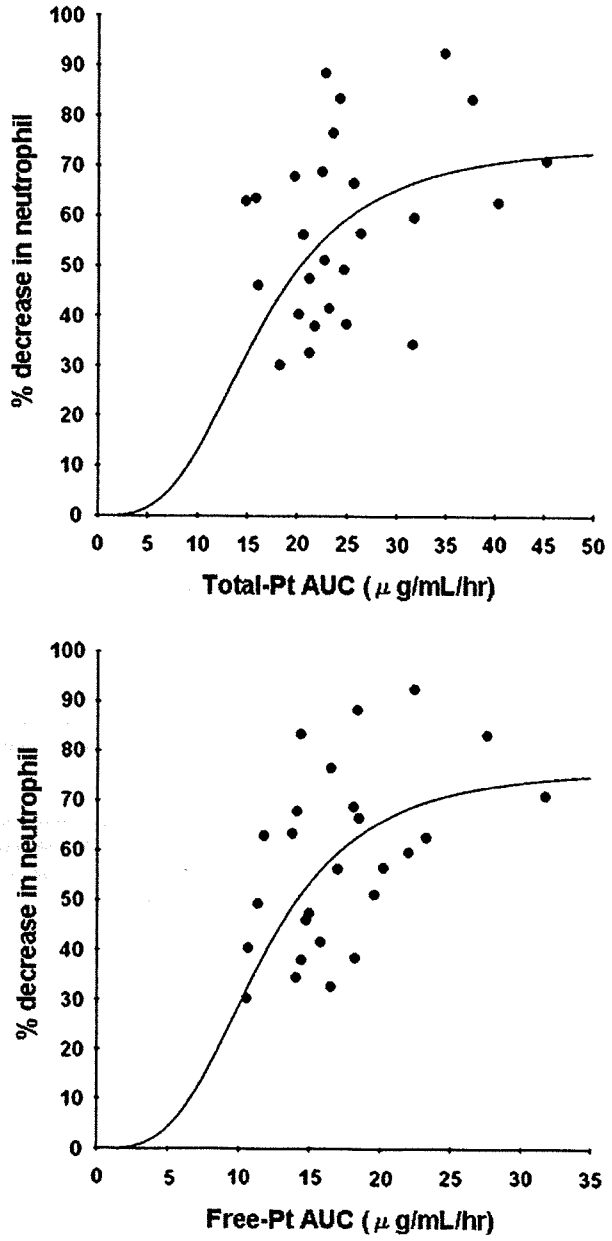

Fig. 2 Relationship between AUCs of total/free-Pt and the percentage decrease in the neutrophil count

In the pharmacokinetic analysis, the free-Pt AUC at a dose of 100 mg/m^2 in Group A seemed similar to that of 80 mg/m^2 in Group B, and there was no significant difference between these two treatment subgroups ($P = 0.336$). These results endorsed an almost equivalent drug exposure in both patient groups, stratified according to renal function. Furthermore, the AUC values in both groups seemed similar to historical data (obtained in a study with a small sample size) for patients aged ≤70 years [14]. However, a significant correlation was not observed between the renal function (i.e., the Ccr value) and the nadir platelet count, as in a previous report examining younger patients. These were possibly attributed to the wide inter-patient physiological and pharmacological variability among elderly patients or just the consequence of the adaptation of dose [11]. For elderly patients, a strict dose calculation of nedaplatin based on renal function, such as the dose calculation for carboplatin using the Calvert formula [18], is not required, and a simple dose selection of nedaplatin stratified according to renal function is considered to be reasonable.

A total of 13 (33%) of the 39 patients achieved partial responses. In this study, 21 patients with squamous cell carcinoma were enrolled, 12 patients achieved PR and the response rate was 57%. The biological mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma of the lung remains unknown. In the pharmacokinetic analysis, no significant differences were observed in responding patients with squamous cell carcinoma compared with non-responding others. However, nedaplatin also has a favorable antitumor activity against head and neck cancer and esophageal cancer, which also have a high frequency of squamous cell histology [19–22]. Although antitumor activity was evaluated only in elderly patients in this study, the development of this activity is worthwhile in the treatment of NSCLC with squamous cell histology. Furthermore, a translational study to identify the biological and/or genetic mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma is also warranted.

In conclusion, the recommended doses of nedaplatin for elderly patients with NSCLC were determined based on renal function, a dose of 100 mg/m^2 every 4 weeks was recommended for patients with a Ccr ≥60 mL/min, and a dose of 80 mg/m^2 every 4 weeks was recommended for patients with 40 ≤ Ccr < 60 mL/min. Nedaplatin can be safely administered to elderly patients with an acceptable level of toxicity and favorable antitumor activities against NSCLC, especially squamous cell carcinoma.

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Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy

Ikuo Sekine[1], Minako Sumi[2], Yoshinori Ito[2], Chiharu Tanai[1], Hiroshi Nokihara[1], Noboru Yamamoto[1], Hideo Kunitoh[1], Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital and [2]Division of Radiation Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

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Objective: To identify any gender differences in the outcomes of concurrent platinum-based chemotherapy and thoracic radiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).
Methods: A comparative retrospective review of the clinical characteristics and treatment outcomes between female and male NSCLC patients receiving chemoradiotherapy.
Results: Of a total of 204 patients, 44 (22%) were females and 160 (78%) were males. There was no difference in age, body weight loss, performance status or disease stage between the sexes, whereas never-smokers and adenocarcinoma were more common in female patients (55% vs. 3%, $P < 0.001$, and 73% vs. 55%, $P = 0.034$, respectively). Full cycles of chemotherapy and radiotherapy at a total dose of 60 Gy were administered to ~70% and >80% of the patients, respectively, of both sexes. Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$), but the median progression-free survival did not differ between the sexes. The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$).
Conclusions: This study failed to show any gender differences in the survival or toxicity among patients treated by concurrent chemoradiotherapy. These results contrast with the better survival in female patients undergoing surgery for localized disease or chemotherapy for metastatic disease.

Key words: gender – female – non-small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Lung cancer in women differs from that in men with respect to its incidence, association with smoking, and histological distribution (1). Several epidemiological studies have shown that female smokers have a 1.5- to 3-fold higher risk of developing lung cancer than male smokers, suggesting that women may have an increased susceptibility to the carcinogens in tobacco. Never-smokers with lung cancer are more likely to be female than male, and in East Asian countries, as high as 70% of the women diagnosed with lung cancer have never smoked in their lives. Women are more likely to develop adenocarcinoma than squamous cell carcinoma, the latter being more common in men. This difference cannot be explained fully by differences in the smoking patterns, and potentially suggests basic differences in the etiology of lung cancer between the sexes (1).

Prospective cohort studies and a large population-based study have consistently shown that female gender is a favorable prognostic factor in patients with non-small cell lung cancer (NSCLC). These studies, however, included patients

For reprints and all correspondence: Ikuo Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

with all stages of cancer, and the therapies administered are not specified (2–4). The existence of a gender difference in survival remains controversial among patients with locally advanced NSCLC receiving radiation-based treatment. Some studies have shown better survival in females than in males (5–7), whereas others have shown no difference in survival between the sexes (8,9). Many patients in these studies, however, received radiotherapy alone, which is no longer the standard treatment for locally advanced disease. Furthermore, all but one of these studies included patients with stage I–II disease who were considered unsuitable for surgical treatment because of poor general condition. One study that addressed gender differences in unresectable stage III NSCLC patients treated by chemoradiotherapy showed a median survival time in women of 19.7 months and in men of 21.7 months ($P = 0.26$) (10). The objectives of this study were to compare the outcomes of concurrent chemoradiotherapy between female and male patients with stage III NSCLC.

PATIENTS AND METHODS

Study Population

Patients with unresectable stage III NSCLC who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1994 and 2005 were eligible for this study. A total of 204 patients were identified. Patients treated by sequential chemotherapy and thoracic radiotherapy were excluded from this study, because we consider that the standard of care for unresectable stage III NSCLC without effusion is concurrent chemoradiotherapy, and sequential treatment is only given to patients in poor general condition or those with tumors too large for radiotherapy initially, which are expected to shrink sufficiently for radiotherapy after chemotherapy. All patients underwent a systematic pre-treatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, computed tomographic (CT) scans of the chest and abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Chemotherapy consisted of cisplatin combined with either vinorelbine ($n = 125$), vindesine with or without mitomycin ($n = 46$), or other drugs ($n = 6$) repeated every 4 weeks, carboplatin and docetaxel ($n = 10$) administered weekly, and nedaplatin and paclitaxel administered every 4 weeks ($n = 17$).

A retrospective review of the medical charts of the patients was conducted to determine the gender, age, smoking history, body weight loss, performance status, clinical stage, histology, success of treatment delivery, incidence/severity of hematological toxicity and esophagitis, tumor responses, and survival parameters. The histological classification of the tumor was based on the criteria of the World Health Organization (11). Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann–Whitney tests were used to evaluate the differences in the categorical and continuous variables, respectively. Overall survival was measured from the start of chemotherapy to death from any cause. For progression-free survival (PFS), both the first evidence of disease progression and death from any cause were counted as an event. A patient who did not develop any event at the last follow-up was censored at that time. Survival curves were calculated according to the Kaplan–Meier method. Cox's proportional hazard models were used to adjust for potential confounding factors such as tumor stage and performance status (13). The significance of P value was set to be <0.05. All of the above-mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Demographics

Of the 204 patients, 44 (22%) were females and 160 (78%) were males (Table 1). There were no differences in age, body weight loss or performance status between the sexes, whereas never-smokers were more common among female patients (55% vs. 3%, $P < 0.001$). Adenocarcinoma accounted for the main histological type in both sexes, but was more common in female patients (73% vs. 55%, $P = 0.034$). No difference in the distribution of the clinical stage was noted between the sexes.

Treatment Delivery

The delivery of chemoradiotherapy was good in both sexes. Three to four cycles of chemotherapy were administered in 68% of the female patients and 69% of the male patients. A total radiation dose of 60 Gy was given to 89% of the female patients and 86% of the male patients.

Toxicities

Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients (Table 2). The frequency of febrile neutropenia was also the same between the sexes. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex.

Treatment after Recurrence

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was evaluated in

43 of the 44 female patients and 153 of the 160 male patients. Gefitinib was given to 7 female and 25 male patients, and erlotinib to 1 female and 1 male patient. Thus, in all, EGFR-TKIs were given to 8 (18.2%) female and 26 (16.3%) male patients.

Table 1. Patient characteristics

Characteristics	Female ($n = 44$)		Male ($n = 160$)		*P* value
	N	%	*N*	%	
Age					
Median (range)	57 (29–74)		58 (35–78)		0.28
Smoking history					
Never	24	55	5	3	<0.001
Former	5	11	77	48	
Current	15	34	78	49	
Body weight loss					
≤4.9%	36	82	126	79	0.66
≥5.0%	8	18	34	21	
Performance status					
0	12	27	51	32	0.62
1	32	73	107	67	
2	0		2	1	
Histology					
Adenocarcinoma	32	73	88	55	0.034
Non-adenocarcinoma	12	27	72	45	
Stage					
IIIA	17	39	69	43	0.53
IIIB	27	61	91	57	
Period					
1994–99	17	39	47	29	0.24
2000–05	27	61	113	71	

Table 2. Grade 3–4 toxicity

Toxicity	Grade	Female ($n = 44$)		Male ($n = 160$)		*P* value
		N	%	*N*	%	
Leukopenia	3	23	52	79	49	0.44
	4	9	21	33	21	
Neutropenia	3	13	30	49	31	0.19
	4	15	34	51	32	
Thrombocytopenia	3	1	2	5	3	0.97
	4	0		1	1	
Febrile neutropenia	3	9	21	37	23	0.59
	4	1	2	1	1	
Esophagitis	3	2	5	14	9	0.79

Response and Survival

There were 3 patients showing complete response (CR), 38 showing partial response (PR) and 2 showing stable disease (SD) among the 43 female patients evaluable for response, and 10 patients showing CR, 116 showing PR, 24 showing SD and 7 showing progressive disease among the 157 male patients evaluable for response. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$). Disease progression was noted in 36 of the 44 (82%) female patients and 131 of the 160 (82%) male patients. The median PFS did not differ significantly between the sexes: 9.2 months in the females and 9.7 months in the males ($P = 0.67$, Fig. 1). The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$, Fig. 2). Survival analyses in subgroups showed the

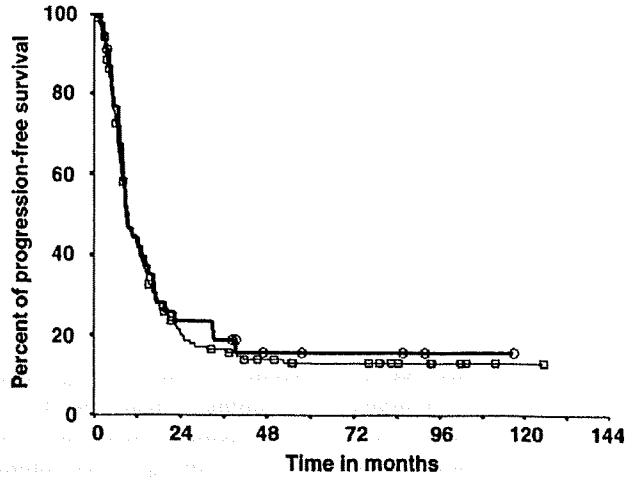

Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

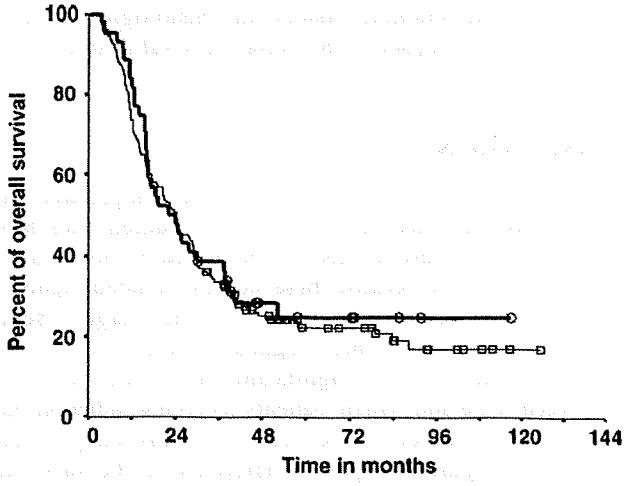

Figure 2. Overall survival by sex. Thick line, females; thin line, males.

Table 3. Factors associated with overall survival

Variables	Hazard ratio (95% confidence interval)	
	Univariate analyses	Multivariate analyses
Age	1.01 (0.99–1.03)	—
Sex		
Female	1	1
Male	1.10 (0.74–1.62)	1.16 (0.71–1.90)
Smoking habit		
No	1	1
Yes	1.00 (0.63–1.59)	0.75 (0.41–1.36)
Body weight loss		
≤4.9%	1	—
≥5.0%	1.19 (0.81–1.75)	—
Performance status		
0	1	1
1–2	1.59 (1.11–2.28)	1.44 (0.97–2.15)
Histology		
Adenocarcinoma	1	1
Non-adenocarcinoma	0.76 (0.53–1.10)	0.74 (0.51–1.08)
Stage		
IIIA	1	1
IIIB	0.96 (0.70–1.32)	0.79 (0.56–1.11)
Period		
1994–99	1	1
2000–05	0.62 (0.45–0.86)	0.65 (0.45–0.92)

absence of any gender differences either among patients with adenocarcinoma or among those with non-adenocarcinoma. Similarly, no gender differences were observed either among smokers or among never-smokers. Univariate Cox's proportional hazard analyses showed that the performance status and treatment period were significantly associated with the survival (Table 3). After adjustment for the smoking history and histological type, the gender had no impact on the overall survival (Table 3).

DISCUSSION

Although prospective cohort studies and a population-based study have reported better survival in women than in men with NSCLC, these results may be biased by potential confounding factors, because these studies included highly heterogeneous patients in terms of the stage, therapy, co-morbidities and other prognostic factors (2–4). Thus, whether there is any significant difference in survival between male and female patients receiving radiation-based treatment remained controversial, and this study failed to show any significant gender difference in the survival in NSCLC patients receiving concurrent chemoradiotherapy.

Several previous studies have suggested a better prognosis in female than in male NSCLC patients treated by surgery (2,14–18), whereas our results were inconsistent with this suggestion. This may be attributable to the difference in the distribution of the disease stage (pathological stages I, II and III) between these studies and our study, including pathological stages I, II and III. The magnitude of the gender difference in survival has been suggested to vary with the disease stage. Some studies have shown a diminishing gender difference as the disease stage advanced from stages I to III, with disappearance of the gender difference among patients with stage III disease (14,15), whereas others have shown relatively constant gender difference through all the disease stages (2,16,17). A study on the gender difference in the survival in surgically resected NSCLC patients showed a better overall survival in women than men, but no significant difference in the cancer-specific survival between the two sexes (18). These results suggest that the gender difference in survival in NSCLC patients undergoing curative surgery, especially patients with early-stage disease, can be explained by the mortality related to diseases other than lung cancer.

Among local or locally advanced NSCLC patients receiving radiotherapy-based treatment, the gender difference in survival has been controversial (5–9), but potential confounding factors in these studies prevent an accurate interpretation of the results. In these studies, as high as 30% of the patients had medically inoperable stage I–II disease and 3–22% of the patients had a performance status of 2. In addition, 36–100% of patients were treated by thoracic radiation alone, whereas the others also received some form of chemotherapy as part of the treatment. Neither the current study nor another previous study showed any gender difference in the survival (10). The patients in both of these studies were limited to stage III NSCLC patients with a performance status of 0–1 who were treated by concurrent chemoradiotherapy.

Several studies have been conducted on the gender differences in survival among patients with stage IIIB–IV disease treated by systemic chemotherapy (19–24). Of these, many showed a better survival in female patients than in male patients (19–22), but the causes of this gender difference in survival remain unknown. Our previous study also showed a better survival in female patients, which was explained partly by the large number of female patients (56% vs. 44%) receiving gefitinib, and the 4-fold longer duration of gefitinib treatment (144 vs. 35 days) in these patients (25). In contrast, only 18% of the female patients and 16% of the male patients received EGFR-TKIs in this study. Thus, treatment with EGFR-TKIs had little influence on the patient survival in this study.

Clear difference in the frequency of adenocarcinoma and smoking history between female and male patients has been reported repeatedly, and this study also showed that adenocarcinoma and never-smokers were more common among the female patients. Thus, it would be reasonable to think that differences in the tumor cell characteristics between the

female and male patients may be responsible for the difference in survival between the two sexes. However, survival analyses conducted separately in subgroups among patients with adenocarcinoma and those with non-adenocarcinoma, or among smokers and non-smokers have failed to reveal any gender differences in the survival among any subgroups. In addition, a multivariate analysis showed no difference in survival between the sexes after adjustment for the tumor histology and smoking history.

The threshold for drug toxicity may also differ between women and men. In general, chemotherapy-related toxicity is reported to be slightly more severe in women, and to the best of our knowledge, there are no reports on the gender difference in radiation-related toxicity. This study showed no difference in the severity of esophagitis or hematological toxicity between the two sexes. We did not examine pulmonary toxicity in this study, because our previous large retrospective study showed no difference in the incidence or grade of pulmonary toxicity between the sexes (26).

Among several limitations of this study, the most important is the small sample size that made it difficult to draw definitive conclusions. Indeed, small difference in survival between the sexes, if any, could not be detected in this small number of patients. It is difficult, however, to expand the study population without an increase in its heterogeneity. A population-based study with >20 000 patients, for example, included patients with all stages of lung cancer, and the therapies administered were not specified. Furthermore, the quality of data on diagnosis and treatment was not uniform (4). Thus, the results of that study may be biased, despite of the huge number of patients. We cannot overlook this problem especially when analyzing stage III NSCLC patients treated with radiation-based treatment, because the quality control of radiotherapy has not been fully developed in Japan, and therefore, indication, methods and outcomes of thoracic radiotherapy may vary among hospitals.

In conclusion, this study failed to reveal any significant differences in the treatment outcomes, including survival and treatment toxicity, between female and male patients with stage III NSCLC receiving concurrent chemoradiotherapy. These results are in sharp contrast to the reported better survival in female patients with localized disease treated by surgery or those with metastatic disease treated by systemic chemotherapy.

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Conflict of interest statement

None declared.

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Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials

C Tanai*[,1], H Nokihara[1], S Yamamoto[2], H Kunitoh[1], N Yamamoto[1], I Sekine[1], Y Ohe[1] and T Tamura[1]

[1]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [2]Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

There are inadequate data on the outcomes of patients who declined to participate in randomised clinical trials as compared with those of participants. We retrospectively reviewed the patient characteristics and treatment outcomes of both participants and non-participants in the two randomised trials for chemotherapy-naive advanced non-small-cell lung cancer. Trial 1 compared four platinum-based combination regimens. Trial 2 compared two sequences of carboplatin plus paclitaxel and gefitinib therapies. Nineteen of 119 (16%) and 153 (37%) patients declined to participate in Trials 1 and 2, respectively. Among the background patient characteristics, the only variable associated with trial participation or declining was the patients' attending physicians ($P<0.001$). Important differences were not observed in the clinical outcomes between participants and non-participants, for whom the response rates were 30.6 *vs* 34.2% and the median survival times were 489 *vs* 461 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 0.965 (95% confidence interval: 0.73 – 1.28). In conclusion, there was no evidence to suggest any difference in the characteristics and clinical outcomes between participants and non-participants. Trial designs and the doctor–patient relationship may have an impact on the patient accrual to randomised trials.
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Randomised clinical trials (RCTs) are the definitive method for comparing the efficacy of treatments and a crucial step in the development of new cancer treatments. There has always been a big problem that their low accrual rates limit their progress (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006).

A number of studies have examined the motivations of patients for accepting or declining entry to RCTs (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Ho *et al*, 2006; Albrecht *et al*, 2008). The results of questionnaire surveys administered to patients regarding clinical trials revealed that two of the most common reasons for entering the trial were the hope for personal benefit and the opportunity to contribute to the research knowledge thereby benefiting others in the future (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Albrecht *et al*, 2008). On the other hand, the common reasons for declining participation were worries about the process of randomisation, overestimation of the benefits of standard therapy and fear of the trial's experimental nature (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Ho *et al*, 2006).

However, inadequate data are available on the actual outcomes of non-participants compared with those participating in RCTs (Schmoor *et al*, 1996; Braunholtz *et al*, 2001; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005). Although several reports and their review (Braunholtz *et al*, 2001) have suggested the existence of a 'trial effect', in which participants enjoy favourable outcomes, others, especially those which attempted to exclude the confounding factors, have refuted this finding (Schmoor *et al*, 1996; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005).

On the other hand, if participation in prospective trials is associated with certain clinical characteristics of the patients, generalisability of the conclusion from the data to the clinical practise, even in patients who meet the restrictive eligibility criteria, should be in question.

The purpose of this study was to analyse the characteristics and outcomes of the patients who met the eligibility criteria but declined to participate in RCTs, as compared with those who did participate, and to search for clues to improve patient accrual to clinical trials.

MATERIALS AND METHODS

Between October 2000 and October 2005, each of the 272 patients, who fulfilled the entry criteria of our top priority studies during the period, was informed of all aspects of RCTs on non-small-cell lung cancer (NSCLC) and was invited to participate in one of the two trials to be conducted at the National Cancer Center Hospital, Tokyo, Japan. We make it a rule for each patient with advanced

*Correspondence: Dr C Tanai, Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; E-mail: ctanai@ncc.go.jp
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lung cancer to be hospitalised for the first-line chemotherapy. All patients are then checked for the eligibility criteria of clinical trials available at the time and recorded in our database, whether or not they are treated on trials.

Signed informed consent was obtained from the patients for future statistical analysis of their clinical courses and outcomes, even when they were treated outside clinical trials.

Trial 1 was conducted to compare the four platinum-based combination regimens (cisplatin–irinotecan, carboplatin–paclitaxel, cisplatin–gemcitabine and cisplatin–vinorelbine) in patients with untreated advanced NSCLC between October 2000 and June 2002 (Ohe *et al*, 2007). When patients declined to participate, cisplatin-based combination regimens, such as cisplatin–irinotecan, the reference arm of the trial, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians.

Trial 2 was conducted between June 2003 and October 2005 to compare the following two treatment arms; (A) four courses of carboplatin and paclitaxel (CP) followed by gefitinib, and (B) gefitinib until disease progression followed by CP, in patients with advanced NSCLC (Nokihara *et al*, 2008). When patients declined to participate, platinum-based combination regimens, such as CP, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians; treatment options included gefitinib as first-line chemotherapy, when the patients and their families wished to start with it.

Patients in each trial had to meet the following criteria: histologically and/or cytologically documented NSCLC; clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy); no earlier systematic chemotherapy; at least one measurable lesion; age 20–74 years old; Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1; adequate haematological, hepatic and renal functions; and partial pressure of arterial oxygen of 60 torr or more. Each patient was required to submit a written informed consent before entry.

Four physicians (A, B, C and D) participated in Trial 1 and five physicians (A, B, C, D and E) in Trial 2. All were male. Physicians A, B, C and D had 16, 14, 11 and 9 years of experience, respectively, at the time of activation of Trial 1 (October 2000), and Physician E had 9 years of experience at the start of Trial 2 (June 2003). One of the five attending staff physicians and one to two residents or trainees attended each consultation. Which doctor actually offered the RCTs depended on each case and was not recorded, but the attending staff physician finally confirmed the decision by the patient.

Paper and/or electronic medical records from the initial visit to our centre to the end of the follow-up were retrospectively reviewed. Demographic data (age, gender, smoking history), medical information (tumour histology, clinical stage, performance status, therapy characteristics), and clinical outcomes (response rate, follow-up time, overall survival time, 1- and 2-year survival rates) were abstracted and analysed. The response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse *et al*, 2000) by the attending physicians. It is our policy to assess clinical responses with RECIST, even in routine practise. Follow-up time at our institution was defined as the period from the initiation of the first day of the initial therapy or decision of no therapy, to the last day at our institution (including death during follow-up). Survival data of the patients who left our institution could be collected by enquiry into official agency for family registry in Japan.

χ^2-tests and logistic regression analysis was used to assess associations between patient characteristics and the rate of declining to participate. Overall survival (OS) curves were produced using the Kaplan–Meier method and compared with the log rank test. All participants (those who agreed to be enroled into the RCT) and non-participants (those who declined to participate in the RCT) were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (age, gender, smoking history, clinical stage and PS) in comparing the OS of participants and non-participants. *P*-values <0.05 were considered statistically significant. The data collected were analysed using an SPSS II statistical package.

Japanese ethics guidelines for clinical and epidemiological studies, which took effect in August 2007, do not mandate institutional review board (IRB) approval for a single-institutional, retrospective data analysis from the medical charts, when the predesignated person of the institution so judges. This study was thus exempted from ethical review of IRB in due process, on the judgment of the responsible official, deputy director of National Cancer Center Hospital.

RESULTS

There were no significant differences in the outcomes between the arms of each trial. In Trial 1, no statistically significant differences in the response rate, progression-free survival and OS were observed between the four regimens. In Trial 2, there were no statistically significant differences in the median survival time (MST) (18.8 and 17.2 months) and the survival rate at 1 year between the two arms. Seventy-five patients declined to participate in those trials, and 1 of the 197 who initially accepted entry withdrew consent, refusing to continue the trial immediately after randomisation.

Table 1 shows the patient characteristics and rate of declining. 100 patients accepted and 19 patients (16%) declined entry to Trial 1, and 96 patients accepted and 57 patients (37%) declined entry to clinical Trial 2 (including the one patient already mentioned who withdrew consent after randomisation) ($P<0.001$). No significant influence on the rate of declining of patient gender, age,

Table 1 Patient characteristics and rate of declining

	Clinical trial 1			Clinical trial 2			Total		
	P	NP	ROD (%)	P	NP	ROD (%)	P	NP	ROD (%)
No.	100	19	16	96	57	37	196	76	28
Gender									
Male	64	12	16	55	34	38	119	46	28
Female	36	7	16	41	23	36	77	30	28
Age									
<60	46	9	16	37	29	44	83	38	31
⩾60	54	10	16	59	28	32	113	38	25
Smoking history									
+	69	9	12	55	33	38	124	43	26
–	31	10	24	41	24	37	72	33	31
Clinical stage									
III	24	6	20	21	19	48	45	25	36
IV	76	13	15	75	38	34	151	51	25
PS									
0	27	4	13	47	19	29	74	23	24
1	73	15	17	49	38	44	122	53	30
Physicians									
A	32	5	14	23	25	52	55	30	35
B	28	0	0	25	1	4	53	1	2
C	18	2	10	34	4	11	52	6	10
D	22	12	35	7	18	72	29	30	51
E	—	—	—	7	9	56	7	9	56

Abbreviations: NP = non-participants, P = participants; PS = performance status; ROD = rate of declining.

Table 2 Prediction of participation or declining to trials

	Univariate analysis[a]		Multivariate analysis[b]	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Gender (male *vs* female)	1.008 (0.586–1.733)	0.977	0.646 (0.300–1.391)	0.264
Age (<60 *vs* ⩾60)	0.735 (0.432–1.250)	0.254	0.701 (0.376–1.310)	0.266
Smoking history (+ *vs* −)	1.394 (0.815–2.386)	0.225	2.538 (1.162–5.541)	0.019
Clinical stage (III *vs* IV)	0.608 (0.339–1.089)	0.093	0.681 (0.346–1.340)	0.266
PS (0 *vs* 1)	1.398 (0.792–2.467)	0.247	0.785 (0.396–1.554)	0.487
Physicians (A–E)		<0.001		<0.001

Abbreviations: NP = non-participant; P = participant; PS = performance status; ROD = rate of declining. [a]By Pearson's χ^2-test. [b]By logistic regression analysis.

Table 3 Number of courses of the first-line chemotherapy

	Clinical trial 1		Clinical trial 2		
	Participants	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
	100	16	96	57	
First-line cycles					
1	10 (10%)	4 (25%)	6 (12%)	4 (9%)	0.418[a]
2	18 (18%)	4 (25%)	8 (16%)	12 (27%)	
3	37 (37%)	7 (44%)	5 (10%)	9 (20%)	
⩾4	35 (35%)	1 (6%)	30 (61%)	20 (44%)	
Gefitinib median duration (day)			73	99	0.118[b]
Range			13–752	34–1065	
IQR			29–204	38.5–512	

Abbreviation: IQR = interquartile range. [a]By Pearson's χ^2-test. [b]By log rank test.

smoking history, tumour histology, clinical stage or PS was observed (Table 2). There were, however, large differences in the rates of decline among the attending physicians who informed the patients about the trials and asked them to participate ($P<0.001$).

The treatment regimens for those who declined participation in the clinical trials were as follows. The majority of those who declined participation in Trial 1 selected one of the four platinum-based combination regimens presented in the trial: cisplatin–irinotecan 4, cisplatin–vinorelbine 3, cisplatin–gemcitabine 1, carboplatin–paclitaxel 4. Three patients in Trial 1 desired to have no more active treatments and opted for supportive care only, but later received active treatment at their referred hospitals. The detail of their therapy is unknown.

The majority of those who declined participation in Trial 2 selected carboplatin-based combination chemotherapy: carboplatin–paclitaxel 34 and carboplatin–gemcitabine 11, there by reflecting the shift to carboplatin for advanced NSCLC in Japan at the time of Trial 2, on the basis of the reports on the activity of the carboplatin-based regimens (Kelly *et al*, 2001; Schiller *et al*, 2002; Ohe *et al*, 2007). Twelve patients (21%) selected gefitinib as first-line chemotherapy.

Survival was analysed for all of the 196 participants and 76 of the non-participants. Post-therapy was analysed for all of the 196 participants and 73 of the non-participants, who were treated at our centre. There was one possible treatment-related death due to perforation of the colon during gefitinib treatment in Trial 2. No other toxic deaths were observed among either participants or non-participants. More participants of both the clinical trials were given four cycles or more of the first-line chemotherapy, probably reflecting protocol regulations (Table 3).

Table 4 summarises the treatment after the initial therapy. There were no significant differences between participants and non-participants in the number of chemotherapy regimens. Six (8%) of those who declined participation in the trial later participated in early-phase clinical trials of experimental therapies.

Table 4 Treatment after the first-line chemotherapy

	Participants 196 (%)	**Non-participants 73 (%)**	***P*-value[a]**
Chemotherapy regimen			
0[b]	26	40	0.108
1	38	26	
2	22	25	
3	9	8	
>4	5	1	
Radiotherapy	49	34	0.031
Pleural or pericardial drainage	10	5	0.227
Operation on metastatic brain tumors	1	3	0.122
Early-phase trials	13	8	0.300

[a]By Pearson's χ^2-test. [b]Patients received first-line chemotherapy only.

We have observed no clinically relevant differences in the clinical outcomes between participants and non-participants (Table 5). Clinical response to the initial therapy was analysed for all of the 196 participants and 73 of the non-participants, excluding three patients who were not treated at our institute. The response rate was 30.6% in participants and 34.2% in non-participants ($P=0.325$). The median follow-up time at our centre was 388 days for participants and 406 days for non-participants, which was not statistically different.

The OS was not different between participants and non-participants (Table 5 and Figure 1), with a hazard ratio of participants *vs* non-participants of 0.998 (95% confidence interval: 0.76–1.32). No significant difference in OS was observed either in Trial 1 (Figure 2) or in Trial 2 (Figure 3).

Table 5 Clinical outcomes

	Clinical trial 1		Clinical trial 2		Total		
	Participants	**Non-participants**	**Participants**	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
Response rate (%)[a]	29 (29/100)	12.5 (2/16)	32.3 (31/96)	40 (23/57)	30.6 (60/196)	34.2 (25/73)	0.569[b]
Median follow-up time (day)	329	339	493	444	388	406	0.846[c]
Range	45–2704	1–2176	36–2036	22–1688	36–2704	1–2176	
IQR	177–665	59–582	213–861	175–658	197–742	146–604	
Median survival time (day)	416	408	573	519	489	461	0.987[c]
Range	34–2704	53–2380	40–2036	35–1688	34–2704	35–2380	
IQR	264–815	140–698	251–938	276–1012	259–863	229–774	
1-year survival (%)	56.0	63.2	65.6	64.9	60.7	64.5	0.567[b]
2-year survival (%)	29.4	21.1	38.5	29.8	33.9	27.6	0.379[b]

Abbreviation: IQR = interquartile range. [a]Excluding three patients who did not receive active treatment at our center. [b]By Pearson's χ^2-test. [c]By log rank test.

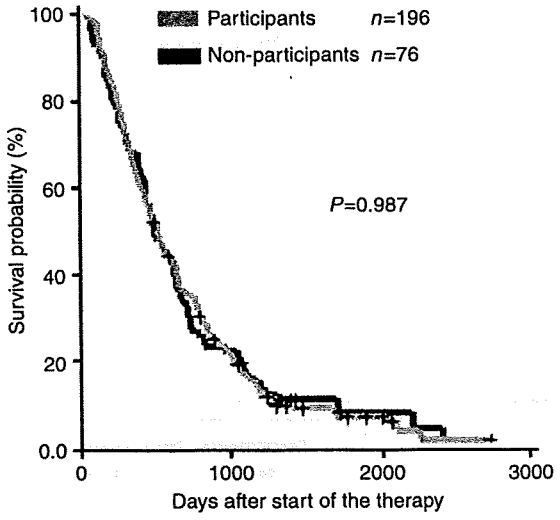

Figure 1 Overall survival of those who declined to participate in randomised trials (blue line, $n = 76$) as compared with the participants (pink line, $n = 196$). No significant difference can be observed.

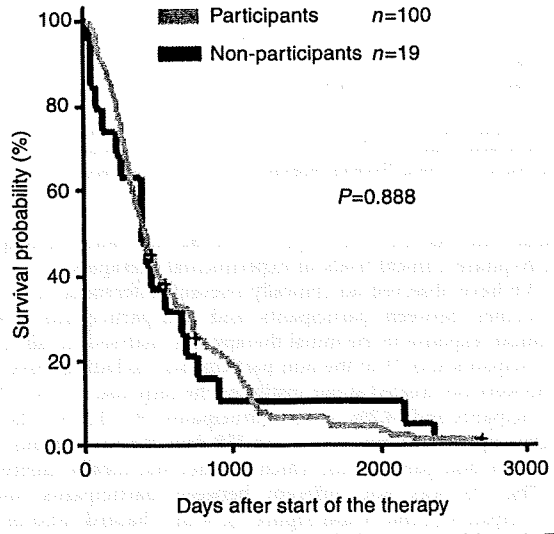

Figure 2 Overall survival of those who declined to participate in Trial 1 (blue line, $n = 19$) as compared with the participants (pink line, $n = 100$). No significant difference can be observed.

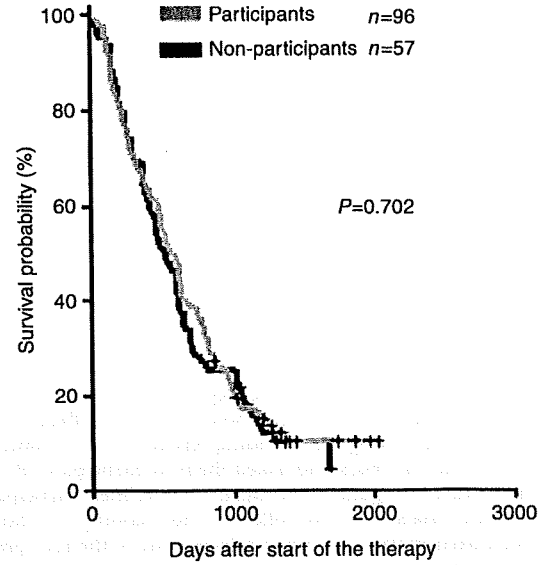

Figure 3 Overall survival of those who declined to participate in Trial 2 (blue line, $n = 57$) as compared with the participants (pink line, $n = 96$). No significant difference can be observed.

With the Cox proportional hazards model adjusted for gender, age, smoking history, clinical stage and PS, the hazard ratio of participants *vs* non-participants was 0.965 (95% confidence interval: 0.73–1.28, $P = 0.805$). Among the patient characteristics, PS was the only significant factor associated with OS in multivariate analysis ($P = 0.006$, by Cox proportional model).

DISCUSSION

It has been argued that trial participants have better outcomes than those who are not enroled in clinical trials. Several investigations have reported a favourable overall trend with trial entry (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004; West *et al*, 2005). This 'trial effect' could derive from several factors, such as protocol effect (the way treatments are delivered), care effect (extra care related to data gathering), Hawthorne effect (changes in doctor or patient behaviour on the basis of the knowledge that they are under observation) or placebo effect (psychologically mediated benefits) (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004).

In majority of the reports comparing outcomes between participants and non-participants of clinical trials, however, the

non-participant 'controls' were chosen from differently pooled database, which could include baseline imbalances between groups and hindsight bias (Davis *et al*, 1985; Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In this study, we compared the characteristics and outcomes of those who met the eligibility criteria but declined to participate in randomised trials, and instead chose to receive standard therapy. We thus aimed at excluding confounding factors as much as possible.

On the other hand, physician triage is pointed out to be one of the barriers to cancer clinical trial accrual (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006; Ho *et al*, 2006). We excluded the barrier by making it a rule to offer clinical trials to every patient with advanced NSCLC who satisfied the eligibility criteria.

The response rate, MST, 1-year and 2-year survival rates were all similar in both groups. We have to admit that response evaluation might not be as strict in off-protocol therapy. However, the hazard ratio for the OS was very close to 1. Although the confidence interval of 0.73 to 1.28 could not rule out the existence of clinically important difference in the treatment effect, it could not by any means be taken as a clinically relevant prognostic factor. We thus believe this confidence interval of the adjusted hazard ratio, 0.73–1.28, was narrow enough to justify the conclusion that the clinical outcomes of trial participants and non-participants were not different in our study. The differences in the number of cycles of chemotherapy given to participants and non-participants may suggest the so-called protocol effect (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), in which explicit careful description of treatment regimens could lead to improvement of outcomes. On the other hand, there clearly existed no 'care effect' representing the differences in incidental aspects of treatment or care between participants and non-participants, which the protocol may require, such as extra follow-up or extra nursing care (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In our cases, the same treatment teams took charge of and followed both groups of patients in the same manner, and found no differences in the post-treatment characteristics or follow-up periods. Thus, our first finding was that the clinical trials themselves seemed to have no influence on the outcomes or pattern of care of the patients.

The second finding was that we could not find any demographic characteristics to influence the patients' willingness to participate in clinical trials. Taken together with the first finding, both the characteristics and outcomes of the non-participants were very similar to the participants. This would imply that the participants ably represented the whole patient population of the disease status who met the eligibility criteria, and that conclusions from the clinical trials could be generalised.

Our study, however, could only show the similarity in the prognosis of the participants and non-participants, and, unlike an earlier report (Link *et al*, 1986), not that of the treatment effect itself. This could not be evaluated because there were no significant differences in the clinical effect between the arms in both Trial 1 and Trial 2. If newer, much more effective experimental treatment were presented in the trials, the outcome could be better in trial participants, which was the case in the adjuvant chemotherapy trial for osteosarcoma (Link *et al*, 1986). In that report, eligible patients who declined randomisation, but were given adjuvant chemotherapy, also had better outcomes. Therefore, a very effective treatment could lead to a better outcome both on and off trial. Ideally, strict comparison of the effects of the study participation itself would require randomised design of the trial participation (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), which is almost impossible to conduct.

Thirdly, the declining rate seemed to be influenced by the trial design. Trial 1 was the comparison of four similar platinum-doublet regimens. On the other hand, Trial 2 was the comparison of two arms with sequentially different types of chemotherapy. In general, people might have the impression that injection therapy would be more effective, and less convenient, than oral administration. It is easy to understand that more patients felt difficulty in accepting the randomisation of different types of therapy, such as Trial 2 (Schmoor *et al*, 1996; Jenkins and Fallowfield, 2000).

The declining rate also seemed to be greatly affected by the attending physician. The attending physician with longer experience as a thoracic oncologist tended to have lower rate of declination. Even though we do not have records on who actually informed the participants regarding the trial, residents or trainees under Physician A seemed to have had more chance to lead the consultation, which might have affected the rate of declination. Trust in the doctor is one of the most important reasons for agreeing to enter an RCT, whereas it has also been cited as the main reason for declining to participate (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Stryker *et al*, 2006). Patients prefer the doctor to make the treatment decisions rather than to be randomised. A recent report emphasises the influence of physicians' clinical communication on patients' decision-making on participation in clinical trials (Albrecht *et al*, 2008). Improving communication and more interventions by clinical research coordinators and other medical staff members in all eligible patients may improve the accrual rate (Fallowfield *et al*, 1998; Wright *et al*, 2004; Stryker *et al*, 2006).

Finally, it was interesting to find that 8% of those who declined the RCTs participated in early-phase trials during follow-up. It is possible that the lack of effective therapies had changed their recognition of clinical trials. However, it might support the psychological states of patients as reported in earlier studies (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Wright *et al*, 2004); patients expect experimental therapies to give them improved effectiveness but with fear of uncertainty. They are reported to have negative opinions regarding the principle of randomisation. Better understanding of the patients' decision-making process and the factors influencing their psychological states may lead to improvement in RCT accrual.

Our study has several limitations. One is that it was conducted at a single academic institution; the situation might well have been different in others or when the research was performed on a multi-institution basis. The second is that we analysed data from only two trials and could not definitely conclude that a trial design would affect the patient accrual. Third, we have no data on the reasons for patient participation. That information would be definitely useful for analysing factors for consent or declining to participate, and would help to improve the accrual rate. Further research is required.

In conclusion, there was no evidence of any difference in the response rates and survival times between participants and non-participants. The declining rate of clinical trials was influenced by the referring physicians and trial designs. Further analysis of the decision-making process of those offered trials is warranted, for it may improve patient accrual to RCTs.

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Differences in the Quality of Information on the Internet about Lung Cancer between the United States and Japan

Yasushi Goto, MD, Ikuo Sekine, MD, PhD,* Hiroshi Sekiguchi, MD,† Kazuhiko Yamada, MD,* Hiroshi Nokihara, MD,* Noboru Yamamoto, MD,* Hideo Kunitoh, MD,* Yuichiro Ohe, MD,* and Tomohide Tamura, MD**

Introduction: Quality of information available over the Internet has been a cause for concern. Our goal was to evaluate the quality of information available on lung cancer in the United States and Japan and assess the differences between the two.

Methods: We conducted a prospective, observational Web review by searching the word "lung cancer" in Japanese and English, using Google Japan (Google-J), Google United States (Google-U), and Yahoo Japan (Yahoo-J). The first 50 Web sites displayed were evaluated from the ethical perspective and for the validity of the information. The administrator of each Web site was also investigated.

Results: Ethical policies were generally well described in the Web sites displayed by Google-U but less well so in the sites displayed by Google-J and Yahoo-J. The differences in the validity of the information available was more striking, in that 80% of the Web sites generated by Google-U described the most appropriate treatment methods, whereas less than 50% of the Web sites displayed by Google-J and Yahoo-J recommended the standard therapy, and more than 10% advertised alternative therapy. Nonprofit organizations and public institutions were the primary Web site administrators in the United States, whereas commercial or personal Web sites were more frequent in Japan.

Conclusion: Differences in the quality of information on lung cancer available over the Internet were apparent between Japan and the United States. The reasons for such differences might be tracked to the administrators of the Web sites. Nonprofit organizations and public institutions are the up-and-coming Web site administrators for relaying reliable medical information.

Key Words: Internet, Information quality, Lung cancer.

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*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan; and †Department of Pulmonary and Critical Care Medicine, Mayo Clinic Minnesota, Rochester, Minnesota.

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Address for correspondence: Yasushi Goto, MD, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: ygoto-tky@umin.net

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The Internet has given rise to an information revolution of unprecedented magnitude. Whereas the Internet has great potential in marshaling the large volume of health information resources available, it is becoming increasingly difficult to discern which of the resources are reliable and accurate or appropriate for the users.[1–6] This issue has become a cause for great concern, especially in the field of oncology, and many studies have evaluated the pros and cons of obtaining information from the Internet.[2–6] Meanwhile, the medical community is being increasingly faced with patients asking us about the medical information available on the Internet. We can no longer neglect the public importance of the information available and have to use it effectively for patients to better understand their disease.

Although one of the main characteristics of the Internet is its worldwide accessibility, differences in language use around the world serve as a bottleneck for collecting information from the Internet. The estimated number of people using the Internet is about the same in the United States and Japan (70 and 67%,[7,8] respectively), and 80% of patients obtain health information via the Internet in the United States.[9] Until now, most studies that have evaluated the quality of the health care information available over the Internet are from the English-speaking community, and very few studies have been conducted in relation to information available in Japanese.[10,11] Furthermore, only a limited number of studies evaluating the differences in the quality of information available between two languages have been published,[12] and no such study comparing such information in the English and Japanese languages has been published.

Our goal was to imitate the search for medical information by the general population in Japan and United States and to evaluate the differences in the process between the two countries. We also investigated the administrators of the Web sites and attempted to identify any correlation existing between the Web site administrators and the quality of information available on the Internet. We focused on information available on lung cancer, which is the leading cause of cancer-related death in both the Unites States and Japan.[13,14] Because search engines are the leading tools to obtain any kind of information, whether general or medical, on the Internet,[15] we used Google and Yahoo, which are the two most commonly used search engines for Web search in both the United States and Japan.

METHODS

Web Site Search

We conducted a prospective, observational Web review by performing keyword searches using Google in both Japanese and English, and Yahoo in Japanese. Japanese searches were conducted by author YG in Japan (Tokyo) on May 29, 2007, and the English search was conducted by author HS in the United States (New York) on May 25, 2007. We used "Hai-gan (both letters in Chinese characters)," "Hai (Chinese character)-gan (hiragana)," and "Hai (Chinese character)-gan (katakana)," for the Japanese search, and "lung cancer" and "lung carcinoma" for the English search. The search word that resulted in the largest number of search results was chosen for the subsequent study.

The first 50 Web sites displayed by Google and Yahoo in Japanese, and Google in English, excluding the advertisement area, were used for further evaluation. Web sites that were inaccessible, not designed to provide health information (i.e., news and advertisement of books), or displayed for the second (or more) time were excluded from the subsequent evaluation. Samples from the Yahoo in English were supplemented to compare the search utility on January 21, 2009.

Site Characteristics

Author YG evaluated the Web sites within a week of the original search. We evaluated the Web sites based on criteria known as the "JAMA" benchmark[16]: display of authorship (authors and contributors, their affiliations, and relevant credentials), attribution (references and sources for all content and all relevant copyright information), disclosure (Web site ownership, sponsorship, advertising, commercial funding arrangements or support, or potential conflicts of interest), and currency (dates on which the contents were posted and updated). We considered each criterion as fulfilled when it was fully displayed. For further evaluation, we focused on the description about the treatment of advanced non-small lung cancer. To our knowledge, there is no established tool-based instrument to evaluate the information available on cancer treatment. Therefore, we classified the information into three categories: acceptable (description of systematic reviews, such as guidelines from authorized facilities,[17–20] links to systematic reviews, or abstracts of systematic reviews), unacceptable (recommendation of alternative medicine or a generally unapproved treatment), and inevaluable (lack of adequate description). The administrators of the Web sites were classified into five categories: nonprofit organization (NPO) or public institution, medical institution, commercial (for specific treatments), personal (pages made by patients or their families), and others.

Analysis

Descriptive statistics were used to determine the numbers and percentages related to the characteristics of the Web sites. To compare the differences between two countries in view of user experience and search utility, Web sites displayed in Google-U was compared with that of Yahoo-J and Google-J, respectively. The χ^2 test or Fisher's exact test was used as appropriate.

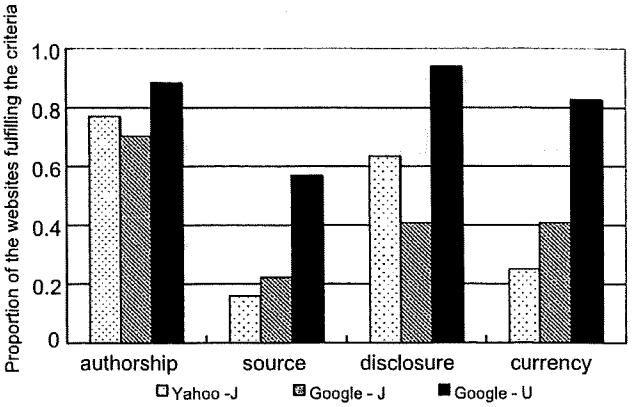

FIGURE 1. JAMA benchmark: Description of the JAMA benchmark[16] is listed by the search engines; display of authorship (authors and contributors, their affiliations, and relevant credentials); attribution (references and sources for all content, and all relevant copyright information); disclosure (Web site ownership, sponsorship, advertising, commercial funding arrangements or support, or potential conflicts of interest); and currency (dates on which the contents were posted and updated).

RESULTS

Differences by Notation

In Google Japan, search using the word "Hai-gan (both letters in Chinese characters)" resulted in a display of approximately 7.7 million Web sites, and in Google United States, search using the phrase "lung cancer" threw up approximately 52 million Web sites. These notations were, therefore, used for the subsequent evaluation. After excluding Web sites that were inaccessible, were not designed to provide health information, or ranked for the second (or more) time in each search, 44, 27, 39, and 35 Web sites displayed by Yahoo Japan (Yahoo-J), Google Japan (Google-J), Yahoo United States (Yahoo-U), and Google United States (Google-U), respectively, were evaluated for further study.

Web Site Characteristics

Figure 1 summarizes the quality of the Web sites that satisfied the criteria of the JAMA benchmark. Authorship was displayed in more than 70% of the Web sites displayed by the three searches: 31 in Google-U (88.6%), 34 in Yahoo-J (70.3%, $p = 0.243$), and 19 in Google-J (88.6%, $p = 0.106$). Attribution of the content was found in 20 (57.1%) of the Web sites in Google-U, and 7 (15.9%, $p < 0.001$) and 6 (22.2%, $p = 0.009$) of the Web sites in Yahoo-J and Google-J, respectively. Twenty-eight (63.6%, $p = 0.001$) Web sites in Yahoo-J, 11 (40.7%, $p < 0.001$) in Google-J, and 33 (94.2%) in Google-U made the disclosure. Display of currency was found in 29 (82.9%) sites in Google-U, but in less than 50% of the Web sites in the Japanese searches; 11 (25.0%, $p < 0.001$) in Yahoo-J and 11 (40.7%, $p = 0.001$) in Google-J.

Quality of Description of the Treatment

Evaluation of the treatment description for advanced non-small cell lung cancer is summarized in Figure 2. The

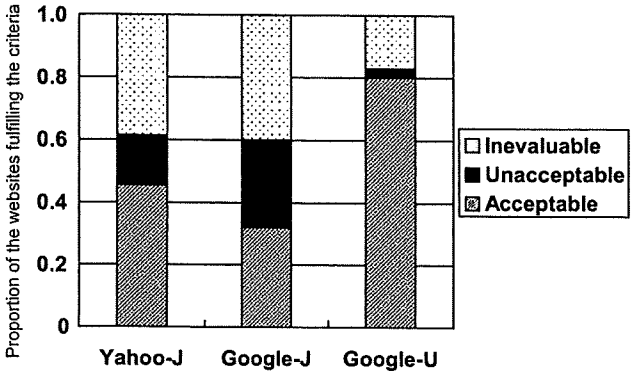

FIGURE 2. Evaluations of the treatment description in the Web sites: The treatment description is classified into three categories: acceptable (description of the systematic review such as guidelines from authorized facilities[17–20]; links to systematic reviews; abstracts of systematic reviews), unacceptable (recommendation of alternative medicine or a generally unapproved treatment), and invaluable (lack of description).

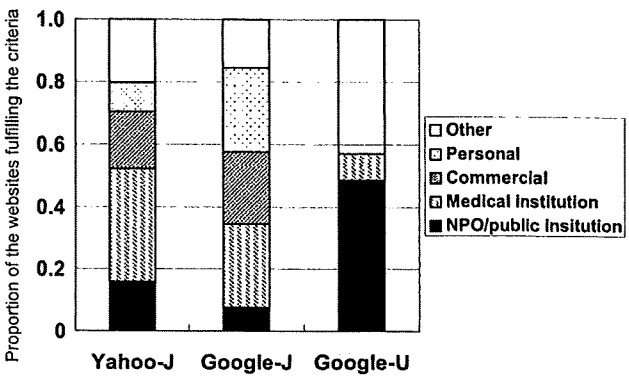

FIGURE 3. Administrators of the Web sites: Administrators were classified into five categories: NPO (nonprofit organization) or public institution, medical institution, commercial (for the specific treatments), personal (pages made by patients or their families), and others.

TABLE 1. Correlation of Sites Between the Top 50 Google and Yahoo, and the Rate of Reliable Sites in Each Engine

	United States	Japan
Correlation of titles in top 50 site of Google and Yahoo	11	10
Percentage of reliable sites in top 50 (%)		
Google	80.0	29.6
Yahoo	71.8[a]	45.5

Correlation of titles in both engines was almost the same in both countries. Proportions of reliable sites were comparable in countries but were not in search engines.

[a] Accessed and evaluated on January 21, 2009.

description was acceptable in 28 (80.0%) of the Web sites generated by Google-U, as these sites described chemotherapy as the standard treatment for advanced lung cancer. Only one site recommended alternative medicine. In Web sites ranked by Yahoo-J and Google-J, standard therapy was only described in 20 (45.5%, $p < 0.001$) and 10 (37.0%, $p < 0.001$) sites, respectively, whereas 7 (15.9%, $p = 0.070$) and 7 (25.9%, $p = 0.017$) sites, respectively, recommended alternative medicine. Table 1 summarizes the quality of the Web sites displayed in Yahoo and Google by both countries. Proportions of reliable sites were comparable in countries but were not in search engines.

Administrators of the Web sites

The administrators of the Web sites are shown in Figure 3. In Google-U, the administrators of 16 (45.7%) Web sites were NPO or public institution, whereas only 7 (15.9%, $p = 0.006$) and 2 (7.4%, $p = 0.001$), respectively, in Yahoo-J and Google-J were managed by them. Commercial site for specific treatments was not displayed in Google-U but was displayed in 8 (18.2%, $p = 0.007$) and 6 (22.2%, $p = 0.005$) Web sites in Yahoo-J and Google-J, respectively. Web sites administered personally by the patients themselves or their families were also not found among the Web site displayed in Google-U, whereas 4 (9.1%, $p = 0.125$) sites in Yahoo-J and 7 (25.9%, $p = 0.002$) sites in Google-J were personally managed.

Administrators and Quality of the Contents of the Web Sites

Table 2 shows the correlation between the Web site administrator and the quality of the contents of the sites. Ten sites generated by both Google-J and Yahoo-J were integrated. There was no site from NPO or public institution category, either Japanese or English, which provided misleading information. Most of the unacceptable sites were managed by commercial or personal sites, neither of which was found in the English-language sites.

DISCUSSION

By comparing the differences of quality of cancer information on the Internet between the different languages, we, for the first time, evaluated the correlation between the Web site administrator and the quality of the medical information in the Web sites. Furthermore, it is one of the few studies to evaluate the information on lung cancer available on the Internet.[15] We also showed that the Web sites displayed in the United States provide information of much higher quality than those displayed by Japanese Web sites, with regard to lung cancer treatment, and this may be related to the quality of the administrators of the displayed Web sites.

It is generally a difficult task to make people access reliable Web sites that would provide the precise information that they are looking for. Regulating access to only trustworthy Web sites that provide useful information is extremely difficult, because a global rule is a necessary step toward controlling the content of the worldwide Web sites. There are also no confirmed tools for weighting the information on the Internet in any field, including medicine. In this chaotic scenario, search engines such as Google and Yahoo have come up with a solution by developing an algorithm to rank the sites. Nowadays, their value is well established in the

TABLE 2. Correlation Between the Quality of the Web site Administrators and the Quality of the Information

	NPO Public Institution	Med Institution	Commercial	Personal	Other	Total
Japanese						
Acceptable	6	10	0	1	5	22
Unacceptable	0	0	10	7	2	19
Inevaluable	2	10	1	1	6	20
Total	8	20	11	9	13	61
English						
Acceptable	15	3	0	0	10	28
Unacceptable	0	0	0	0	1	1
Inevaluable	2	0	0	0	4	6
Total	17	3	0	0	15	35

Ten sites generated by both Google-J and Yahoo-J were integrated. No site from the NPO or public institution category provided misleading information in either the Japanese or the English search. Commercial administrators recommending specific treatments and personal sites accounted entirely for the sites providing unacceptable information.

Internet, and people are generally using this tool for searching medical and other information. Even though there is a concern that the order in which the sites are placed by these tools is not entirely appropriate for the field of medicine,[3,21,22] the high frequency at which these are used has made it meaningless to say that they pose a problem in one-particular field. Therefore, what we must consider now is how to provide reliable information using these tools.

Why is misleading and nonreliable information provided on the Internet? One key characteristic of the Internet is the interaction between the provider and the consumer (in the medical field, patient). Web sites that are not accessed frequently will be ranked lower in the search engine system. Therefore, when discussing the results of Web sites ranked by the search engine, we should consider it from both the standpoint of the provider and the consumer. People access the Internet by requesting the information they want. Many cancer patients suffer from an incurable disease and look for a ray of hope in the Internet. This situation is most advantageous to the information senders. They can promote their treatment as the treatment that would bring about the miraculous cure that the patients are seeking. In this study, most of the sources recommending alternative or unapproved drugs were from commercial and personal sites. Information on medical subjects should be correct and be of assistance to the users to help them better understand their disease. People should be protected from disruptive information. Creating confusion in the minds of people by providing misleading information for profit to the administrator is a vexing situation.

One of the interesting findings in this study was that the correlation between the quality of the Web site administrator and the quality of the contents of the site was seen not only for sites providing misleading information but also for those providing reliable information. At present, there are two major administrators providing reliable information, namely, medical institutions and specialized organizations for information administered by patient advocate NPO or public institution. However, the type of information provided differed between the two types of administrators. In general, each medical institution provides reliable messages but not review articles, whereas the patient advocate group NPO and public institution provide a path to the review articles. This is not surprising because the aims of providing information are different between the two types of administrators. For each medical institution, the goal is to display the treatment that they are interested in, and describing the entire medical consensus is outside their reach. Therefore, sites specialized in providing information are the ones that can be most expected to provide general information. Differences in the number of reliable sites between the languages in this study may be because of the difference in the number of such organizations between the countries. The number of public institution sites may depend on the countries in which each language is spoken in, and the growth in the number of patient advocate NPO may depend on the social system or the differences in culture. However, it is noteworthy that patient advocate NPO can play a major role in providing reliable health information.

There were several limitations in this study. One is that we evaluated sites only from Yahoo Japan and Google Japan, and Google United States. We chose Google United States as the reference, because most previous studies on the Internet have been conducted in the United States, and Google is the most popular search engine in the United States.[23] In Japan, Yahoo ranks first as the most frequently used search engine, followed next by Google,[24] which is the reason we selected these two as the representative search engines for our search of Web sites in Japanese. Although this approach may limit evaluation of the overall Internet situation in the two countries, we believe that this was the closest way to reproduce the way people browse the Internet. Another concern is the number of sites generated by these tools. The total number of Web sites displayed by our search using the keywords differs between the two languages and maybe attributable to the differences in the quality of the administrators. Google-U generated approximately seven times as many Web sites as Google-J. This discrepancy could be because of the difference in the number of people using the two languages. However, we only evaluated the top 50 sites, which is far short of the total number of sites displayed but may already

be too much for anyone seeking any type of information. Because the ranking system has prevailed, the quality of the highest ranked Web sites and not the total number of sites displayed is important to the user. Lastly, another important problem is whether people in the United States and Japan desire the same answers from the Internet. In general, search engines attempt to rank the Web sites sought by the users. If these differed between countries, the ranking would also reflect these differences. Differences in the social backgrounds of the populations in the two countries were confounding factors in this study. However, no studies evaluating the topic from this perspective have been conducted. These are topics of interest that need further investigation.

In this era of abundance of information, it is absolutely essential for people to make their choices based on the quality. As medical professionals, we have the responsibility of providing appropriate information to people who are unaware and anxious about their future. In the new era of the Internet technology, facilitating easy access to reliable information, and providing reliable information is important. This study may facilitate an understanding of the actual status of dispersal of information and pave the way for discussing methods to achieve better accessibility to high-quality health information.

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REVIEW ARTICLE

Ikuo Sekine · Chikako Shimizu · Kazuto Nishio
Nagahiro Saijo · Tomohide Tamura

A literature review of molecular markers predictive of clinical response to cytotoxic chemotherapy in patients with breast cancer

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Abstract
Background. We aimed to identify, through a review of the literature, candidate genes for a prospective predictive chemosensitivity test in patients with breast cancer.
Methods. Papers demonstrating an association between gene alterations in tumor tissue and clinical chemosensitivity in breast cancer patients were selected by Medline searches. We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) of response rates for patients who had tumors with or without gene alteration. Combined ORs and CIs were estimated using the DerSimonian-Laird method.
Results. A total of 18 genes were evaluated for association with clinical chemosensitivity in 6378 patients registered in 69 studies. The median (range) number of patients in each study was 73 (29–319). Overexpression of *ABCB1* (P-glycoprotein) was associated with poor responses to first-line chemotherapy (combined OR [CI], 0.16 [0.05–0.59]; n = 322). Overexpression and amplification of *TOP2A* (topoisomerase II-alfa) were more frequently observed in patients who responded to first-line chemotherapy (combined OR [CI], 2.73 [1.02–7.27]; n = 323). Overexpression of *ERBB2* (c-erbB2) was associated with favorable responses in patients treated with both first-line anthracycline-based chemotherapy and second-line taxane-based chemotherapy (combined ORs [CIs], 1.60 [1.19–2.17]; n = 1807 and 2.24 [1.06–4.74]; n = 259, respectively). *BCL2* overexpression was associated with resistance to first-line chemotherapy (combined OR [CI], 0.44 [0.21–0.91]; n = 816).
Conclusion. *ABCB1*, *TOP2A*, *ERBB2*, and *BCL2* were good candidates for future clinical trials of predictive chemosensitivity tests in patients with breast cancer.

Key words Chemotherapy · Sensitivity · Drug resistance · Breast cancer · Gene alterations

I. Sekine (✉) · T. Tamura
Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3542-3815
e-mail: isekine@ncc.go.jp

C. Shimizu
Division of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

K. Nishio
Department of Genome Biology, Kinki University School of Medicine, Osaka, Japan

N. Saijo
Division of Internal Medicine, National Cancer Center Hospital East, Kashiwa, Japan

Introduction

Breast cancer remains a major medical problem in women in spite of dramatic advances in the past three decades in the understanding of the biologic and clinical nature of the disease. About 1% to 5% of patients with breast cancer have distant metastasis at the time of initial diagnosis and 20% to 30% of patients develop systemic recurrence after surgery for local disease.[1] Chemotherapy for these patients, however, has limited efficacy, such that clinical objective response rates to standard chemotherapy regimens are 20%–40% at most, and such that patients with distant metastases rarely live long.[1] In addition, 40% to 80% of patients with breast cancer who undergo surgical resection receive adjuvant chemotherapy without its efficacy ever being monitored.

Tumor response to chemotherapy varies from one patient to another. Thus, it would be extremely useful to know ahead of time which patients have tumors that would respond to chemotherapeutic agents and also which tumors would be resistant to such therapy. For this purpose, cell culture-based chemosensitivity tests have been developed for more than 20 years, but they are not widely accepted because of technical problems, including the large amount of surgical material required, a low success rate for primary