adjuvant chemotherapy improved OS and disease-free survival (DFS), the final analysis failed to show a significant benefit in survival [median OS time (MST), 78 months in the observation group vs. 95 months in the chemotherapy group; HR, 0.83 (95 % CI, 0.64–1.08); $p = 0.12$]. An exploratory analysis demonstrated a significant OS benefit for patients who had tumors of ≥4 cm in diameter [HR, 0.69 (95 % CI, 0.48–0.99); $p = 0.043$] [11].

The NATCH trial, another trial with carboplatin plus paclitaxel, was a unique trial, which examined whether postoperative adjuvant chemotherapy or preoperative chemotherapy improved DFS as the primary endpoint. A total of 624 patients with clinical (c-) stage IA, with tumor size of >2 cm in diameter, IB, II, or T3N1 NSCLC were randomly assigned to surgery-alone group (control group), surgery followed by adjuvant chemotherapy with carboplatin plus paclitaxel (postoperative adjuvant group), or chemotherapy with carboplatin plus paclitaxel followed by surgery (preoperative induction group). No differences were observed between the control group and the postoperative adjuvant group in DFS [5-year DFS rate, 34.1 vs. 36.6 %; HR, 0.96 (95 % CI, 0.75–1.22); $p = 0.74$] or OS [5-year OS rate, 44 vs. 45.5 %; HR, 0.99 (95 % CI, 0.75–1.3); $p = 0.93$] [12].

Based on the evidence above, postoperative adjuvant chemotherapy with cisplatin-based regimens, especially cisplatin plus vinorelbine, is now recommended for p-stage II and IIIA patients, but not for p-stage I patients [6, 13, 14]. For unresectable c-stage IV patients with non-squamous NSCLC, pemetrexed in combination with a platinum agent is recommended as a first-line chemotherapy regimen [15], because treatment-by-histology analyses in a RCT indicated that pemetrexed plus cisplatin was superior to gemcitabine plus cisplatin for the treatment of non-squamous NSCLC patients [16]. In the postoperative adjuvant setting, whether pemetrexed plus cisplatin is the optimal chemotherapy regimen for non-squamous NSCLC patients remains unclear. This will be revealed by an ongoing Japanese trial comparing pemetrexed plus cisplatin with vinorelbine plus cisplatin (JIPANG trial).

Uracil-tegafur (UFT)

Uracil-tegafur (also referred to as UFT), the combination drug of uracil and tegafur at a molar ratio of 4:1, is an oral antimetabolite agent; tegafur is a pro-drug that is gradually converted to 5-fluorouracil (5-FU), and uracil is an inhibitor of dihydropyrimidine dehydrogenase (DPD) that is responsible for 5-FU degradation [17–20]. Uracil-tegafur can generate a higher serum and intra-tumoral concentration of 5-FU released from tegafur through the inhibition of DPD activity by uracil. Unfortunately, for advanced NSCLC patients, chemotherapy with uracil-tegafur failed to provide a significant anti-tumor effect, with response rates of only 6–8 % [18, 20].

In contrast, for completely resected NSCLC patients, especially those with p-stage I disease, adjuvant chemotherapy with uracil-tegafur was shown to provide a significant OS benefit in several RCTs conducted in Japan (Table 3) [21–27]. The 2nd-study conducted by the West Japan Study Group for Lung Cancer Surgery (WJSG) was the first study to clearly show a significant survival benefit of adjuvant chemotherapy with uracil-tegafur. In the trial, patients with completely resected p-stage I-III NSCLC were randomly assigned to the control group (surgery alone), the UFT group (surgery followed by chemotherapy with uracil-tegafur), or the CVUft group (surgery followed by a chemotherapy regimen that consisted of cisplatin plus vindesine followed by uracil-tegafur). The UFT group showed the most favorable survival with a statistically significant difference in comparison with the control group ($p = 0.022$) [21].

The Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy (JLCRG) trial was the largest adjuvant trial of uracil-tegafur to be conducted in Japan. In the trial, only p-stage I adenocarcinoma patients were randomly assigned to the control group (surgery alone) or the UFT group (surgery followed by uracil-tegafur), and the UFT group showed a significantly favorable survival benefit in comparison with the control group [HR, 0.71 (0.52–0.98); $p = 0.04$]. The survival benefit was significant in p-stage IB (T2) patients (5-year OS, 74 % for the control group vs. 85 % for the UFT group; HR, 0.48; $P = 0.005$), but was not seen in p-stage IA (T1) patients [5-year OS, 90 vs. 89 %; HR, 0.97 (95 % CI, 0.64–1.46); $p = 0.87$] [26].

A meta-analysis of six randomized trials was conducted which compared surgery-alone with surgery followed by uracil-tegafur. A total of 2003 patients, most with p-stage I disease, were included. The 5-year and 7-year overall survival rates were higher in the surgery plus uracil-tegafur group (81.5 and 76.5 %, respectively) than in surgery-alone group (77.2 and 69.5 %) with a significant difference ($p = 0.011$ and $p = 0.001$, respectively). The overall pooled HR was 0.74 [(95 % CI, 0.61–0.88); $p = 0.001$] [28]. A further exploratory analysis of the data from the meta-analysis showed that chemotherapy with uracil-tegafur was effective for the T1b subset (tumor diameter, >2 to ≤3 cm) of p-stage IA disease [29]. No treatment-related deaths (TRD) were reported in any of the adjuvant trials, indicating the clinical advantage of the use of uracil-tegafur, which has a mild toxicity profile.

In Japan, it is generally accepted that postoperative uracil-tegafur chemotherapy is effective and it is recommended for the T1b subset of p-stage IA disease and for p-stage IB disease. Because all adjuvant trials with uracil-tegafur were conducted in Japan, the use of uracil-tegafur after complete resection is not recommended outside of Japan [6].

Table 3 Randomized controlled trials of adjuvant tegafur-uracil chemotherapy for non-small cell lung cancer (NSCLC)

Trial (year of publication)	Inclusion criteria	No of pts	Chemotherapy	Overall survival rate at 5-years after surgery (%)	HR (95 % CI) *P* value
Chubu Japan (1995)	Stage I, II, III	154	No	58.1	$P = 0.347$ ($P = 0.044$ after adjustment)
		155	CDDP + DXR followed by UFT	61.8	
WJSG-2nd (1996)	Stage I, II, III	100	No	49.0	$P = 0.053$ (among 3 arms)
		108	UFT	64.1	0.55 (0.36-0.86) (multivariate analysis) $P = 0.022$ (vs surgery-alone)
		115	CDDP + VDS followed by UFT	60.6	0.64 (0.42–0.97) (multivariate analysis) $P = 0.083$ (vs surgery-alone)
WJSG-3rd (1999)	Stage I, II	116	No	71.1	$P = 0.39$ ($p = 0.03$ for T1N0M0)
		109	CDDP + VDS + MMC followed by UFT	76.8	
WJSG-4th (2005)	Stage I	169	No	75.9	0.723 (0.464–1.125) [multivariate analysis] $P = 0.105$ ($P = 0.036$ for T1N0M0)
		163	UFT	82.2	
WJSG-5th (2005)[#]	Stage IIIA(N2)	30	UFT	47	$P = 0.401$
		28	CDDP + VDS followed by UFT	46	
Northeast Japan (2003)	Stage I, II	110	No	75	1.134 (0.654–1.965) $P = 0.7013$
		109	UFT	79	
ACTLC (2005)	Stage I	50	No	66.3	$P = 0.113$ (among 3 arms)
		50	UFT	67.7	0.94 (0.48–1.82) $P = 0.076$ (vs surgery-alone)
		50	CDDP + DVS followed by UFT	87.9	0.47 (0.22–1.01) $P = 0.045$ (vs surgery-alone)
OCLSG (2006)	Stage I	87	No	57.6 (at 8-years)	0.57 (0.32–0.98) $P = 0.046$
		85	UFT	74.2 (at 8-years)	
	Stage II-IIIA	48	No	36.8 (at 8-years)	$P = 0.53$
		47	CDDP + VDS followed by UFT	38.0 (at 8-years)	
JLCRG (2004)	Stage I adenocarcinoma, only	488	No	85	0.71 (0.52-0.98) $P = 0.04$ ($P = 0.005$ for T2N0M0)
		491	UFT	88	
WJTOG0101 (2011)[#]	Stage IB-IIIA (N2, one station only)	304	UFT	68	0.948 $P = 0.343$
		305	GEM	70	

No treatment-related death (TRD) reported in any trial

HR hazard ratio, *CI* confidence interval, *TRD* treatment-related death, *CDDP* cisplatin, *MMC* mitomycin C, *VDS* vindesine, *VNB* vinorelbine, *IFO* ifosfamide, *VBL* vinblastine

[#] Year of presentation, because not yet published

Adjuvant chemotherapy with targeting agents

Today, two major classes of targeting agents, those that inhibit tumor angiogenesis and those that inhibit "driver oncogenes," play important roles in chemotherapy for patients with unresectable metastatic NSCLC [30]. In the postoperative adjuvant setting, chemotherapy using targeting agents may provide a survival benefit, but the safety and efficacy remain unclear and should be investigated.

Angiogenesis inhibitors

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is the first clinically available angiogenesis inhibitor. In a phase 2 trial for advanced NSCLC, life-threatening pulmonary hemorrhage occurred in 6 of 66 patients who received bevacizumab, and serious hemorrhage events appeared to be more common among patients with predominantly squamous cell

carcinomas [31]. Based on these results, only non-squamous NSCLC patients were enrolled in further randomized trials [32]. The ECOG 4599 is a landmark trial showing a significant improvement in OS with the addition of bevacizumab to carboplatin plus paclitaxel as the first-line chemotherapy for advanced non-squamous NSCLC [median OS time (MST), 10.3 vs. 12.3 months; HR, 0.79 (95 % CI, 0.67–0.92); $p = 0.003$] [33]. A meta-analysis of four randomized trials, including the ECOG 4599 trial, showed that bevacizumab significantly improved OS when it was combined with platinum-based chemotherapy [HR, 0.90 (95 % CI, 0.81–0.99; $p = 0.03$)] [31], and the addition of bevacizumab was recommended in first-line chemotherapy for selected non-squamous NSCLC patients [15]. Ramucirumab, an antibody against a certain receptor of VEGF (VEGFR-2), is another angiogenesis inhibitor. A phase 3 trial comparing docetaxel alone and docetaxel plus ramucirumab in second-line chemotherapy for advanced NSCLC of all histologic types, including squamous cell carcinoma, showed a significant OS benefit from the addition of ramucirumab (MST, 9.1 vs. 10.5 months) [34]. In December 2014, the addition of ramucirumab was approved in the USA.

Whether the addition of bevacizumab to cisplatin-based chemotherapy can provide a survival benefit postoperative adjuvant setting is currently being evaluated in an ongoing phase 3 trial (ECOG1505). [35]. Patients with completely resected p-stage IB (≥4 cm in diameter)–IIIA NSCLC are eligible for participation in the study and are randomly assigned to chemotherapy-alone group or chemotherapy plus bevacizumab group. Patients assigned to the chemotherapy-alone group receive four cycles of a cisplatin-based chemotherapy, which is chosen (by physicians) from four different regimens: cisplatin plus either vinorelbine, gemcitabine, docetaxel, or pemetrexed (pemetrexed is only used for the treatment of non-squamous NSCLC patients). Patients assigned to the chemotherapy plus bevacizumab group receive 15 mg/kg of bevacizumab every 3 weeks for 1 year in addition to four cycles of cisplatin-based chemotherapy. An interim analysis of the trial showed no unexpected toxicity caused by the addition of bevacizumab in the postoperative adjuvant setting; however, treatment-related mortality seemed high in both groups (2.5 % in the chemotherapy-alone group and 3.8 % in the chemotherapy plus bevacizumab group) [36], considering the relatively low mortality after recent lung cancer surgery (<1 % in Japan) [37]. Patient accrual into the study has been completed, and the safety and efficacy of the addition of bevacizumab in the postoperative adjuvant setting will be revealed in near future.

Tyrosine-kinase inhibitors (TKIs)

The discovery of "driver oncogenes" such as mutations in the *epidermal growth factor receptor* (*EGFR*) gene and chromosomal alterations in the *anaplastic lymphoma kinase* (*ALK*) gene has provided new insights into chemotherapy for metastatic NSCLC [30, 38–42]. A strong correlation between the presence of *EGFR* gene mutations (deletions in exon 19 or point mutations in exon 21) activating the tyrosine-kinase activity of EGFR and a significant clinical response to the administration of tyrosine-kinase inhibitor of EGFR (EGFR-TKI, gefitinib) was first reported in 2004 [38, 39]. The subsequent subgroup analyses of a phase 3 study comparing carboplatin plus paclitaxel and gefitinib, as first-line chemotherapies for lung adenocarcinoma patients, showed that the presence of EGFR-activating mutations strongly predicted prolonged progression-free survival (PFS) and a higher response rate [43]. In addition, all phase 3 trials comparing platinum-based regimens with EGFR-TKI (gefitinib [44, 45], erlotinib [46, 47], or afatinib [48, 49]) as the first-line chemotherapy for patients with NSCLC harboring EGFR-activating mutations showed a significantly longer PFS in patients treated with EGFR-TKI. Similarly, as a first-line treatment for metastatic NSCLC with ALK-alteration, a phase 3 trial comparing pemetrexed plus platinum agent (cisplatin or carboplatin) and an ALK-TKI (crizotinib) showed a significantly better PFS and response rate in patients treated with crizotinib [50]. Based on these results, systemic treatment with TKIs is currently recommended for patients with metastatic NSCLC who harbor "driver oncogenes" [15].

Several phase 3 studies comparing surgery-alone and surgery followed by EGFR-TKI administration have been conducted in a postoperative adjuvant setting (Table 4) [51–53]. The V-15-3 trial (conducted in Japan) and the BR 19 trial (conducted in North America) were RCTs of adjuvant gefitinib administration for mutation-unselected NSCLC patients. All patients with completely resected p-stage IB, II, or IIIA NSCLC were eligible for inclusion in the study, regardless of EGFR-status, because *EGFR*-activating mutations had not been discovered when the studies were planned. The V-15-31 trial was halted very early because of increased incidence of interstitial lung disease (ILD). The safety data for the 38 recruited patients showed no unexpected adverse events related to gefitinib treatment; however, it should be noted that one of the 18 patients assigned to the gefitinib group died of ILD [51].

The BR 19 trial was also closed early, after the random assignment of 503 of the 1242 planned patients (252 to the placebo group and 251 to the gefitinib group), because two RCTs for advanced NSCLC [Iressa Survival Evaluation in Lung Cancer (ISEL) [54] and S0023 [55]] showed no survival benefit from the administration of gefitinib. The survival data analyses for all patients enrolled in the BR 19 trial showed no difference in OS (primary endpoint) or DFS (secondary endpoint) between the placebo group and the gefitinib group. The exploratory analyses showed

Table 4 Randomized controlled trials of adjuvant treatment with EGFR-TKI for non-small cell lung cancer (NSCLC)

Trial (year of publication)	Inclusion criteria	No of pts	Chemotherapy	Disease-free survival		Overall survival		TRD
				Median time	HR (95 % CI); *P* value	Median time	HR (95 % CI); *P* value	
V-15-31 (2005)	Stage IB, II, IIIA	20	No (Placebo)	NE		NE		–
		18	Gefitinib	NE		NE		5.6 %
BR19 (2013)	Stage IB, II, IIIA	252	No (Placebo)	NR	1.22 (0.93–1.61); *P* = 0.15	NR	1.24 (0.94–1.64); *P* = 0.14	–
		251	Gefitinib	4.2 years		5.1 years		1.2 %
	Subgroup analysis for EGFR-mutated tumor, only	8	No (Placebo)	NR	1.84 (0.44–7.73); *P* = 0.40	NR	3.16 (0.61–16.45); *P* = 0.15	
		7	Gefitinib					
RADIANT (2014)[#]	Stage IB, II, IIIA (EGFR positive, only*)	350	No (Placebo)	48.2 months	0.90 (0.741–1.104); *P* = 0.3235	NR	1.13 (0.881–1.448); *P* = 0.3350	–
		623	Erlotinib	50.5 months		NR		0 %
	Subgroup analysis for EGFR-mutated tumor, only	59	No (Placebo)	28.5 months	0.61 (0.384–0.981); *P* = 0.0391	NR	1.09 (0.545–2.161); *P* = 0.8153	
		102	Erlotinib	46.4 months		NR		

HR hazard ratio, *CI* confidence interval, *TRD* treatment-related death, *NE* not evaluated, *NR* not reached

[#] The year of presentation (not yet published)

* EGFR expression was found to be positive by immunohistochemistry (IHC) or fluorescence in situ hybridization analysis

no survival benefit from gefitinib administration, even in patients with tumors harboring EGFR-activating mutations [52].

In the RADIANT trial, an international trial of adjuvant erlotinib treatment for p-stage IB, II, or IIIA NSCLC, patients were eligible only when the expression of EGFR was found to be positive by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). DFS for all eligible patients, the primary endpoint of the trial, was similar in the placebo group and in the erlotinib group (HR, 0.90). DFS for patients with *EGFR* mutations, an added secondary endpoint, favored the erlotinib group (HR, 0.61); however, the difference was not statistically significant [53].

Accordingly, adjuvant EGFR-TKI administration should not be indicated for mutation-unselected patients, but might be evaluated in clinical trials for patients with *EGFR* mutations. An RCT comparing cisplatin plus vinorelbine and gefitinib as the postoperative adjuvant chemotherapy for p-stage II-III NSCLC patients with EGFR mutations (IMPACT trial) is currently underway in Japan [56].

Adjuvant radiotherapy

A meta-analysis of postoperative radiotherapy (PORT) conducted in 1998 showed a significant adverse effect of postoperative radiotherapy on survival [HR, 1.21 (95 % CI, 1.08–1.34)] [57], and the updated meta-analyses showed similar results indicating the detrimental effect of postoperative radiotherapy [58–60]. However, subgroup analyses showed that postoperative radiotherapy was increasingly detrimental with decreasing stage and lower nodal stage and that it was not detrimental in the treatment of p-N2 disease (HRs, 1.41, 1.21, and 0.96 for N0, N1, and N2 diseases, respectively) [60].

Some studies have shown that postoperative radiotherapy might improve survival in p-N2 disease [60, 61]. A retrospective review of the population-based data [data from the surveillance, epidemiology, and end results (SEER) database, in the USA] showed a significant association between the performance of postoperative radiotherapy and favorable survival [HR, 0.855 (95 % CI, 0.762–0.959); $P = 0.0077$] [61]. A subgroup analysis of the ANITA01 trial, an RCT of adjuvant chemotherapy with cisplatin plus vinorelbine in which postoperative radiotherapy was optional [10], showed that postoperative radiotherapy significantly improved survival both in patients assigned to receive adjuvant chemotherapy (5-year OS rate, 34 vs. 47 %) and in those assigned to receive no chemotherapy (5-year OS rate, 17 vs. 21 %) [10, 62]. These results suggest that postoperative radiotherapy may benefit some patients with p-N2 disease, but the role of postoperative radiotherapy remains unclear due to a lack of high-level clinical evidence. This will be clarified in ongoing RCTs such as the Lung Adjuvant Radiotherapy Trial (LUNG ART) [63]. Accordingly, postoperative radiotherapy is not recommended for unselected p-N2 patients, but might be considered for carefully selected p-N2 patients with a high risk of local recurrence [13].

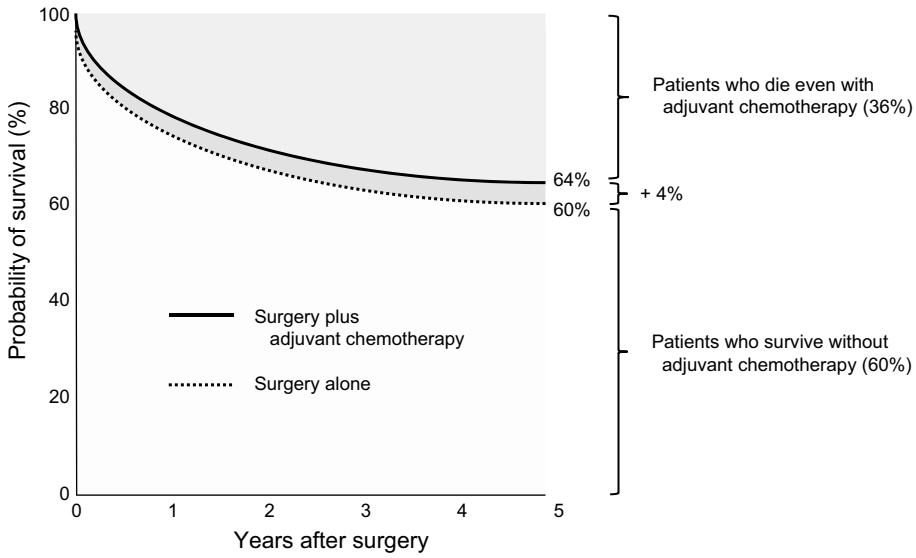

Fig. 1 Survival curves showing the survival benefit from adjuvant chemotherapy following surgery. Adjuvant chemotherapy is essentially unnecessary for 60 % of patients, who can be expected to survive without adjuvant chemotherapy, and is ineffective for 36 % of patients who can be expected to die despite receiving adjuvant chemotherapy. As a result, adjuvant chemotherapy has been found to only be beneficial for 4 % of the patients who received the treatment, although the survival benefit of 4 % at 5-years after surgery was found to be statistically significant in clinical trials

Future perspectives: biomarker-oriented individualized adjuvant chemotherapy

Today, adjuvant chemotherapy with cytotoxic agents [uracil-tegafur for p-stage IA disease (tumor diameter >2 cm) and IB disease, and cisplatin-based regimens for p-stage II-IIIA disease] has been established as the "standard treatment of care" for completely resected NSCLC. However, adjuvant chemotherapy was shown to provide only a modest survival benefit of 4 % at 5 years (from 60 to 64 %) in a meta-analysis [5]. In other words, only 4 of 100 patients who receive adjuvant chemotherapy will benefit from the therapy. The 5-year survival rate of 60 % in the surgery-alone group means that 60 of 100 patients survive without adjuvant chemotherapy and that the remaining 40 patients actually need adjuvant chemotherapy. The 5-year survival rate of 64 %, which corresponds to a 5-year mortality rate of 36 %, in the adjuvant chemotherapy group means that 36 of the 40 patients die from tumor relapse despite undergoing treatment with adjuvant chemotherapy. Simply put, in a group of 100 patients who receive adjuvant chemotherapy, the "evidence-based" findings suggest that adjuvant chemotherapy would not be necessary for 60 patients and not be effective for 36. Adjuvant chemotherapy would only be beneficial for the 4 remaining patients (Fig. 1). In addition to the modest survival benefit, adjuvant chemotherapy, especially cisplatin-based chemotherapy, may cause adverse effects that are severe and sometimes fatal. Accordingly, 96 of 100 patients who received adjuvant chemotherapy to prevent 4 lung cancer deaths would experience certain, sometimes fatal, adverse effects without any individual benefit from the treatment.

To improve the risk–benefit balance of adjuvant chemotherapy, a promising approach may be biomarker-oriented individualization. After selecting patients by biomarkers that predict prognosis (prognostic markers) as well as those that predict the efficacy or toxicity of chemotherapy (predictive markers), adjuvant chemotherapy is prescribed only to the selected patients who are likely to benefit from the treatment (Fig. 2). Prescribing adjuvant chemotherapy only to patients in whom a higher risk of recurrence is identified by prognostic markers means that the other patients will not receive unnecessary chemotherapy. The ability to prescribe adjuvant chemotherapy only to patients who are expected, due to the presence of predictive markers, to receive a significant survival benefit from chemotherapy means that the patients who are not expected to benefit will not receive ineffective chemotherapy. A number of biomarkers such as excision repair cross-complementation group 1 (ERCC1) have been investigated in postoperative adjuvant setting [64–73], but no optimal biomarker has been established (Table 5) [64]. The establishment of new biomarkers is necessary to realize individualized adjuvant chemotherapy with a favorable risk–benefit balance.

ERCC1

ERCC1 is an important enzyme that is responsible for the repair of damage to deoxyribonucleic acids (DNA). It has been investigated as a potential prognostic and predictive marker in a number of studies [65]. The IALT Bio study was conducted to assess whether IHC-determined biomarkers can predict a significant survival benefit from adjuvant cisplatin-based chemotherapy [66]. Among all of the 1867 patients enrolled in the IALT trial, adjuvant cisplatin-based

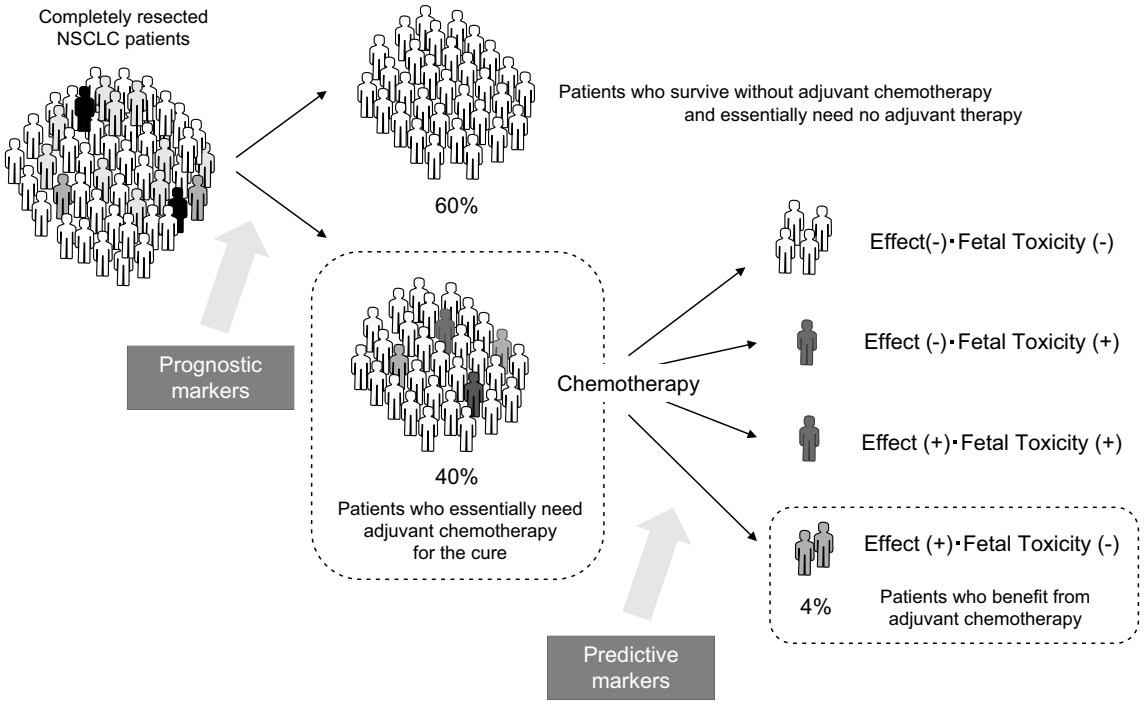

Fig. 2 Individualized adjuvant chemotherapy based on prognostic and predictive biomarkers. The selection of patients who truly need adjuvant chemotherapy by prognostic markers and those who will truly benefit from adjuvant chemotherapy by predictive markers may improve the risk–benefit balance of adjuvant chemotherapy

chemotherapy provided only a modest survival benefit, with a 4.1 % improvement in 5-year OS [8]. The IALT Bio study showed a significant association between a survival benefit from adjuvant chemotherapy and the absence of ERCC1 expression (test for interaction, $P = 0.009$). When stratified by ERCC1 expression status, the survival benefit was greater among patients with ERCC1-negative tumors [5-year OS rate, 39–47 %; HR, 0.65 (95 % CI, 0.50–0.86); $P = 0.002$], but was not seen in patients with ERCC1-positive tumors [5-year OS rate, 55–50 %; HR, 1.14 (95 % CI, 0.84–1.55); $P = 0.40$]. Among patients assigned to receive no chemotherapy, patients with ERCC1-positive tumors survived significantly longer than those with ERCC1-negative tumors [5-year OS rate, 46 vs. 39 %; HR, 0.66 (95 % CI, 0.49–0.90); $P = 0.009$]. These results suggest that the absence of ERCC1 expression is a significant prognostic factor in the prediction of a poor prognosis [66].

Nevertheless, a subsequent study to validate the prognostic and predictive effects of ERCC1 expression status failed to show a significant association between ERCC1 expression status and the prognosis or efficacy of cisplatin-based adjuvant chemotherapy [67]. A meta-analysis of published studies that investigated the clinical significance of ERCC1 status in NSCLC showed that high ERCC1 expression was associated with poor survival in patients treated with platinum-containing chemotherapy. In spite of these findings, there is no clear evidence to support the use of ERCC1 status in clinical practice, mainly due to small sample size of each study as well as the non-standardized protocols that they employed, including the assay and cut-off values for ERCC1 expression [64]. The evidence that is currently available suggests that ERCC1 status should be investigated within clinical trials. To evaluate the feasibility of individualized adjuvant chemotherapy based on ERCC1 expression and *EGFR* mutations, a randomized phase 2 trial [IFCT-0802, the phase 2 part of the tailored postsurgical therapy in early-stage NSCLC (TASTE)] was conducted in France. The primary endpoint of the study, the feasibility as defined by 80 % of patients being able to start adjuvant therapy within 2 months after surgery, was met. However, the phase 3 part of the TASTE was canceled due to the poor reliability that the IHC assay demonstrated in the evaluation of ERCC1 expression [67, 74].

Gene signatures

Microarray studies have provided a large number of gene signatures that may be used to predict clinical outcomes by evaluating the expression of multiple genes (not a single gene) in tumor tissues. In breast cancer, the prognostic significance of gene signatures evaluated by commercially available assays such as “Oncotype DX” and

Table 5 Biomarkers investigated in adjuvant chemotherapy trials (modified from Tables 3, 4, 5 in [64])

Marker	Study	Results	
ERCC1 (IHC)	IALT Bio	Prognostic, but not validated	High ERCC1 expression associated with a favorable OS (HR = 0.88 (95 % CI, 0.71–1.10); $P = 0.26$) [66], but the prognostic value not validated in the subsequent study [67]
	IALT Bio	Predictive, but not validated	High ERCC1 expression predictive of lack of survival benefit from adjuvant cisplatin-based chemotherapy [66], but the predictive value not validated in the subsequent study [67]
p27 expression (IHC)	IALT Bio	Predictive	p27 expression negatively associated with longer OS from adjuvant cisplatin-vinorelbine chemotherapy (HR, 0.66 versus 1.09; P value for interaction, 0.02) [68]
K-ras mutations	E3590	Not prognostic	K-ras mutations not prognostic for OS (MST, 30 months versus 42 months; $P = 0.38$) [69]
	JBR. 10	Not prognostic	K-ras mutations not prognostic for OS [HR, 1.23 (95 % CI, 0.76–1.71)] [70]
	JBR. 10	Predictive, but not significant	Suggests lack of survival benefit with adjuvant cisplatin-vinorelbine chemotherapy for patients with K-ras mutated tumors (HR, 0.69 versus 0.95; P value for interaction, 0.29), but test for statistical interaction negative [69]
p53 mutations	E3590	Not prognostic	*p53* mutations not prognostic for PFS or OS (MST, 38 months versus 52 months; $P = 0.83$) [69]
	JBR. 10	Not prognostic	p53 mutations not prognostic for OS [HR, 1.15 (95 % CI, 0.75–1.77)] [69]
	JBR. 10	Predictive	Suggests lack of survival benefit with adjuvant cisplatin-vinorelbine chemotherapy for patients with *p53*-mutated tumors [69]
p53 expression (IHC)	E3590	Not prognostic	p53 overexpression not prognostic for PFS or OS (1-year OS, 85 vs. 77 %; $P = 0.93$) [69]
	JBR. 10	Prognostic	p53 overexpression associated with worse OS [HR, 1.89 (95 % CI, 1.07–3.34)] [70]
	JBR. 10	Predictive	p53 expression associated with improved OS from adjuvant cisplatin-vinorelbine chemotherapy (HR, 0.54 versus 1.40; P value for interaction, 0.02) [69]
Tubulin expression (IHC)	LACE-Bio	Prognostic	Tubulin expression positivity prognostic for worse DFS [HR, 1.30 (95 % CI, 1.11–1.5)] and OS [HR, 1.27 [95 % CI, 1.07–1.51)] in early NSCLC [71]
	LACE-Bio	Not predictive	Tubulin expression not associated with OS benefit from adjuvant cisplatin-based chemotherapy (HR, 1.03 vs. 0.83; P value for interaction, 0.20) [71]
15-gene signature	JBR. 10	Prognostic	A 15-gene signature separated patients assigned to the surgery-alone group into "high-risk" and "low-risk" mortality subgroups with significantly different OS [HR, 15.02 (95 % CI, 5.12–44.04); $P < 0.001$) [72], which was validated in an independent cohort [73]
	JBR. 10	Predictive	A 15-gene signature predictive of improved OS after adjuvant chemotherapy in "high-risk" patients [HR, 15.02 (95 % CI, 5.12–44.04); $P < 0.001$] [72]

"MammaPrint" has been established, with gene signatures being used in decision-making related to the administration of adjuvant chemotherapy [75].

A number of studies have identified different gene signatures that may be used to predict the prognosis or survival benefit associated with adjuvant chemotherapy in NSCLC; however, no signatures have been established for use in clinical practice [76, 77]. For example, Potti et al. [78] reported that a gene signature (the "metagene model") predicted the risk of recurrence following surgery, but the article was retracted because the results were not validated.

Recently, some promising gene signatures, which have been validated in independent cohorts, were identified. The prognostic significance of a 15-gene signature, identified as a prognostic and predictive marker in a cohort of patients enrolled in an adjuvant cisplatin plus vinorelbine chemotherapy trial (JBR10) [72], was validated in an independent cohort of resected NSCLC patients [73]. In addition, another gene signature incorporating 14 genes was identified as a prognostic marker in a cohort of resected non-squamous NSCLC patients, which was validated in 2 independent cohorts [79]. The "14-gene signature assay" is the only commercially available laboratory test to evaluate a prognostic gene signature in NSCLC (Perveniom RS test, Life Technologies, Inc., Grand Island, NY), but the test may not be useful in prediction of a benefit from adjuvant chemotherapy.

Circulating tumor cells (CTCs)

Circulating tumor cells (CTCs) are tumor cells that are shed from a primary tumor and circulate in the peripheral blood [80]. CTCs, which can even be detected in the early stage of the development and progression of malignant tumors,

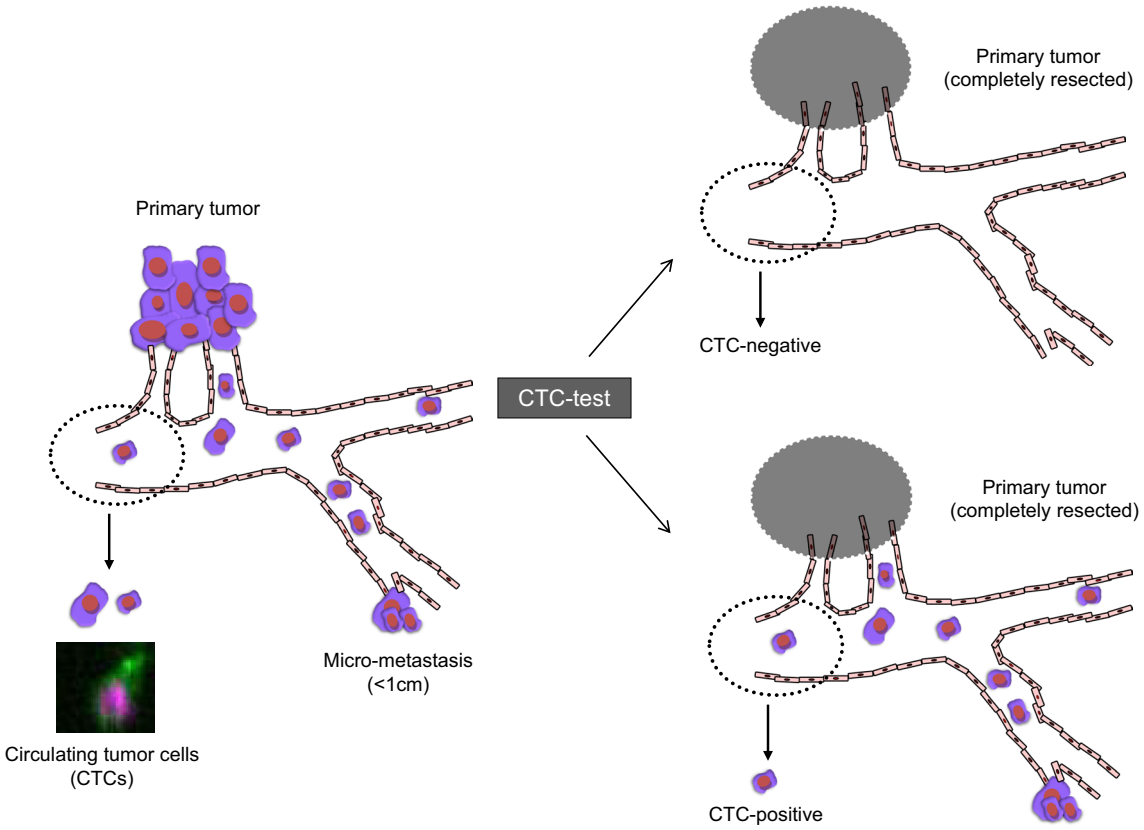

Fig. 3 Circulating tumor cells (CTCs) are tumor cells that are shed from a primary tumor and circulate in the peripheral blood. The detection of CTCs by the peripheral blood sampling (CTC test) may predict the presence of micro-metastatic foci, which will develop and result in postoperative recurrence

can be a surrogate of micro-metastasis. The presence of CTCs may indicate the presence of micro-metastatic foci, which will develop into clinically apparent metastatic foci. Accordingly, among all patients who underwent complete resection, patients who truly need adjuvant chemotherapy due to a high-risk of recurrence can be identified and selected as "CTC positive" by a CTC test (Fig. 3). In addition, a CTC test can be repeatedly and noninvasively performed by peripheral blood sampling, which may indicate another advantage of the CTC test: It can be used for the real-time monitoring of the therapeutic effects of adjuvant chemotherapy.

Despite such potential advantages of CTCs as a biomarker, the detection of rare CTC contaminants in a large number of normal blood cells may present a technical challenge. The CellSearch System (Veridex LLC, Raritan, NJ) is a semi-automated system for the quantitative evaluation of CTCs, in which CTCs are immunomagnetically captured with an antibody against epithelial cell adhesion molecule (EpCAM) [81]. The most important advantage of the CellSearch system is the reproducibility of its results across different laboratories [82], A CTC test using the CellSearch system has been approved in the USA by the Food and Drug Administration (FDA) for the monitoring of blood from metastatic breast and colon cancer patients. In lung cancer, however, little has been reported. We assessed the clinical usefulness of the CTC test in a series of prospective studies [83–85] and showed that CTCs were more frequently detected in small cell lung cancer (SCLC) patients than in NSCLC patients (66.7 vs. 27.6 %) [84] and that the CTC test provided a significant prognostic performance in SCLC [85]. The diagnostic performance of the CTC test in predicting the presence of distant metastasis was significant [area under receiver operating characteristic curve (AUC-ROC), 0.783 (95 % CI, 0.669–0.886); $P < 0.001$), but the sensitivity was only 71.0 % [84]. The relatively low sensitivity (<100 %) in predicting the presence of "clinically detectable" metastasis may indicate that the CTC test is not sensitive enough to predict the presence of micro-metastasis. For the clinical application of a CTC test in decision-making related to the performance of adjuvant chemotherapy for completely resected NSCLC patients, it will be essential to develop detection systems with a higher degree of sensitivity.

Conclusions

Adjuvant chemotherapy for completely resected NSCLC has been established as the "standard treatment of care" based on the abundant evidence that has been yielded by RCTs. However, current adjuvant chemotherapy provides only a modest survival benefit and sometimes causes fatal side effects when it is prescribed for all patients according to "evidence-based" guidelines. Future studies may focus on the individualization of adjuvant chemotherapy based on biomarkers such as gene signatures, which will improve the risk–benefit balance of adjuvant chemotherapy.

Conflict of interest Fumihiro Tanaka received research grant from Taiho Pharmaceutical, Astra Zeneca, Chugai Pharmaceutical, Eli Lilly, and Boehringer Ingelheim. Fumihiro Tanaka received lecture fees from Taiho Pharmaceutical, Astra Zeneca, Chugai Pharmaceutical, Eli Lilly, and Boehringer Ingelheim.

References

1. Goldstraw P, Crowly J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007;2:706–14.
2. Sawabata N, Asamura H, Goya T, Mori M, Nakanishi Y, Eguchi K, et al. Japanese Lung Cancer Registry Study: first prospective enrollment of a large number of surgical and nonsurgical cases in 2002. J Thorac Oncol 2010;5:1369–75.
3. Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol. 2011;6:1229–35.
4. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ. 1995;311:899–909.
5. NSCLC Meta-analysis Collaborative Group, Arriagada R, Auperin A, Burdett S, Higgins JP, Stewart LA, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375:1267–77.
6. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 suppl):e278s–313s.
7. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26:3552–9.
8. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350:351–60.
9. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2004;352:2589–97.
10. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzáles-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer [Adjuvant Navelbine International Trialist Association (ANITA)]: a randomised controlled trial. Lancet Oncol. 2006;7:719–27.
11. Strauss GM, Herndon JE 2nd, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol. 2008;26:5043–51.
12. Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, Morán T, Astudillo J, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol. 2010;28:3138–45.
13. Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, et al. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e314S–40S.
14. Crinò L, Weder W, van Meerbeeck J, Felip E. ESMO Guidelines Working Group. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v103–15.
15. Socinski MA, Evans T, Gettinger S, Hensing TA, Sequist LV, Ireland B, et al. Treatment of stage IV non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e341S–68S.
16. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26:3543–5.
17. Fujii S, Kitano S, Ikenaka K, Shirasaka T. Effect of coadministration of uracil or cytosine on the anti-tumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. Gann (Cancer Sci). 1979;70:209–14.
18. Tanaka F, Fukuse T, Wada H, Fukushima M. The history, mechanism and clinical use of oral 5-fluorouracil derivative agents. Curr Pharm Biotech. 2000;1:137–64.
19. Uchida J, Sato K, Okabe H, Saito H, Nakano K, Fujioka A, et al. Experimental postoperative adjuvant chemotherapy by UFT using primary tumor amputation model. Int J Mol Med. 2000;5:357–62.
20. Tanaka F. UFT (tegafur and uracil) as postoperative adjuvant chemotherapy for solid tumors (carcinoma of the lung, stomach, colon/rectum, and breast): clinical evidence, mechanism of action, and future direction. Surg Today. 2007;37:923–43.
21. Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. West Japan Study Group for Lung Cancer Surgery. J Clin Oncol. 1996;14:1048–54.
22. Nakagawa M, Tanaka F, Tsubota N, Ohta M, Takao M, Wada H. A randomized phase III trial of adjuvant chemotherapy with UFT for completely resected pathological stage I non-small cell lung cancer: the West Japan Study Group for Lung Cancer Surgery (WJSG)–the 4th study. Ann Oncol. 2005;16:75–80.
23. Endo C, Saito Y, Iwanami H, Tsushima T, Imai T, Kawamura M, et al. A randomized trial of postoperative UFT therapy in p-stage I- II non-small cell lung cancer: North-east Japan Study Group for Lung Cancer Surgery. Lung Cancer. 2003;40:181–6.

24. Imaizumi M. Postoperative adjuvant cisplatin, vindesine, plus uracil-tegafur chemotherapy increased survival of patients with completely resected p-stage I non-small cell lung cancer. Lung Cancer. 2005;49:85–94.
25. Nakagawa K, Tada H, Akashi A, Yasumitsu T, Iuchi K, Taki T, et al. Randomized study of adjuvant chemotherapy for completely resected p-stage I-IIIA non-small cell lung cancer. Br J Cancer. 2006;95:817–21.
26. Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med. 2004;350:1713–21.
27. Mitsudomi T, Tada H, Ichinose Y, Yokoi K, Katakami N, Oda M, et al. Randomized phase III trial of adjuvant chemotherapy with gemcitabine compared with oral tegafur-uracil (UFT) in resected, stage IB-IIIa non-small cell lung cancer (WJTOG 0101). Eur J Cancer. 2011;47(supp 1):s594 **abstract #9008**.
28. Hamada C, Tanaka F, Ohta M, Fujimura S, Kodama K, Imaizumi M, et al. Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. J Clin Oncol. 2005;23:4999–5006.
29. Hamada C, Tsuboi M, Ohta M, Fujimura S, Kodama K, Imaizumi M, et al. Wada H. Effect of postoperative adjuvant chemotherapy with tegafur-uracil on survival in patients with stage IA non-small cell lung cancer: an exploratory analysis from a meta-analysis of six randomized controlled trials. J Thorac Oncol. 2009;4:1511–6.
30. Johnson DH, Schiller JH, Bunn PA. Recent clinical advances in lung cancer management. J Clin Oncol. 2014;32:973–82.
31. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004;22:2184–91.
32. Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013;24:20–30.
33. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542–50.
34. Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384:665–73.
35. Socinski MA. An overview of adjuvant chemotherapy for resected non-small cell lung cancer: focus on the ECOG 1505 phase III trial. Community Oncol. 2008;5:457–63.
36. Wakelee HA, Dahlberg SE, Keller SM, Gandara, Graziano SL, Leighl NB, et al. Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small cell lung cancer (NSCLC). J Clin Oncol. 2011;29(May 20 suppl):456s **abstract #7013**.
37. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Masuda M, Kuwano H, Okumura M, Amano J, Arai H, Endo S, et al. Thoracic and cardiovascular surgery in Japan during 2012 : Annual report by The Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg. 2014;62:734–64.
38. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350:2129–39.
39. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304:1497–500.
40. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561–6.
41. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363:1693–703.
42. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013;8:823–59.
43. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57.
44. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380–8.
45. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11:121–8.
46. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–46.
47. Zhou C, Wu YL, Chen G, Freg J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12:735–42.
48. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31:3327–34.
49. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:213–22.
50. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371:2167–77.
51. Tsuboi M, Kato H, Nagai K, Tsuchiya R, Wada H, Tada H, et al. Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer. Anticancer Drugs. 2005;16:1123–8.
52. Goss GD, O'Callaghan C, Lorimer I, Tsao MS, Masters GA, Jett J, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol. 2013;31:3320–6.
53. Kelly K, Altorki NK, Eberhardt WEE, O'Brien MER, Spigel, Crino L, et al. A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results. J Clin Oncol. 2014;32(May 20 supplement):477 s **abstract #7501**.

54. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005;366:1527–37.
55. Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol. 2008;26:2450–6.
56. Mitsudomi T, Tada H. EGFR gene mutations: is it prognostic or predictive in surgically resected lung cancer? J Thorac Oncol. 2012;7:1739–41.
57. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet. 1998;352:257–63.
58. Burdett S, Stewart L. PORT Meta-analysis Group. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. Lung Cancer. 2005;47:81–3.
59. Burdett S, Rydzewska L, Tierney JF, Fisher DJ. PORT Meta-analysis Trialist Group. A closer look at the effects of postoperative radiotherapy by stage and nodal status: updated results of an individual participant data meta-analysis in non-small-cell lung cancer. Lung Cancer. 2013;80:350–2.
60. PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2005;2:CD002142.
61. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non–small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol. 2006;24:2998–3006.
62. Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA. Adjuvant Navelbine International Trialist Association. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys. 2008;72:695–701.
63. Le Pechoux C. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment on new data. Oncologist. 2011;16:672–81.
64. Ellis PM, Blais N, Soulieres D, Ionescu DN, Kashyap M, Liu G, et al. A systematic review and Canadian consensus recommendations on the use of biomarkers in the treatment of non-small cell lung cancer. J Thorac Oncol. 2011;6:1379–91.
65. Hubner RA, Riley RD, Billingham LJ, Popat S. Excision repair cross-complementation group 1 (ERCC1) status and lung cancer outcomes: a meta-analysis of published studies and recommendations. PLoS ONE. 2011;6:e25164.
66. Olaussen KA, Dunant A, Fouret P, Brambilla E, André F, Haddad V, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med. 2006;355:983–91.
67. Friboulet L, Olaussen KA, Pignon JP, Shepherd FA, Tsao MS, Graziano S, et al. ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med. 2013;368:1101–10.
68. Filipits M, Pirker R, Dunant A, Lantuejoul S, Schmid K, Huynh A, et al. Cell cycle regulators and outcome of adjuvant cisplatin-based chemotherapy in completely resected non-small-cell lung cancer: the International Adjuvant Lung Cancer Trial Biologic Program. J Clin Oncol. 2007;25:2735–40.
69. Scjiller JH, Adak S, Feins RH, Keller SM, Fry WA, Livingston RB, et al. Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small-cell lung cancer on E4592: A Laboratory Ancillary Study on an Eastern Cooperative Oncology Group Prospective Randomized Trial of Postoperative Adjuvant Therapy. J Clin Oncol. 2001;19:448–57.
70. Tsao MS, Aviel-Ronen S, Ding K, Lau D, Liu N, Sakurada A, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. J Clin Oncol. 2007;25:5240–7.
71. Reiman T, Lai R, Veillard AS, Paris E, Soria JC, Rosell R, et al. Cross-validation study of class III beta-tubulin as a predictive marker for benefit from adjuvant chemotherapy in resected non-small-cell lung cancer: analysis of four randomized trials. Ann Oncol. 2012;23:86–93.
72. Zhu CQ, Ding K, Strumpf D, Weir BA, Meyerson M, Pennell N, et al. Prognostic and predictive gene signature for adjuvant chemotherapy in resected non-small-cell lung cancer. J Clin Oncol. 2010;28:4417–24.
73. Der SD, Sykes J, Pintilie M, Zhu CQ, Strumpf D, Liu N, et al. Validation of a histology-independent prognostic gene signature for early-stage, non-small-cell lung cancer including stage IA patients. J Thorac Oncol. 2014;9:59–64.
74. Wislez M, Barlesi F, Besse B, Mazieres J, Merle P, Cadranel J, et al. Customized adjuvant phase II trial in patients with non-small-cell lung cancer: IFCT-0801 TASTE. J Clin Oncol. 2014;32:1256–61.
75. Marrone M, Stewart A, Dotson WD. Clinical utility of gene-expression profiling in women with early breast cancer: an overview of systematic reviews. Genet Med. 2014. doi:10.1038/gim.2014.140.
76. Boutros PC, Lau SK, Pintilie M, Liu N, Shepherd FA, Der SD, et al. Prognostic gene signatures for non-small-cell lung cancer. Proc Natl Acad Sci. 2009;106:2824–8.
77. Bunn PA Jr, Hirsh FR, Aiser DL. Is there clinical value to prognostic signatures in early-stage NSCLC? Clin Cancer Res. 2014;20:1727–9.
78. Potti A, Mukherjee S, Petersen R, Dressman HK, Bild A, Koontz J, et al. Retraction: a genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med. 2011;364:1176.
79. Kratz JR, He J, Van Den Eeden SK, Zhu ZH, Gao W, Pham PT, et al. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. Lancet. 2012;379:823–32.
80. Alix-Panabières C, Riethdorf S, Pantel K. Circulating tumor cells and bone marrow micrometastasis. Clin Cancer Res. 2008;14:5013–21.
81. Pierga JY, Pierga JY, Bonneton C, Vincent-Salomon A, de Cremoux P, Nos C, et al. Clinical significance of immunocytochemical detection of tumor cells using digital microscopy in peripheral blood and bone marrow of breast cancer patients. Clin Cancer Res. 2004;10:1392–400.
82. Muller V, Stahmann N, Riethdorf S, Rau T, Zabel T, Goetz A, et al. Circulating tumor cells in breast cancer: correlation to bone marrow micrometastases, heterogeneous response to systemic therapy and low proliferative activity. Clin Cancer Res. 2005;11:3678–85.
83. Okumura Y, Tanaka F, Yoneda K, Hashimoto M, Takuwa T, Kondo N, et al. Circulating tumor cells in pulmonary venous blood of primary lung cancer patients. Ann Thorac Surg. 2009;87:1669–75.
84. Tanaka F, Yoneda K, Kondo N, Hashimoto M, Takuwa T, Matsumoto S, et al. Circulating tumor cells as a diagnostic marker in primary lung cancer. Clin Cancer Res. 2009;15:6980–6.
85. Naito T, Tanaka F, Ono A, Yoneda K, Takahashi T, Murakami H, et al. Prognostic impact of circulating tumor cells in patients with small-cell lung cancer. J Thorac Oncol. 2012;7:512–9.