Table 2 Response rate

Response	$N = 20$	% (95% CI)
Partial response	14	70
Stable disease	4	20
Progressive disease	1	5
Inevaluable	1	5
Overall response rate	14	70 % (45.7–88.1)
Disease control rate	18	90 % (68.3–98.7)

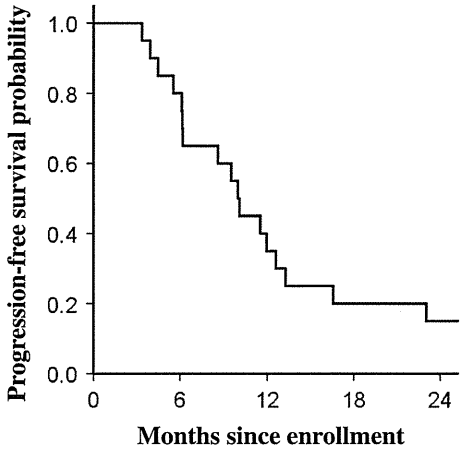

Fig. 1 Kaplan–Meier progression-free survival curve with gefitinib

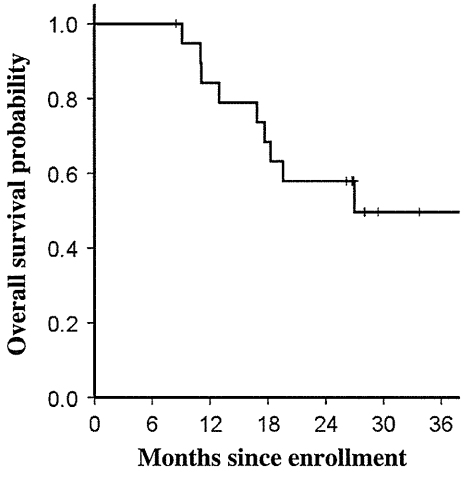

Fig. 2 Kaplan–Meier survival curve with gefitinib

Quality-of-life assessment

All 20 patients completed the FACT-LCS questionnaire at registration and after 4, 8, and 12 weeks of treatment. The adjusted mean FACT-LCS score was 22.8 ± 1.0 at baseline and 25.1 ± 0.7 at 4 weeks. The score improved

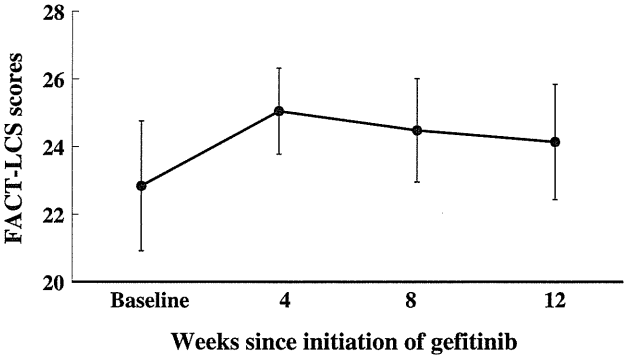

Fig. 3 FACT-LCS scores before treatment and at 4, 8, and 12 weeks after initiation of gefitinib. *Abbreviation FACT-LCS* Functional Assessment of Cancer Therapy-Lung Cancer Subscale

significantly at 4 weeks ($P = 0.037$) and maintained favorably during the 12-week assessment period (Fig. 3). FACT-LCS consisted of seven items: shortness of breath, cough, chest tightness, ease of breathing, changes in appetite, body weight loss, and disruptions to clear thinking. Among those seven items, shortness of breath and cough improved significantly after 4 weeks of treatment ($P = 0.046$ and $P = 0.008$, respectively).

Toxicity

Toxicity data for all 20 patients are listed in Table 3. Non-hematologic toxicity was the principal toxicity from gefitinib treatment and mainly consisted of liver dysfunction, skin rash, anorexia, diarrhea, and fatigue. Grade 3 or Grade 4 liver dysfunction occurred in 3 patients (15 %) but no other Grade 3 or Grade 4 toxicity was occurred. One case of Grade 1 pneumonitis developed in an 87-year-old woman. She had no specific symptoms; however, routine chest X-ray on day 14 showed an increase in density in the bilateral lower lung fields. Since subsequent chest computed tomography revealed bilateral diffuse interstitial opacities and the bronchoalveolar lavage findings were consistent

Table 3 Adverse events ($N = 20$)

	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3–4
AST/ALT	8	4	2	1	3
Rash	8	10	0	0	0
Anorexia	8	2	0	0	0
Diarrhea	6	2	0	0	0
Fatigue	6	2	0	0	0
Mucositis	1	3	0	0	0
Nausea	3	0	0	0	0
Pneumonitis	1	0	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

with pneumonitis, gefitinib was discontinued and the treatment with oral prednisolone (0.5 mg/kg/day) was started. Although the pneumonitis was stable, pulmonary and brain metastases gradually progressed and she died of progression of lung cancer 6 months after the occurrence of this adverse event. No treatment-related death was observed.

Discussion

The present study evaluated the efficacy and feasibility of first-line gefitinib treatment for elderly patients harboring EGFR mutation, achieving the response rate of 70 % and disease control rate of 90 %. After we started this phase II study, three groups reported comparable results of response rates from 45.5 to 74 %, and progression-free survival of 9.7–12.9 months for similar populations [17–19]. Efficacy of the present study is also comparable to the results obtained from non-elderly phase III studies. Two prospective studies (WJTOG3405 and NEJ002) and subset analysis of EGFR-mutated patients in the IPASS showed response rates of 62.1–73.7 % and progression-free survival of 9.2–10.8 months [11–13, 20]. From these data, gefitinib treatment for elderly EGFR-mutated patients appears to be as effective as that for the younger population. A randomized trial of EGFR-TKI focusing on efficacy is needed to further improve survival of elderly patients.

We also revealed that disease-related symptoms improved significantly with gefitinib therapy. FACT-LCS score improved more than two points, which is considered a clinically meaningful change [21]. Although superior QOL results were reported with gefitinib versus chemotherapy in the IPASS and NEJ002 studies, the QOL benefit for the elderly population has not been reported [22, 23]. Among the seven items of FACT-LCS, shortness of breath and cough improved significantly. This finding is in accordance with two previous QOL analyses during gefitinib treatment. Cella et al. [24] found that more patients showed an improvement in the pulmonary items of FACT-LCS, such as shortness of breath, cough, or chest tightness than in the non-pulmonary items in the IDEAL2 study, which evaluated two doses of gefitinib for the mutation-unselected population. Oizumi et al. [23] reported that more patients showed an improvement in pain and shortness of breath in the gefitinib arm in the NEJ002 study. With regard to the speed of symptom improvement, our data demonstrated significant improvement at the first follow-up, namely at 4 weeks of treatment. A former analysis reported that the median time to symptom improvement was as immediate as 10 days with gefitinib [24]. In light of its rapid effect, gefitinib could be a good treatment option for patients suffering from pulmonary symptoms like cough or dyspnea.

Toxicity in the present study was generally mild and well tolerated. Grade 3 or Grade 4 adverse events were only in three cases of liver dysfunction. No unpredicted toxicity or treatment-related death was observed. On the other hand, a subgroup analysis of a phase III study of erlotinib treatment indicated that elderly patients experienced significantly more toxicity and tended to discontinue treatment more than their younger counterparts [25]. This difference may be partly explained by the difference in EGFR-TKIs. Gefitinib 250 mg is about one-third of the maximum tolerated dose, and erlotinib 150 mg is just the maximum tolerated dose [26, 27]. Accordingly, gefitinib may have some safety margin, especially for the frail population. In the present study, the oldest patient, aged 90 years, was able to continue gefitinib therapy for about 7 months with side effects no more severe than Grade 2 mucositis and Grade 2 rash.

Pneumonitis is one of the most serious adverse events related to EGFR-TKI therapy. In our previous study evaluating gefitinib in mutation-unselected elderly NSCLC patients, three out of 30 patients (10 %) had pneumonitis, two of them with a Grade $\geq$3 [28]. In the present study, Grade 1 pneumonitis developed in one patient (5 %). Since risk factors of pneumonitis include smoking, preexisting interstitial lung disease, and older age, careful monitoring is desirable for elderly patients [29, 30].

In conclusion, the present study revealed that first-line therapy with gefitinib is effective and feasible for elderly patients harboring EGFR mutation, and improves disease-related symptoms.

Conflict of interest Kosuke Takahashi, Hiroshi Saito, Yoshinori Hasegawa, Yasuteru Sugino, and Joe Shindoh received honoraria from AstraZeneca. Yoshinori Hasegawa received research funding for his institute from AstraZeneca.

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Human papilloma virus in non-small cell lung cancer in never smokers: A systematic review of the literature

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ABSTRACT

Non-small cell lung cancer (NSCLC) in never smokers has emerged as a global public health issue. The cause is still unclear, and few studies have focused on the prevalence of human papillomavirus (HPV) in the never smokers. We performed a systematic search of PubMed for articles of HPV infection in human subjects with NSCLC up to September 2012. Although smoking status was not fully reported in all studies, we contacted the authors by e-mail to supplement this information. Differences in the distribution of patients with and without HPV infection were tested with the Chi squared test. We identified 46 eligible articles, including 23 from Asian countries ($N = 2337$ NSCLC cases), 19 from European countries ($N = 1553$) and 4 from North and South America ($N = 160$). The HPV prevalence was 28.1% (95% confidence interval (CI) 26.6–30.3%), 8.4% (95% CI 7.1–9.9%) and 21.3% (95% CI 15.2–28.4%), respectively. Eleven studies from East Asia ($N = 1110$) and 4 from Europe ($N = 569$) provided information on smoking status. The number of never smoker was 392 patients (33.9%) in East Asia and 54 patients (14.8%) in Europe. The HPV prevalence in East Asian countries was similar between never and ever smokers (33.9% vs 39.2%, $P = 0.080$). Based on the literature confirming the presence of HPV in lung cancer in never smokers, the virus plays a role in carcinogenesis in the disease. There were different patterns of HPV prevalence between Asian and European countries in the never smokers as well as in ever smokers.

1. Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Although tobacco smoking is responsible for about 90% of lung cancer cases, the epidemiology of lung cancers remains partially unresolved since the vast majority of tobacco users do not develop such tumors. In fact, there were about 30% never smokers in Japan in a large cohort study including more than 20,000 patients with non-small cell lung cancer (NSCLC) [1]. In the global estimates, never smoker lung cancer mortality would rank as the seventh most common fatal cancer [2], and it is as common a cause of death as cancer of the liver or of the esophagus [3]. NSCLC in never smokers has emerged as a global public health concern. Identification of the molecular mechanism for this disease is urgently needed to improve therapeutic strategies. In addition to tobacco smoking, a number of etiological factors have been proposed and the infection with oncogenic type of human papillomavirus (HPV) has been considered as one of those [4].

It is well known that certain HPV types cause essentially all human cervical cancer. Several studies have examined the possible involvement of HPV in non-genital cancers and have proposed the presence of HPV in esophageal, laryngeal, oropharyngeal, urothelial, breast, colon and lung cancers during the last two decades [5]. Since the virus can infect oral mucosa and subsequently larynx and bronchial tissue, this may be the main source of HPV detected in the lung [6]. Actually, Carpagnano demonstrated the presence of HPV in the exhaled breath condensate of lung cancer patients [7]. A meta-analysis showed that the prevalence of HPV in lung cancer is highly

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variable around the world and the higher frequencies are found in East Asian countries when compared with European countries [8]. The association between HPV infection and lung cancer was suggested to be geographical and race dependent.

Although HPV infection to NSCLC has been widely investigated in Asia, few studies have focused on prevalence of HPV in NSCLC in never smokers. We conducted and report here a systematic review on the issue above.

2. Materials and methods

2.1. Literature search and data extraction

We performed a systematic search of MEDLINE database using PubMed for articles of HPV infection in human subjects with NSCLC up to September 2012. Systematic search was performed using the keywords, "lung or bronchogenic", "cancer or carcinoma or neoplasm" and "HPV or human papillomavirus." All searches were limited to human studies and the English language. We included studies that used the lung tissue of patients diagnosed by histopathology to have primary NSCLC and excluded studies that used blood samples. The polymerase chain reaction (PCR) as the primary HPV detection method was included in our analysis. Therefore, studies were excluded because the primary method was in situ hybridization, immunohistochemistry, Southern blot, and Hybrid Capture II.

All studies were retrieved independently by two investigators (Y.H. and S.Y.) to assess the reliability of data extraction. After selection of potential studies, the investigators reviewed each other's selected studies and excluded inappropriate studies with the agreement of both. Disagreements were adjudicated by a third reviewer after referring to the original articles.

If the smoking status was not reported in a study, we contacted the authors by e-mail to supplement this information.

2.2. Statistical analysis

Differences in the distribution of patients with and without HPV infection were tested with the Chi squared test. The I^2 statistics was used to assess heterogeneity across studies, and $I^2 < 25$, $25 \leq I^2 < 50$, and $50 \leq I^2$ was interpreted as signifying low-level, intermediate-level, and high-level heterogeneity, respectively [9].

A P-value <0.05 was considered statistically significant, and all reported P-values were two-sided. The Eggers' test and Begg's funnel plots were calculated using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ). All other statistical analyses were performed with SPSS 16.0 for Windows software (SPSS, Chicago, IL).

3. Results

3.1. HPV prevalence

We identified 46 eligible articles (supplemental Table A1), including 23 from Asian countries ($N = 2337$ NSCLC cases), 19 from European countries ($N = 1553$) and 4 from North and South America ($N = 160$). The HPV prevalence was 28.1% (95% confidence interval (CI) 26.6–30.3%), 8.4% (95% CI 7.1–9.9%) and 21.3% (95% CI 15.2–28.4%), respectively. From these studies, there were regional differences between Asian, European and American studies (Fig. 1) including a significantly higher prevalence of HPV among lung cancer patients in Asia compared with European and American studies. When the analysis was limited to HPV types 16 and 18 which have higher oncogenic risk, a significantly higher prevalence was observed in Asia (23.1%, 95% CI 21.5–25.2%, $N = 2307$)

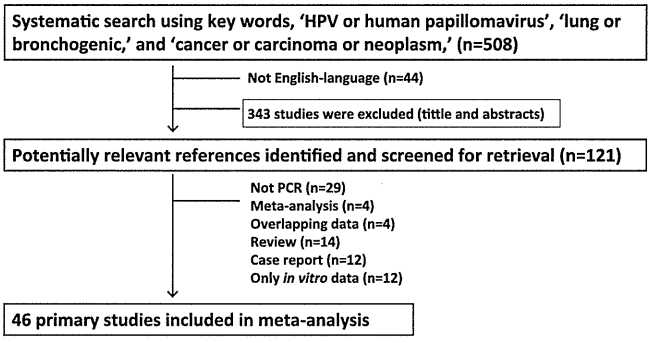

Fig. 1. Flow chart diagram showing retrieved citations from literature searches and the number of trials analyzed.

than in Europe (4.4%, 95% CI 3.5–5.2%, $N = 1434$, $P < 0.001$) or America (15.6%, 95% CI 10.3–22.1%, $N = 160$, $P = 0.003$). Apart from the worldwide regional difference, lung cancer associated with HPV infection was not evenly distributed within Japan. It was particularly high in Okinawa (43.9%, 95% CI 37.7–50.2%, $N = 255$), south of mainland Japan, but it was notably low in Tokyo (0.3%, 95% CI 0.7–1.6%, $N = 341$).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.10.002.

The prevalence of HPV in adenocarcinoma patients was slightly higher in Asia (9.8%, 95% CI 7.8–12.1%, $N = 796$) than in Europe (6.8%, 95% CI 4.8–9.2%, $N = 564$). Additionally, the prevalence of HPV in squamous cell carcinoma is significantly higher in Asia (33.2%, 95% CI 30.4–36.1%, $N = 796$) than in Europe (9.5%, 95% CI 7.5–11.9%, $N = 1090$, $P < 0.001$).

3.2. HPV prevalence in lung cancer in never smokers

Because smoking status was not fully reported in all studies, we contacted the authors by e-mail to supplement this information. Eleven studies from East Asia [10–20] ($N = 1110$), four from Europe [7,21–23] ($N = 569$) and one from America [24] ($N = 30$) provided information on smoking status (Table 1). These data showed the distribution of HPV infection with NSCLC in never smokers (31.4%, 95% CI 27.2–35.9%, $N = 452$). However, there was no HPV detected in the two studies in Japan, one study in China, Italy and Croatia. Almost half of these studies in East Asia consisted of those from Japan. Geographically lung cancer associated with HPV in never smokers was not evenly distributed in Japan. It was relatively high in Kagoshima (23.7%, 95% CI 11.4–40.2%, $N = 38$), the southwestern tip of the mainland Japan. The prevalence of HPV in never smokers was significantly higher in East Asia (33.9%, 95% CI 29.2–38.9%, $N = 392$) than in Europe (14.8%, 95% CI 6.6–27.1%, $N = 58$, $P = 0.005$). While the HPV prevalence in East Asia was similar between never and ever smokers (33.9% vs 39.2%, $P = 0.080$), it was significantly higher in never smokers than in ever smokers (14.8% vs 2.9%, $P < 0.001$) in Europe (Fig. 2).

The pie chart in East Asian shows that not only smokers were prone to HPV but also never smokers (Fig. 3). The prevalence of HPV in never smokers was 68.7% (95% CI 58.6–77.6%, $N = 105$) in Taiwan, 60.0% (95% CI 36.1–80.9%, $N = 20$) in Korea, 23.8% (95% CI 17.6–31.0%, $N = 168$) in central part of China and 12.4% (95% CI 6.8–20.2%, $N = 105$) in Japan.

3.3. Publication bias

Potential publication bias was evaluated using the Eggers' test and Begg's funnel plots with log-transformed hazards calculated from prevalence rate (horizontal axis) as the outcome and their

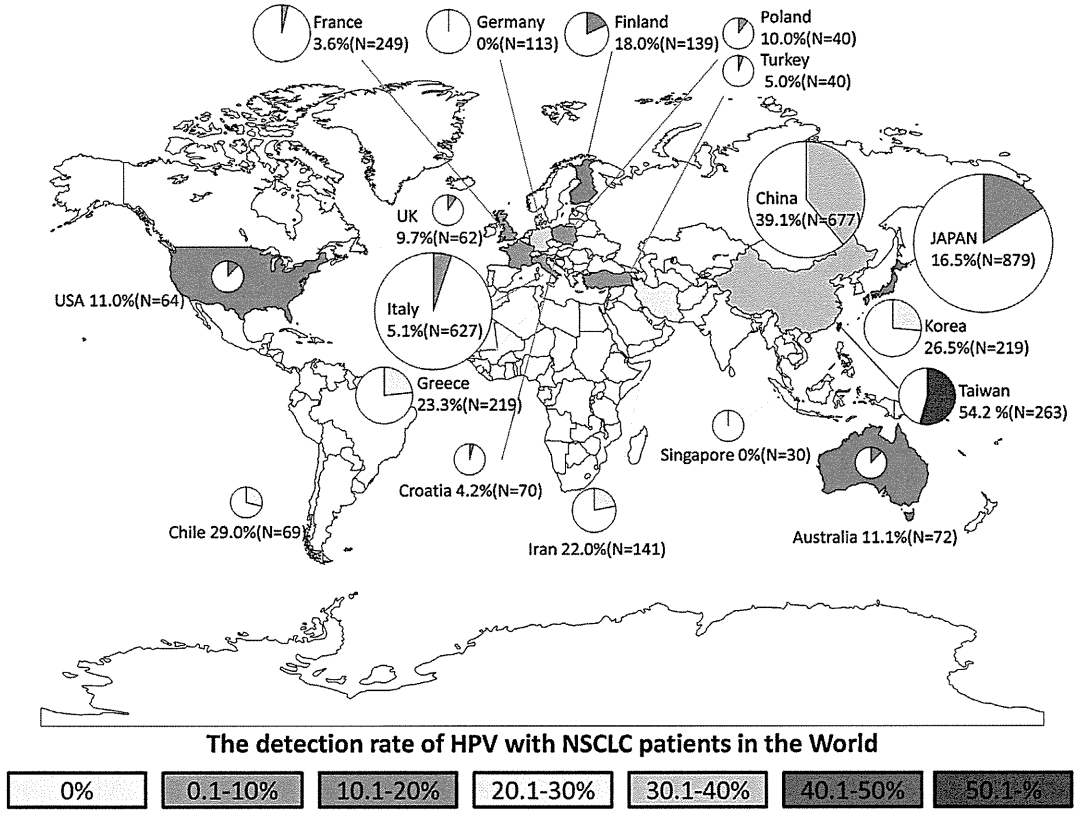

Fig. 2. The detection rate of HPV with NSCLC patients in the world. The size of each pie chart correlates with the number of patients examined in the studies. The colors of the countries are the HPV detection rate.

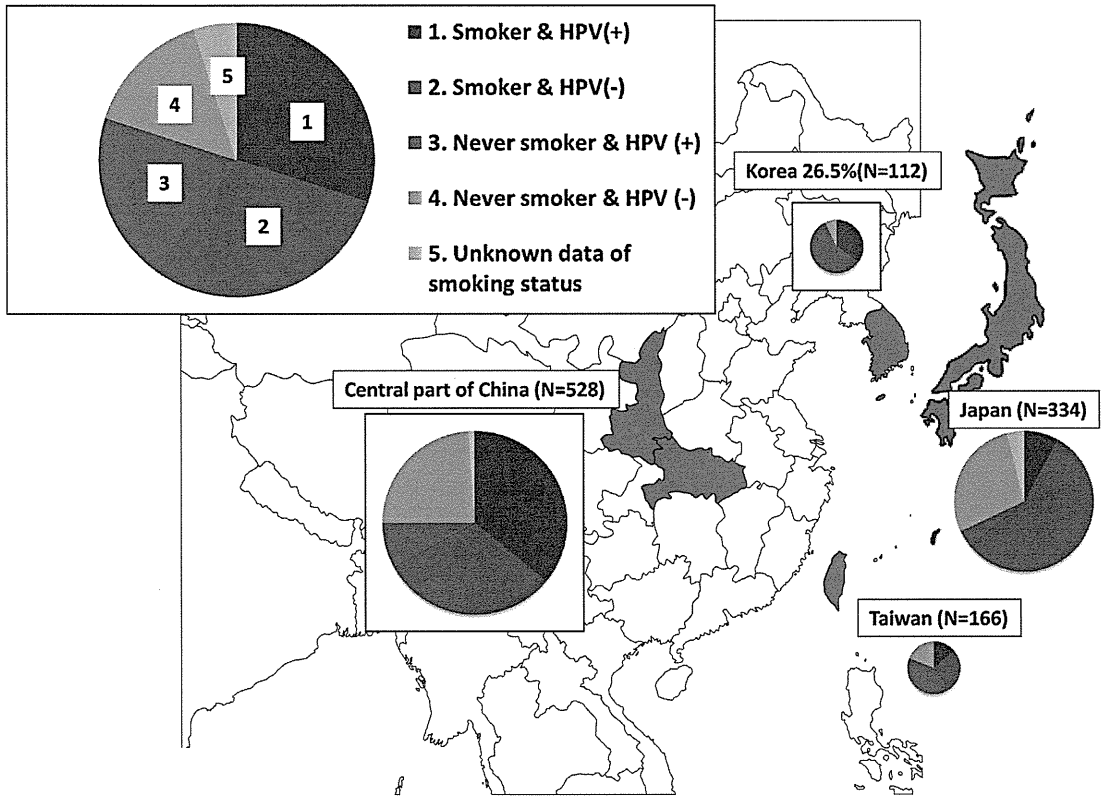

Fig. 3. The detection rate of HPV with NSCLC patients in East Asia according to smoking status. The size of each pie chart correlates with the number of patients examined in the studies.

Table 1
The detection rate of HPV according to smoking status.

Author	Year	Country	City	No. of cases	HPV positive (%)	No. of cases (smoker)	HPV positive (smoker) (%)	No. of cases (never smoker)	HPV positive (never smoker) (%)	No. of cases (unknown data)
Asia										
Kato et al. [10]	2012	Japan	Kagoshima	42	16.7	21	14.3	21	19.0	–
Goto et al. [11]	2011	Japan	Tokyo	44	2.3	39	2.6	5	0.0	–
Wang et al. [12]	2010	China	Xiangfan	45	42.2	27	70.4	12	0.0	6
Iwakawa et al. [13]	2010	Japan	Tokyo, Saitama	275	0.0	71	0.0	57	0.0	147
Baba et al. [14]	2010	Japan	Kagoshima	57	22.8	40	20.0	17	29.4	–
Yu et al. [15]	20092011	China	Xi'an	170	44.1	119	55.5	51	17.6	–
Wang et al. [16]	2008	China	Wuhan	313	44.1	208	51.4	105	29.5	–
Park et al. [17]	2007	Korea	Seoul	112	45.5	92	42.4	20	60.0	–
Wu et al. [18]	2005	Taiwan	Taichung	166	54.8	67	34.3	99	68.7	–
Tsuhako et al. [19]	1998	Japan	Okinawa	23	78.3	15	73.3	4	75.0	4
Hirayasu et al. [20]	1996	Japan	Niigata	30	30	19	26.3	1	100.0	10
Europe										
Carpagnano et al. [7]	2011	Italy	Foggia	73	16.4	61	8.2	12	58.3	–
Koshiol et al. [21]	2011	Italy	Brescia, Moilano, Monza, Pavia, Varese	388	0	361	0	27	0	–
Branica et al. [22]	2010	Croatia	Zagreb	70	4.2	59	5.1	11	0	–
Ciotti et al. [23]	2006	Italy	Rome	38	21.1	34	20.6	4	25.0	–
America										
Joh et al. [24]	2010	USA	Louisville	30	16.7	24	16.7	4	25.0	–

standard errors (vertical axis) as the index for accuracy (Supplemental Figure A1). The funnel plots were not symmetrical, with $P<0.001$ in the Egger's test for all studies. The statistical analysis showed that the heterogeneity was high between the studies (Table 2). Overall, these data indicate that there is some evidence of publication bias detected.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.10.002.

4. Discussion

In most studies relevant to HPV, analysis on lung cancer in never smokers has not been reported. Our analysis demonstrated the distribution of HPV infection with NSCLC in never smokers all over the world at a certain probability (31.4%, 95% CI 27.2–35.9%, $N=452$). The virus plays some roles in carcinogenesis in the disease. The HPV prevalence rate was 33.9% in East Asia from eleven studies including 68.7% in Taiwan, 60.0% in Korea, 23.8% in central part of China and 12.4% in Japan. There were also regional differences observed in Japan, and it was interesting that there was a relatively high prevalence in Kagoshima, which is geographically close to Taiwan. There were different patterns of the HPV prevalence in never smokers between Asian and European countries. Several epidemiological studies noted the higher incidence of lung cancer in never smokers in East Asia compared to elsewhere [2]. This may be related to the geographic differences of the HPV prevalence shown in this study.

Several possible mechanisms of molecular pathogenesis of HPV induced lung cancer were reported [25]. Previous study showed that Taiwanese never smokers had a significantly high prevalence of HPV16/18, suggesting HPV infection as a possible etiological agent of lung cancer in never smokers [26]. Epidermal growth factor receptor (EGFR) mutations are more frequent in never smokers, women, Asian ethnicity, and those with adenocarcinoma. Interestingly, these clinicopathological features seem to be evident in this Taiwan study. Indeed, one study in Japanese patients with lung cancer shows a significant association between high-risk type HPVs and EGFR mutations [10]. Estrogen contributes to a large extent to the onset of HPV infection and tumor progression [27] and estrogen signaling plays a biological role in both the epithelium and the mesenchyme in the lung and that estrogen could potentially promote lung cancer [28]. The well-established crosstalk between ER and EGFR in head and neck cancers arbitrates this action which is further validated by the colocalized membrane ER and EGFR in the lung tumors [29]. This ER-EGFR crosstalk could occur in the lung tissue, which can consequently favor HPV persistence and malignant transformation of the lung tissue. Furthermore, when this probable crosstalk fits in position, the increased vulnerability of female never smokers to develop HPV induced lung cancer as well as the histologic affinity of HPV to NSCLC is better explained [25].

The statistical analysis showed that the heterogeneity was high and the funnel plot was asymmetric, which limited our study. The large variation in the prevalence of HPV in tumor tissues within Japan is concerning, as is the evidence of substantial publication bias. Contamination in detecting of HPV in the samples might also explain the heterogeneity in the results between studies. However, the data with regard to likelihood of the contamination is not available in our retrospective analysis. There are many methods applied to detect HPV in the samples, such as in situ hybridization, different PCR assays with different primer pairs and immunohistochemical staining. PCR has been used extensively for HPV typing in many clinical and epidemiological studies because of its high sensitivity and specificity [30]. A systematic review showed that the sensitivity and specificity of high grade cervical squamous intraepithelial

Table 2
Heterogeneity across the studies.

		No. of studies	No. of cases	I^2	Cochran's Q	P-value
Region						
Asia		23	2337	97.1	768.8	<0.0001
Europe		19	1553	94.0	300.2	<0.0001
America		4	160	67.7	9.3	0.0258
Histology and region						
Ad	Asia	12	796	91.8	134.5	<0.0001
	Europe	15	564	87.0	107.4	<0.0001
	America	3	63	40.5	3.4	0.1861
Sq	Asia	16	1090	94.4	266.0	<0.0001
	Europe	17	744	91.0	178.4	<0.0001
	America	4	92	85.3	20.3	<0.0001
Total		46	4050	96.8	1386.9	<0.0001

Ad, adenocarcinoma; Sq, squamous cell carcinoma.

lesion was 0.85 (95% CI 0.84–0.86) and 0.62 (95% CI 0.62–0.64), respectively [31]. Based on the published data, PCR was chosen as the primary HPV detection method in our analysis. Different primer systems targeting relatively conserved nucleotide sequences have been developed with the aim of detecting a wide spectrum of HPV types. The sets used most frequently are GP5+/6+, MY09/11, PGMY and SPF10 [32]. These consensus methods were used mainly in the studies in our research. Another potential limitation of our research is the limited assessment on HPV subtypes. In majority of studies in our analysis, the high-risk subtypes of HPV were focused on HPV 16 and 18. However, other high-risk HPV types were also reported: HPV 31 and 33 were detected in 11/14 studies and 8/21 studies, respectively. The higher prevalence of HPV 33 infection was reported in Korean lung cancer patients (31.3%, $N=112$) compared to other Asian and Western countries (3.1%, $N=511$) [17]. Since only limited data are available currently with regard to the prevalence of minor HPV infections, future studies assessing more comprehensive HPV infections are warranted.

The important finding here is the fact of existing HPV in lung cancer in never smokers and our review highlights the potential of HPV as a risk factor for lung cancer in never smokers. The Japan Molecular Epidemiology Study (UMIN#000008177) is on-going, which is a nationwide and prospective large study and partly focusing on the virus in NSCLC. Although the numbers of never smokers from European studies are very small, the different patterns of HPV prevalence from Asian and European countries are intriguing and deserve further study.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Predictive power of prothrombin time and serum total bilirubin for postoperative mortality after major hepatectomy with extrahepatic bile duct resection

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Background. *In 2011, the International Study Group of Liver Surgery defined posthepatectomy liver failure using the prothrombin time–international normalized ratio (PT-INR) and total serum bilirubin concentration (T-Bil). Data analyzing the clinical impact of PT-INR and T-Bil on postoperative mortality, however, remain limited, especially for major hepatectomy with extrahepatic bile duct resection (HEBR).*

Methods. *Prospectively collected data from 545 patients who underwent HEBR in a single institution from 2002 to 2011 were analyzed. Receiver operating characteristics (ROC) analyses of PT-INR and T-Bil on postoperative days (POD) 1, 3, and 5 were used to determine optimal cu-off values for predicting postoperative mortality.*

Results. *Most of the treated diseases were biliary tract cancers, including perihilar cholangiocarcinoma (n = 418), gallbladder carcinoma (n = 52), and intrahepatic cholangiocarcinoma (n = 27). The mean values for PT-INR and T-Bil on POD 1, 3, and 5 were significantly greater in the patients who died owing to postoperative complications than in the patients who survived. On POD 5, the area under the ROC curve for predicting postoperative mortality and the optimal cutoff value for PT-INR were 0.876 and 1.68, respectively, whereas those of T-Bil were 0.889 and 4.0 mg/dL, respectively. A combination of PT-INR and T-Bil showed strong predictive power (ie, >40% of the patients with values beyond the cutoff value for both PT-INR and T-Bil on POD 5 died).*

Conclusion. *We recommend monitoring both PT-INR and T-Bil to predict accurately which patients are at a high risk after HEBR. (Surgery 2014;155:504-11.)*

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DESPITE ADVANCES IN SURGICAL TECHNIQUES AND PERIOPERATIVE MANAGEMENT, the complication rate after a major hepatectomy remains unsatisfactory. Posthepatectomy liver failure (PHLF) is among the most serious complications that leads to surgery-related death after a major hepatectomy. The incidence of PHLF and its impact on the postoperative course in previous reports are quite variable because of the difference in the definition of PHLF, the type of treated disease (ie, hepatocellular carcinoma, colorectal liver metastasis, biliary malignancies), and the extent of operative intervention in each report.[1-6]

In 2011, the International Study Group of Liver Surgery (ISGLS) proposed a definition and grading system of PHLF.[7] Thereafter, Rahbari et al[8] analyzed retrospectively 807 patients and found that the definition and grading system of PHLF by the ISGLS enables adequate risk stratification for perioperative mortality. Two of the major criteria for evaluating liver function used in the ISGLS grading system were the prothrombin time–international normalized ratio (PT-INR) and total serum bilirubin concentration (T-Bil). In the ISGLS definition, a greater PT-INR and an increased T-Bil level on or after

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postoperative day (POD) 5 have been included as major criteria.[7] PT-INR and T-Bil have also been used frequently in the definition of PHLF in other reports.[3,9,10]

"Hepatectomy" includes a wide range of interventions, including a partial hepatectomy, subsegmental hepatectomy, segmental hepatectomy, and sectionectomy. In some patients, especially in the patients with perihilar malignancies, a major hepatectomy with extrahepatic bile duct resection (HEBR) is necessary. In this type of resection, hepaticojejunostomy after resection of the tumor is mandatory, and thus the extent of the operative intervention and the risk of postoperative morbidity and mortality are different from a "simple hepatectomy," which only requires a hepatic parenchymal resection. Because the HEBR is not a common procedure among the various types of hepatectomies, precise data on the postoperative morbidity and mortality in this type of operation are lacking. Moreover, it is unclear whether the criteria of the ISGLS definition (ie, PT-INR and T-Bil) are valid for predicting postoperative mortality after HEBR.

In this study, we analyzed retrospectively 545 consecutive patients who underwent HEBR with hepaticojejunostomy in a single institution and determined the value of the PT-INR and T-Bil during the early postoperative course for predicting postoperative mortality.

PATIENTS AND METHODS

From March 2002 to December 2011, 545 patients underwent HEBR with hepaticojejunostomy at the First Department of Surgery, Nagoya University Hospital, Nagoya, Japan. A major hepatectomy in this study included a resection of ≥3 Couinaud segments. Clinical data in these patients were analyzed retrospectively.

Preoperative patient management. When the patients had jaundice, biliary drainage, either by endoscopic nasobiliary drainage, endoscopic biliary stent, or percutaneous transhepatic biliary drainage, was performed. The measurement of the plasma disappearance rate of indocyanine green (ICGK) and computed tomography volumetry were performed routinely to evaluate the functional reserve of the future liver remnant.[11] Preoperative portal vein embolization was performed when the extent of liver resection exceeded 60% and/or functional reserve of the future liver remnant was considered to be insufficient.[12] Preoperative autologous blood donation (200–800 mL) was performed for patients who had hemoglobin concentrations >11 g/dL.[13]

Operative procedure. Liver resections were conducted under the condition of intermittent clamping of both the portal vein and the hepatic artery (clamping for 15 or 20 minutes at 5-minute intervals). Either the ultrasonic dissector or the clamp crushing technique was used for the hepatic parenchymal dissection according to the surgeon's preference. A hepaticojejunostomy was performed by Roux-en-Y anastomosis in all patients as reported previously.[3,14] All anastomosed bile ducts were stented and externally drained with a 6-Fr, polyvinyl chloride tube (percutaneous transhepatic biliary drainage tube; Hakko, Chikuma, Japan) through the jejunal stump used for the hepaticojejunostomy (transjejunal route).[3] No patient developed severe dilatation of the biliary tree owing to anastomotic stenosis, which was confirmed by computed tomography performed routinely on POD 6 or 7. In some patients, a hepatopancreatoduodenectomy was necessary because of tumor extension to the distal bile duct or suspected lymph node metastasis in the peripancreatic region.[15] All preoperatively collected autologous blood was transfused during the operation. Allogeneic red cell concentrates, fresh frozen plasma, or platelet concentrates were transfused only if necessary.

Recording of clinical data and postoperative complications. Detailed daily clinical records were kept for all patients. Serum levels of PT-INR and T-Bil were measured on POD 1, 3, and 5 whenever possible. PHLF and posthepatectomy bile leakage were defined according to the criteria of the ISGLS definition.[7,8] Postoperative infectious complications, including pneumonia, surgical site infections, and bacteremia as detected by the culture method, were also recorded for ≤30 days after the procedure. The diagnosis of pneumonia required radiologic evidence of consolidation with leukocytosis. Surgical site infection included superficial/deep incisional infections and organ space infections.[16] Bacteremia was diagnosed when a blood culture grew an isolate of organisms, with no contamination of the skin flora.

Statistical analysis. Data were analyzed using the JMP version 8 for Windows (SAS Institute Inc, Cary, NC) or Dr SPSS II version 11.01 J for Windows (SPSS Inc, Chicago, IL). Results are expressed as the mean values ± standard deviation. Continuous data were compared between 2 groups using the Student *t*-test. When data were not normally distributed, a univariate analysis using a nonparametric test was used. Categorical data were compared using the Chi-square test or Fisher's exact test, as appropriate. The prognostic

value of PT-INR and T-Bil in predicting postoperative mortality was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve and the cutoff point were determined. Factors with significant impact on postoperative mortality as determined by univariate analysis were explored with multivariate logistic regression analysis to examine the relationship between the postoperative mortality and the perioperative variables.

RESULTS

Clinical characteristics. The mean age of the study patients was 64.9 years (range, 22–83). There were 341 men (63%) and 204 women (37%). Most of the treated diseases (approximately 90%) were biliary tract cancers, including perihilar cholangiocarcinoma (n = 418; 76%), gallbladder carcinoma (n = 52; 9%), and intrahepatic cholangiocarcinoma (n = 27; 5%). Other diseases included hepatocellular carcinoma (n = 8; 2%), colorectal liver metastasis (n = 8; 2%), other malignancies (n = 4; 1%), hepatolithiasis (n = 9; 2%), and benign biliary stricture (n = 19; 3%). For the malignant diseases, no neoadjuvant chemotherapy or radiotherapy was performed. The mean maximum T-Bil level at the time of diagnosis was 6.5 mg/dL (range, 0.3–40.4), and preoperative biliary drainage was performed for the patients with jaundice (n = 455; 83%). When preoperative cholangitis was suspected, it was controlled by biliary drainage and/or antibiotic treatment targeting the bacteria isolated by bile culture (n = 72; 13%) and the operation was postponed until the symptoms of cholangitis subsided. To increase the volume of the future liver remnant, 324 patients (59%) underwent preoperative portal vein embolization. The indocyanine green clearance test was performed when the serum T-Bil levels were <2.0 mg/dL. The mean ICGK was 0.161 (range, 0.102–0.261) and the mean proportion of the future liver remnant was 51.5% (range, 24.5–95.2%).

Operative procedures and intraoperative information. The operative procedure for the major hepatectomy included a right hepatectomy (n = 218; 40%), left hepatectomy (n = 150; 28%), left trisectionectomy (n = 123; 23%), right trisectionectomy (n = 41; 7%), and central bisectionectomy (n = 13; 2%). In most patients (n = 533; 98%), a caudate lobectomy was combined with a major hepatectomy. All patients underwent HEBR with a hepaticojejunostomy. In 96 patients (18%), a pancreatoduodenectomy was also performed. Resection and reconstruction of the portal vein (n = 203; 37%) or hepatic artery (n = 90; 17%) were performed when tumor invasion was suspected.[17,18] In total, 67 patients (12%) underwent both portal vein and hepatic artery resection. The mean operation time was 625 minutes (range, 329–1,264 minutes), and the mean amount of intraoperative bleeding was 2,022 mL (range, 235–47,200 mL). The mean total vascular occlusion time was 75 minutes, which consisted of 5 rounds of 15 minutes of intermittent ischemia. In 400 patients (73%), only autologous blood was transfused during the operation, and allogeneic blood was not used. In other patients (n = 145; 27%), allogeneic red cell concentrates were transfused owing to a low hemoglobin level (<7 g/dL) or low blood pressure. Allogeneic fresh frozen plasma (n = 101; 19%) and platelet concentrates (n = 13; 2%) were transfused according to the decision of the surgeons and anesthesiologists.

Postoperative outcomes. The overall morbidity rate was 44%. The most common complication was infectious (29%), including pneumonia, surgical site infection, and sepsis. Bile leakage according to the definition of the ISGLS occurred in 78 patients (14%)[19]; 20 patients (4%) had leakage from the hepaticojejunostomy. Liver failure according to the definition of the ISGLS occurred in 321 patients (59%; Table I).[7] Among these patients, 205 (38%) had clinically relevant liver failure (grades B and C). The postoperative mortality rate in the patients with grades A, B, and C PHLF was 0%, 0.6%, and 48.5%, respectively. Of 545 patients, 17 (3%) died secondary to postoperative complications (Table I). The median postoperative survival time of these patients was 55 days (range, 15–148). Among the 17 patients who died, 9 (53%) underwent reoperation owing to intestinal perforation (n = 4), intra-abdominal bleeding (n = 2), or portal vein thrombosis (n = 3); all 17 patients died as a result of hepatic failure in their terminal stage (10 patients were with multiple organ failure). In contrast with patients who died postoperatively, reoperation was required in only 8 patients among 528 who survived the operation (2%).

PT-INR/T-Bil and postoperative mortality. When the patients were dichotomized by the incidence of postoperative mortality, the mean PT-INR and T-Bil on POD 1, 3, and 5 were significantly greater in the patients who died owing to postoperative complications (nonsurvivors) than in the patients who survived (survivors; Fig 1, *A* and B). Among the survivors, the peak levels of PT-INR were observed on POD 1, and these levels decreased gradually on POD 3 and 5. In contrast, the levels of PT-INR peaked on POD 1 and were sustained at a high level through POD 3 and 5 in the nonsurvivors.

Table I. Postoperative outcome

Outcome	n *(%)*
Overall morbidity	241 (44)
Overall infectious complications	159 (29)
Pneumonia	10 (2)
SSI (superficial/deep incisional)	62 (11)
SSI (organ space)	104 (19)
Sepsis	35 (6)
Bile leakage	
None	467 (86)
Grade A	8 (1)
Grade B	69 (13)
Grade C	1
Liver failure*	
None	224 (41)
Grade A	116 (21)
Grade B	172 (32)
Grade C	33 (6)
Overall mortality	17 (3)

*According to the ISGLS definition.[7]
SSI, Surgical site infection.

The peak levels of T-Bil were also observed on POD 1 in the survivors; however, the levels of T-Bil continued to increase through POD 5 in the nonsurvivors.

Risk factors associated with postoperative mortality. Possible risk factors associated with postoperative mortality were analyzed. Univariate analysis indicated that ICGK (<0.125), combined pancreatoduodenectomy, combined portal vein resection, operation time (>600 minutes), and intraoperative blood loss (>2,000 mL) were significantly associated with postoperative mortality (Table II). To evaluate whether PT-INR and T-Bil were independently associated with operation-related death, both variables were included in the multivariate logistic regression model adjusted for ICGK, combined portal vein resection, operation time, and intraoperative blood loss (Table III). In this multivariate analysis, both PT-INR (on POD 1, 3, and 5) and T-Bil (on POD 1 and 3) were identified as significant risk factors for postoperative mortality. The odds ratios for an increment of 0.1 in PT-INR on POD 1, 3, and 5 were 1.10, 1.59, and 1.26, respectively. The odds ratios for an increment of 1.0 mg/dL in T-Bil on POD1, 3, and 5 were 1.69, 1.29, and 1.20, respectively. The area under the ROC curve based on the multivariate logistic regression model on POD 1, 3, and 5 were 0.946 (95% confidence interval, 0.893–1.000), 0.967 (0.922–1.000), and 0.963 (0.933–0.992), respectively.

ROC curve analysis for PT-INR and T-Bil. To evaluate the predictive value of PT-INR and T-Bil for postoperative mortality, ROC curve analysis was performed based on the logistic regression in which postoperative mortality was associated with PT-INR and T-Bil (Table III). The area under the ROC curve for PT-INR was 0.843, 0.922, and 0.876, on POD 1, 3, and 5, respectively (Fig 2, *A*). The area under the ROC curve for T-Bil was 0.837, 0.860, and 0.889, on POD 1, 3, and 5, respectively (Fig 2, *B*). The cutoff values of the PT-INR and T-Bil were determined based on the ROC curve in consideration of an appropriate trade-off between the sensitivity and specificity. As a result, the optimal cutoff value of PT-INR for predicting postoperative mortality on POD 1, 3, and 5 was 1.81, 1.62, and 1.68, respectively. These levels were relatively constant for POD 1, 3, and 5. The optimal cutoff value of T-Bil for predicting postoperative mortality on POD 1, 3, and 5 was 2.7, 3.3, and 4.0, respectively. In contrast with PT-INR, the optimal cutoff value for T-Bil increased gradually in the early postoperative course.

Combination of PT-INR and T-Bil. Although the predictive power of PT-INR and T-Bil for postoperative mortality was sufficient, each factor reflects a different aspect of liver function (ie, PT-INR reflects the capacity of the liver to synthesize coagulating factors, whereas T-Bil reflects bilirubin metabolism). Moreover, as shown in Fig 1, the dynamics of PT-INR and T-Bil during the early postoperative course are different. Therefore, we next hypothesized that a combination of PT-INR and T-Bil would be more predictive of postoperative mortality than a single factor. As expected, a combination using a cutoff value for both PT-INR and T-Bil showed a better predictive power for postoperative mortality at every time point (POD 1, 3, and 5; Table IV). Although the overall mortality rate was 3% in all study population, that in the patients whose PT-INR and T-Bil levels were beyond cutoff values on POD 5 was >40%.

DISCUSSION

Before the ISGLS's proposal, the definition of PHLF differed substantially in previous reports.[5,20-25] Mullen et al[6] analyzed 1,059 noncirrhotic patients who underwent a major hepatectomy (resection of ≥3 liver segments); from the ROC curve analysis, these authors concluded that the optimal cutoffs that predict liver-related death were a peak PT-INR of 2.0 and a peak T-Bil of 7.0 mg/dL. Balzan et al[2] analyzed 775 elective liver resections, including minor and major hepatectomies for benign and malignant diseases. They proposed that a PT of <50% and T-Bil >50 μmol/L (2.9 mg/dL) on POD 5 was a simple, early, and accurate predictor of a >50% mortality rate after hepatectomy, known as a "50–50 criteria." Because the type of treated disease and the extent of operative resection in these reports

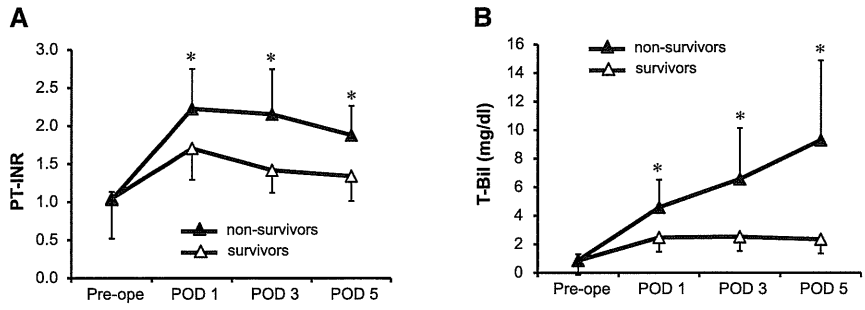


Fig 1. The levels of prothrombin time–international normalized ratio (*A*) and total bilirubin (*B*) before the operation (Pre-op) and on postoperative days (POD) 1, 3, and 5. The patients were dichotomized by the incidence of postoperative mortality (ie, survivors vs nonsurvivors). $*P < .05$ versus survivors.

Table II. Possible risk factors associated with postoperative mortality

			Univariate	
Variables	*No. of patients*	*Mortality (%)*	*Odds ratio (95% CI)*	P *value*
Age (y)				
≤70	360	12 (3.3)	1.00	.688
>70	185	5 (2.7)	0.81 (0.28–2.32)	
Gender				
Female	204	7 (3.4)	1.00	.746
Male	341	10 (2.9)	1.18 (0.44–3.14)	
Extent of liver resection (%)				
≤60	426	12 (2.8)	1.00	.442
>60	119	5 (4.2)	1.51 (0.52–4.38)	
ICGK				
≥0.125	471	12 (2.5)	1.00	.013
<0.125	58	5 (8.6)	3.61 (1.22–10.64)	
Preoperative PVE				
No	221	5 (2.3)	1.00	.342
Yes	324	12 (3.7)	1.66 (0.58–4.78)	
Combined PD				
No	449	10 (2.2)	1.00	.010
Yes	96	7 (7.3)	3.45 (1.28–9.32)	
Combined PV resection				
No	342	5 (1.5)	1.00	.004
Yes	203	12 (5.9)	4.24 (1.47–12.20)	
Combined HA resection				
No	455	15 (3.3)	1.00	.592
Yes	90	2 (2.2)	0.67 (0.15–2.97)	
Operation time (min)				
≤600	263	1 (0.4)	1.00	<.001
>600	282	16 (5.7)	15.76 (2.08–119.69)	
Blood loss (mL)				
≤2,000	369	2 (0.5)	1.00	<.001
>2,000	176	15 (8.5)	17.10 (3.87–75.63)	

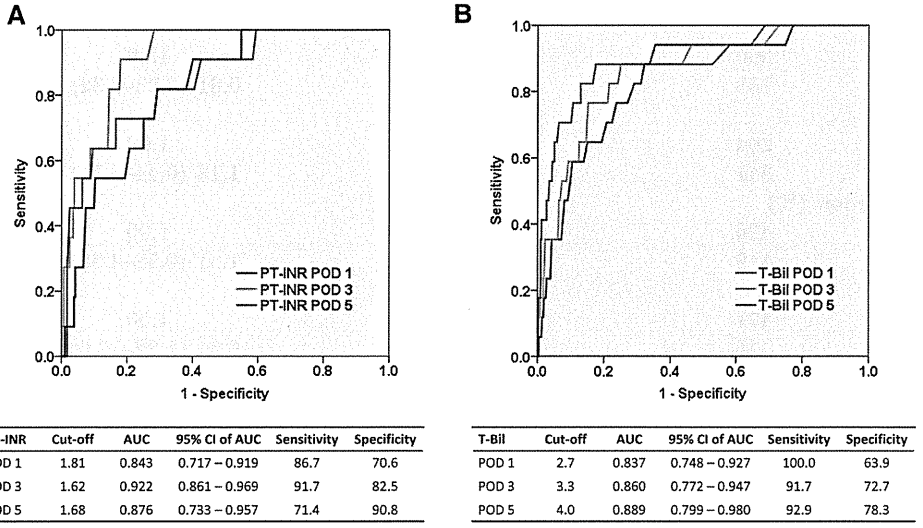
HA, Hepatic artery; *ICGK*, plasma disappearance rate of indocyanine green; *ICGK-F*, ICGK of the future liver remnant; *PD*, pancreatoduodenctomy; *PV*, portal vein; *PVE*, portal vein embolization.

were variable, the actual incidence rate and severity of PHLF may not be comparable. After the ISGLS defined their set of criteria for PHLF, the data have been standardized, and it has become easier to compare the incidence of PHLF among reports. Nevertheless, the reports using the ISGLS definition for PHLF remain limited.[8] It is important to collect prospectively the PHLF data according to the definition of ISGLS to further refine its criteria. It is also important to reevaluate whether the definition of

Table III. Results of logistic regression analysis

		Univariate		*Multivariate**	
Variables	*No. of patients*	*Odds ratio† (95% CI)*	P *value*	*Odds ratio† (95% CI)*	P *value*
POD 1					
PT-INR	492	1.14 (1.06–1.23)	<.001	1.10 (1.01–1.19)	.026
T-Bil	538	1.79 (1.42–2.30)	<.001	1.69 (1.22–2.43)	.002
POD 3					
PT-INR	369	1.39 (1.23–1.60)	<.001	1.59 (1.23–2.31)	.004
T-Bil	537	1.59 (1.36–1.89)	<.001	1.29 (0.99–1.77)	.077
POD 5					
PT-INR	330	1.25 (1.12–1.43)	<.001	1.26 (1.10–1.46)	.001
T-Bil	538	1.47 (1.31–1.68)	<.001	1.20 (1.03–1.43)	.023

*PT-INR, T-BIL, ICGK, and combined PV resection, operation time, and blood loss were included in the multivariate logistic regression model.
†Odds ratio is for each increment of 0.1 in PT-INR or 1 in T-Bil.
CI, Confidence interval; *ICGK,* plasma disappearance rate of indocyanine green; *POD,* postoperative day; *PT-INR,* prothrombin time–international normalized ratio; *T-Bil,* total bilirubin.



PT-INR	Cut-off	AUC	95% CI of AUC	Sensitivity	Specificity
POD 1	1.81	0.843	0.717 – 0.919	86.7	70.6
POD 3	1.62	0.922	0.861 – 0.969	91.7	82.5
POD 5	1.68	0.876	0.733 – 0.957	71.4	90.8

T-Bil	Cut-off	AUC	95% CI of AUC	Sensitivity	Specificity
POD 1	2.7	0.837	0.748 – 0.927	100.0	63.9
POD 3	3.3	0.860	0.772 – 0.947	91.7	72.7
POD 5	4.0	0.889	0.799 – 0.980	92.9	78.3

Fig 2. Receiver operating characteristics curve of the prothrombin time–international normalized ratio (*A*) and total bilirubin (*B*) for the prediction of postoperative mortality (ie, survivors versus nonsurvivors).

PHLF is valid for predicting postoperative mortality. In this regard, Rahbari et al[8] analyzed retrospectively consecutive hepatectomy patients after publishing the ISGLS definition and reported that the ISGLS definition of PHLF is useful for predicting postoperative mortality.

The hepatectomies included various extents of invasion ranging from a minimum hepatic parenchymal resection to a systematic major hepatectomy. In the case of perihilar biliary malignancies, HEBR in combination with a major hepatectomy is mandatory. In addition, combined resection of the hepatic vasculatures (ie, portal vein and hepatic artery) or the addition of a pancreatoduodenectomy was necessary for advanced cases. Therefore, the incidence rate of postoperative morbidity and mortality after HEBR would be expected to differ from that after a simple hepatectomy. Nevertheless, the incidence of PHLF and its association with the dynamics of PT-INR and T-Bil during the postoperative course after HEBR have never been reported. It is also unknown whether the PT-INR or T-Bil values are useful for predicting postoperative mortality in this type of operation; if these values are useful, the optimal cutoffs are also unknown. As far as we know, this is the largest study that demonstrates clearly the dynamics of PT-INR and T-Bil and their association with postoperative mortality after HEBR.

Interestingly, in agreement with the report of Rahbari et al, PT-INR and T-Bil predicted postoperative mortality in our study. The area under the curve was >0.8 for the ROC curve of both PT-INR and T-Bil on POD 1, 3, and 5 (Fig 2). These observations validate the ISGLS definition of

Table IV. Predictive value of combined prothrombin time–international normalized ratio (PT-INR) and total bilirubin (T-Bil)

Parameter	*Survivors,* n *(%)*	*Nonsurvivors,** n *(%)*	*Total*
POD 1			
PT-INR <1.81 and T-Bil <2.7	226 (100)	0	226
PT-INR ≥1.81 and T-Bil <2.7	78 (100)	0	78
PT-INR <1.81 and T-Bil ≥2.7	110 (98.2)	2 (1.8)	112
PT-INR ≥1.81 and T-Bil ≥2.7	62 (82.7)	13 (17.3)	75
Total	476	15	491
POD 3			
PT-INR <1.62 and T-Bil <3.3	226 (99.6)	1 (0.4)	227
PT-INR ≥1.62 and T-Bil <3.3	32 (100)	0	32
PT-INR <1.62 and T-Bil ≥3.3	67 (100)	0	67
PT-INR ≥1.62 and T-Bil ≥3.3	30 (73.2)	11 (26.8)	41
Total	355	12	367
POD 5			
PT-INR <1.68 and T-Bil <4.0	230 (100)	0	230
PT-INR ≥1.68 and T-Bil <4.0	16 (94.1)	1 (5.9)	17
PT-INR <1.68 and T-Bil ≥4.0	55 (93.2)	4 (6.8)	59
PT-INR ≥1.68 and T-Bil ≥4.0	13 (59.1)	9 (40.9)	22
Total	314	14	328

*Nonsurvivors are patients who died of a postoperative complication.
POD, Postoperative day.

PHLF even in the cases of HEBR. The cutoff value of PT-INR in our study on POD 5 was 1.68, whereas that of T-Bil on POD 5 was 4.0 mg/dL. The levels are also compatible with those of "50–50 criteria." Results of the multivariate analysis adjusted for perioperative factors that showed an association with postoperative mortality in crude analyses and revealed that both the PT-INR and T-Bil values were strong and independent predictors for postoperative mortality on POD 1, 3, and 5.

Although the levels of both PT-INR and T-Bil on POD 1, 3, and 5 were significantly greater in the patients with postoperative mortality than those in the patients without postoperative mortality, the dynamics of each factor were different (Fig 1). The reasons for this difference are unknown. PT-INR and T-Bil levels reflect different aspect of liver function. The level of PT-INR reflects the ability of the liver to synthesize coagulating factors, whereas the level of T-Bil reflects the function of glucuronidation and the ability to secrete conjugated bilirubin (heme metabolites) into the bile duct. Therefore, it can be speculated that, in the later phase of liver failure, bilirubin metabolism is more severely damaged than the ability of the liver to synthesize coagulating factors. We recommend monitoring both PT-INR and T-Bil to diagnose accurately the presence of PHLF and to predict the patients who are at high risk for postoperative mortality. Although these patients need intense postoperative care owing to a highly impaired liver function, by monitoring both PT-INR and T-Bil we can correct precisely the impaired liver function by supporting either synthetic or metabolic aspect. Nevertheless, further investigations are required to elucidate the mechanistic reason for the increased PT-INR and T-Bil levels after a major hepatectomy.

The transfusion of allogeneic fresh frozen plasma affects the level of PT-INR, whereas transfusion of red cell concentrates affects the level of serum T-Bil level. We separately use fresh frozen plasma and red cell concentrates selectively depending on the patients' condition, and these transfusions may have altered the levels of PT-INR and T-Bil to some extent. It may be extremely difficult to estimate accurately this extent, especially under the condition with substantial deterioration of liver function postoperatively; therefore, in this study we analyzed our data irrespective of the performance of blood transfusions.

In conclusion, our study demonstrated the predictive value of PT-INR and T-Bil for postoperative mortality in patients who underwent HEBR. The combined use of these criteria for the definition of PHLF is appropriate and valid. Further data collection may be necessary to determine the exact cutoff value of PT-INR and T-Bil to accurately predict postoperative mortality.

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ORIGINAL REPORT

Phase III Study Comparing Amrubicin Plus Cisplatin With Irinotecan Plus Cisplatin in the Treatment of Extensive-Disease Small-Cell Lung Cancer: JCOG 0509

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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Clinical trial information: UMIN000000720 (registered at University Hospital Medical Information Network Clinical Trials Registry).

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ABSTRACT

Purpose
This randomized phase III trial was conducted to confirm noninferiority of amrubicin plus cisplatin (AP) compared with irinotecan plus cisplatin (IP) in terms of overall survival (OS) in chemotherapy-naive patients with extensive-disease (ED) small-cell lung cancer (SCLC).

Patients and Methods
Chemotherapy-naive patients with ED-SCLC were randomly assigned to receive IP, composed of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks, or AP, composed of amrubicin 40 mg/m^2 on days 1, 2, and 3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks.

Results
A total of 284 patients were randomly assigned to IP (n = 142) and AP (n = 142) arms. The point estimate of OS hazard ratio (HR) for AP to IP in the second interim analysis exceeded the noninferior margin (HR, 1.31), resulting in early publication because of futility. In updated analysis, median survival time was 17.7 (IP) versus 15.0 months (AP; HR, 1.43; 95% CI, 1.10 to 1.85), median progression-free survival was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.16 to 1.73), and response rate was 72.3% (IP) versus 77.9% (AP; $P = .33$). Adverse events observed in IP and AP arms were grade 4 neutropenia (22.5% *v* 79.3%), grade 3 to 4 febrile neutropenia (10.6% *v* 32.1%), and grade 3 to 4 diarrhea (7.7% *v* 1.4%).

Conclusion
AP proved inferior to IP in this trial, perhaps because the efficacy of amrubicin as a salvage therapy was differentially beneficial to IP. IP remains the standard treatment for extensive-stage SCLC in Japan.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide,[1] and small-cell lung cancer (SCLC) accounts for almost 13% of all new cases.[2] More than half of these patients are diagnosed with extensive-disease (ED) SCLC.[3] SCLC refers to a rapidly proliferating tumor that is highly sensitive to chemotherapy. However, rapid emergence of clinical drug resistance has resulted in poor prognosis, with almost all such patients dead within 2 years of initial diagnosis.[3] Thus, there is a need for new and effective therapeutic options for ED-SCLC.

The combination of etoposide and cisplatin (EP) has been standard treatment for ED-SCLC for decades. In 2002, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG 9511) demonstrated the superiority of irinotecan plus cisplatin (IP) over EP for patients with ED-SCLC.[4] Median survival time (MST) and 1-year survival for the IP and EP arms were 12.8 versus 9.4 months and 58.4% versus 37.7%, respectively, but patients in the IP arm experienced a significantly higher proportion of grade 3 to 4 diarrhea. Although two randomized phase III trials have failed to confirm the superiority of IP over EP for chemotherapy-naive patients with SCLC in North America and Australia,[5-7] IP is considered equivalent to EP and one of the standard ED-SCLC regimens in Japan.

Amrubicin is a completely synthetic anthracycline derivative that is converted to an active metabolite, amrubicinol, and it is a potent topoisomerase

II inhibitor.[7] The high degree of therapeutic activity of amrubicin is caused by the selective distribution of amrubicinol, which is 10× to 100× more cytotoxic than its parent compound, amrubicin.[8,9]

A phase II study of amrubicin as single-agent therapy for previously untreated ED-SCLC yielded a response rate (RR) of 76%, complete response (CR) rate of 9%, and MST of 11.7 months,[10] similar to outcomes for platinum-based doublets at the time. Moreover, a phase I/II study of amrubicin plus cisplatin (AP) recommended administration of amrubicin 40 mg/m^2 on days 1, 2, and 3 with cisplatin 60 mg/m^2 on day 1 every 3 weeks. An RR of 87.8% and MST of 13.6 months were demonstrated in the patients treated with the recommended dose.[11] The major toxicity of the AP regimen was hematologic, which was acceptable because of the absence of febrile neutropenia (FN). Moreover, the incidence of grade 3 to 4 diarrhea, a concern with IP, was only 4.9%. Therefore, we believed AP might be a new effective treatment option for ED-SCLC, with a more favorable toxicity profile than IP. We undertook a multicenter, randomized, phase III noninferiority trial of AP compared with IP in previously untreated patients with ED-SCLC.

PATIENTS AND METHODS

Patient Selection

Patients were considered eligible if they met the following criteria: histologically or cytologically demonstrated ED-stage SCLC (defined as ≥ one of following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion, pericardial effusion), chemotherapy naive, age 20 to 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to1, no prior chemotherapy or radiotherapy for any cancers, and adequate organ function, defined as leukocyte count ≥ 4,000/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, AST ≤ 100 IU/L, ALT ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL, and partial pressure of arterial blood gas without oxygen inhalation ≥ 70 torr. Patients had normal ECG and were asked to respond to a quality-of-life (QOL) questionnaire before enrollment. Patients were excluded if they had other unrelated invasive malignancies requiring ongoing therapy, serious tumor-related complication, active bacterial or fungal infection, diarrhea, intestinal paralysis or obstruction, evidence of interstitial pneumonia or pulmonary fibrosis on chest x-ray, received or expected to receive long-term treatment (≥ 50 days) with nonsteroidal anti-inflammatory drugs or steroids, serious cardiac disease, serious psychiatric disorder, pregnancy, active gastroduodenal ulcer, or history of myocardial infarction within 12 months. All enrolled patients provided written informed consent to participate in the study.

Treatment Plan

Patients were randomly assigned at a one-to-one ratio to receive either AP or IP. Random assignment was adjusted according to the following stratification factors: ECOG PS, institution, and sex. The IP regimen consisted of four cycles of irinotecan 60 mg/m^2 intravenously (IV) on days 1, 8, and 15 and cisplatin 60 mg/m^2 IV on day 1. Cycle length for this arm was 4 weeks. The AP regimen initially consisted of four cycles of amrubicin 40 mg/m^2 IV on days 1, 2, and 3 and cisplatin 60 mg/m^2 IV on day 1 every 3 weeks. However, because of the high incidence of severe hematologic toxicities, the protocol was revised to reduce the initial dose of amrubicin to 35 mg/m^2 in the AP group after 66% of patients (94 of 142) in the AP arm had been enrolled. The subsequent cycles of both arms were begun if absolute leukocyte count ≥ 3,000/μL, platelet count ≥ 100,000/μL, serum creatinine ≤ 1.5 mg/dL, and treatment-related nonhematologic toxicities (excluding alopecia, weight loss, and hyponatremia) had been resolved to grade ≤ 1. In regard to dose modification, if during the previous course the patient presented with thrombocytopenia (platelet count < 20,000/mm^3) and/or grade 3 nonhematologic toxicity including FN and diarrhea, the dose of irinotecan was reduced by 10 mg/m^2 and the dose of amrubicin by 5 mg/m^2 in the next cycle. The dose of cisplatin was reduced by 20 mg/m^2 for subsequent courses in the event of any of the following toxicities: creatinine > 1.5 to ≤ 2.0 mg/dL, grade 3 nonhematologic toxicity, grade ≥ 2 neuropathy (sensory or motor), and grade ≥ 2 muscle or joint pain. Prophylactic administration of granulocyte colony-stimulating factor was not allowed in the first cycle. After the fourth cycle, initially prophylactic cranial irradiation (PCI) was conducted as per institutional policy. However, because of the report at the 2007 Annual Meeting of the American Society of Clinical Oncology stating that addition of PCI for ED-SCLC responders significantly extended survival,[12] the protocol was revised just 4 months after the start of patient enrollment so that patients with CR or tumor elimination would additionally receive PCI.

Response and Toxicity Evaluations

Baseline evaluation consisted of complete medical history and physical examination, ECG, ECOG PS, complete blood count, blood chemistry, blood gas analysis, computed tomography (CT) scan of the chest, CT or ultrasound of the abdomen, magnetic resonance imaging or CT of the brain, and bone scan or positron emission tomography. During treatment within the study, complete blood count, blood chemistry, and complete physical examination with clinical assessment were performed at least every week. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3). Chest x-ray was performed every cycle during protocol treatment, whether or not there was evidence of progression. All responses were defined according to RECIST (version 1.0). We evaluated patient QOL twice—once at baseline and once after completion of the second course (8 weeks in IP arm, 6 weeks in AP arm after treatment initiation)—using a QOL questionnaire for patients with cancer treated with anticancer drugs (QOL-ACD) and QOL Questionnaire Core 30 (QLQ-C30; diarrhea score). The primary metric used to analyze QOL was a comparison between arms in terms of improvement of physical status score over baseline QOL questionnaire.

End Points

The objective of this randomized phase III study was to establish the noninferiority of AP compared with IP as first-line therapy in patients with ED-SCLC. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), RR, adverse events (AEs), grade 3 to 4 diarrhea, and QOL.

Study Design and Statistical Analysis

This trial was a multicenter randomized trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution.

The trial was designed to achieve at least 70% power to confirm noninferiority of AP compared with IP, with a noninferiority margin of 1.31 in terms of hazard ratio (HR), MST of 12.8 months in both arms, and one-sided α = 0.05. We believed 3 months would be the maximum allowable noninferiority margin in the case of a less-toxic regimen with a different toxicity profile—a profile that we had expected from the phase I/II study. An MST 3 months shorter than that of the IP arm would correspond to an HR of 1.31. The planned sample size was 282 patients, determined by the methods of Schoenfeld and Richter,[13] with 3 years of accrual and 3 years of follow-up. Because of an insufficient accrual rate during the study, the accrual period was revised to 4 years.

An interim analysis was scheduled because of the futility of the trial at the halfway mark of registration. The results from the interim analysis were reviewed by the JCOG Data and Safety Monitoring Committee, and investigators were blinded for the results. After the first interim analysis, the protocol was revised to add second interim analysis after all patients had been registered. Multiplicity for the primary end point was adjusted using O'Brien-Fleming–type alpha spending function.[14] The primary end point—OS—was analyzed using stratified Cox regression analysis with PS (0 *v* 1) and sex (male *v* female) as strata for all eligible patients. Except for the primary analysis, OS and PFS were analyzed using unstratified Cox regression analysis. OS and PFS were estimated using the Kaplan-Meier method. RRs were compared using Fisher's exact test. QOL scores were analyzed using logistic regression with covariate, treatment arm, and QOL scores at baseline. All *P* values are two sided, except for the primary analysis of the noninferiority hypothesis. Statistical analyses were conducted using SAS software (version 9.1 or 9.2; SAS Institute, Cary, NC).