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厚生労働科学研究費補助金

がん臨床研究事業

限局型小細胞肺癌に対する新たな標準的治療の確立に関する研究

平成21年度 総括研究報告書

研究代表者 田村 友秀

平成22(2010)年 3月

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総括研究報告書

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研究代表者 田村 友秀 国立がんセンター中央病院 総合病棟部長

研究要旨

限局型小細胞肺癌に対する次期第 III 相試験の試験治療を選択する目的で、「エトポシド+シスプラチン (EP) 療法 1 コースと加速多分割胸部放射線療法 (AH-TRT) の同時併用 (EP/AH-TRT) 後の、シスプラチン+ビンクリスチン+ドキソルビシン+エトポシド (CODE) 療法とアムルビシン+シスプラチン (AC) 療法のランダム化第 II 相試験」を計画した。本年度は「EP/AH-TRT 後の AC 療法の安全性確認試験」の症例登録を完了し、21 例の安全性を確認した。ランダム化第 II 相試験の実施計画書を作成し、まもなく試験を開始する見込みである。

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*1 平成 21 年 4 月 1 日～平成 21 年 12 月 31 日

*2 平成 22 年 1 月 4 日～平成 22 年 3 月 31 日

A. 研究目的

限局型小細胞肺癌を対象として、

(1) 「エトポシド+シスプラチン (EP) 療法 1 コースと加速多分割胸部放射線療法 (AH-TRT) の

同時併用 (EP/AH-TRT) 後のアムルビシン+シスプラチン (AC) 療法の安全性確認試験を行い、実施可能性を評価する。

(2) EP/AH-TRT 後の、シスプラチン+ビンクリスチン+ドキソルビシン+エトポシド (CODE) 療法と AC 療法のランダム化第 II 相試験」を実施し、次期第 III 相試験の試験治療群を選択する。

B. 研究方法

(1) EP/AH-TRT 後の AC 療法の安全性確認試験

ランダム化第 II 相試験の治療群のひとつとなる EP/AH-TRT 後の AC 療法の安全性を確認する。ランダム化第 II 相試験と同一の対象症例として、6 症例で忍容性を評価し、その後ランダム化第 II 相試験の開始までにさらに 6-15 例を追加して安全性を確認する。

(2) ランダム化第 II 相試験

全国 38 施設の多施設共同試験とし、主要評価項目は 1 年無増悪生存割合とする

対象は、限局型かつ初回治療の小細胞肺癌で、70 才以下、ECOG Performance Status (PS) 0-1、測定可能病変を有し、主要臓器機能が保持された症例とする。

治療内容は、EP/AH-TRT を実施後、CODE 療法 6 週間あるいは AC 療法 3 コースの治療を実施する。

EP 療法： エトポシド 100 mg/m² day 1,2,3

シスプラチン 80 mg/m² day 1

加速多分割胸部放射線療法(AH-TRT)：45Gy/30fr./3weeks

CODE 療法： シスプラチン 25mg/m² week 1-6

ビンクリスチン 1mg/m² week 2, 4, 6

ドキソルビシン 40mg/m² week 1, 3, 5

エトポシド 80mg/m² x3d week 1, 3, 5

AC 療法： アムルビシン 40mg/m² day 1-3

シスプラチン 60mg/m² day 1

3 週毎に 3 コース

予定症例数は、80例、集積期間は1.5年とする。
(倫理面の配慮)

ヘルシンキ宣言や米国ベルモントレポート等の国際的倫理原則、臨床研究に関する倫理指針(平成20年厚生労働省)に従い以下を遵守する。(1)各施設IRB承認を必須とする。(2)説明文書を用いた十分な説明を行い考慮の時間を設けた後、自由意思による同意を本人より文書で得る。(3)直接個人が識別できる情報を用いず、データベースのセキュリティを確保し、個人情報(プライバシー)保護を厳守する。(4)臨床試験審査委員会、効果・安全性評価委員会を組織し、研究の第三者的監視を行う。

C. 研究結果

(1)「EP/AH-TRT後のAC療法の忍容性確認試験」の登録を完了、安全性を確認した。

ランダム化第II相試験の実施の準備段階として、EP/AH-TRT後のAC療法の忍容性を確認するためにまず「限局型小細胞肺癌に対する、EP/AH-TRTに引き続く、AC療法の安全性確認試験」を実施し、本年6月に予定症例21例の登録を完了した。

試験結果では、21例全例がEP/AH-TRTを完了し、18例(86%)がその後のAC療法3コースを完遂できた。7例でAMRの減量を必要とした。主な毒性は血液毒性であり、Grade4の好中球減少は17例(81%)に認められた。発熱性好中球減少を9例に認めたが、そのうち5例でその持続期間は1日のみであった。G-CSFは16例(76%)に投与されていた。治療関連死はなかった。以上の結果から、治癒を期待しうる治療であることも考慮し、十分耐容可能であると結論した。なお、今後の治療実施にあたってはG-CSF使用法を工夫する余地もあると考えられた。抗腫瘍効果は、CR+good PR 18例(81%)、PR 1例、NE 1例、奏効率95%であった。

(2)ランダム化第II相試験の実施計画書を作成中で、今年度中に完成見込みである。

ランダム化第II相試験の実施計画書は、上記の安全性確認試験で6例の安全性確認後の平成20年9月にJCOG運営委員会にプロトコールコンセプトを提出、同12月に承認を得て、実施計画書の作成を開始した。本年4月に実施計画書第1版を、同7月に修正版を作成して提出した。まもなくJCOGプロトコール審査委員会の審査、承認を得る見込みである。

D. 考察

我々は、限局型小細胞肺癌に対する標準的治療として、EP/AH-TRT療法後EP3コースの治療法を確立した。次いで小細胞肺癌に対して最強の化学療法とされるIP療法を取り入れたEP/AH-TRT療法後のIP3コースの治療を考案し、有用性を検

証する第III相試験(JCOG0202)を実施してきた。限局型小細胞肺癌に対する現在の標準治療成績は、生存期間中央値24か月、5年生存率20%程度であり、さらに強力な化学放射線療法の確立が必要である。今回、評価するCODE療法あるいはAC療法を追加した化学放射線療法は現時点で最も期待される治療法といえる。

我々は、新たな治療法の確立によって、5年生存率が現状より10%程度向上することを期待している。我が国の全肺癌死亡数は年間5万人にのぼる。小細胞肺癌は全肺癌の約15%を占め、その半数は限局型である。限局型小細胞肺癌の治癒率の向上は国民福祉への多大なる貢献であると同時に、再発後の化学療法、姑息的放射線療法、支持療法とこのための入院などの医療費を削減する経済的効果も大きいと思われる。さらにこの成果は、世界のトップにある我が国の肺癌治療のレベルの高さを改めて世界に示すこととなり、医療の発展のための国際協調の中で極めて大きな貢献となると考える。

E. 結論

EP/AH-TRT後のAC療法の安全性確認試験において安全性を評価した。ランダム化第II相試験の実施計画書を作成し、まもなく試験を開始する見込みである。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

- 1) Sekine, I., Sumi, M., Ito, Y., Tanai, C., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y., Tamura, T. Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy. Jpn J Clin Oncol., 39(11): 707-712, 2009.
- 2) Goto, Y., Sekine, I., Sekiguchi, H., Yamada, K., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y., Tamura, T. Differences in the quality of information on the internet about lung cancer between the United States and Japan. J Thorac Oncol., 4: 829-833, 2009.
- 3) Sanuki-Fujimoto, N., Ishikura, S., Hayakawa, K., Kubota, K., Nishiwaki, Y., Tamura, T. Radiotherapy quality assurance review in a multi-center randomized trial of limited-disease small cell lung cancer: the Japan

- Clinical Oncology Group (JCOG) trial 0202. *Radiat Oncol.*, 4:16, 2009.
- 4) Sanuki-Fujimoto, N., Sumi, M., Ito, Y., Imai, A., Kagami, Y., Sekine, I., Kunitoh, H., Ohe, Y., Tamura, T., Ikeda, H. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiother Oncol.*, 91(3):433-437, 2009.
- 5) Kano, Y., Mori, K. Schedule-dependent synergism and antagonism between pemetrexed and docetaxel in human lung cancer cell lines in vitro. *Cancer Chemo Pharm.*, 64: 1129-1137, 2009.
- 6) Fujii, T., Kunikane, H., Okamoto, H., Watanabe, K., Kunitoh, H., Mori, K., Yokoyama, A., Fukuda, H., Tamura, T., Saijo, N. A Phase II Study of Cisplatin and Irinotecan as Induction Chemotherapy Followed by Accelerated Hyperfractionated Thoracic Radiotherapy with Daily Low-dose Carboplatin in Unresectable Stage III Non-small Cell Lung Cancer: JCOG 9510. *Jpn J Clin Oncol.*, 39: 784-790, 2009.
- 7) Tomita, N., Kodaira, T., Hida, T., Tachibana, H., Nakamura, T., Nakahara, R., Inokuchi, H. The Impact of Radiation Dose and Fractionation on Outcomes for Limited-Stage Small-Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.*, in press, 2009.
- 8) Kunitoh, H., Tamura, T., Shibata, T., Nakagawa, K., Takeda, K., Nishiwaki, Y., Osaki, Y., Noda, K., Yokoyama, A., Saijo, N.; JCOG Lung Cancer Study Group, Tokyo, Japan. A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9605). *Br J Cancer*, 101(9): 1549-1554, 2009.
- 9) Okamoto, K., Okamoto, I., Takezawa, K., Tachibana, I., Fukuoka, M., Nishimura, Y., Nakagawa, K. Cisplatin and Etoposide Chemotherapy Combined with Early Concurrent Twice-daily Thoracic Radiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients. *Jpn J Clin Oncol.*, 40(1): 54-59, 2009.
- 10) Oze, I., Hotta, K., Kiura, K., Ochi, N., Takigawa, N., Fujiwara, Y., Tabata, M., Tanimoto, M. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. *PLoS One*, 4(11): e7835, 2009.
- 11) Hotta, K., Kiura, K., Fujiwara, Y., Takigawa, N., Oze, I., Ochi, N., Tabata, M., Tanimoto, M. Association between incremental gains in the objective response rate and survival improvement in phase III trials of first-line chemotherapy for extensive disease small-cell lung cancer. *Ann Oncol.*, 20(5): 829-834, 2009.

H. 知的財産権の出願・登録状況

(予定も含む)

1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

研究成果の刊行に関する一覧表

雑誌

	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
1	Sekine, I., Sumi, M., Ito, Y., Tanai, C., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y., <u>Tamura, T.</u>	Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy.	Jpn J Clin Oncol.	39(11)	707-712	2009
2	Goto, Y., Sekine, I., Sekiguchi, H., Yamada, K., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y., <u>Tamura, T.</u>	Differences in the quality of information on the internet about lung cancer between the United States and Japan.	J Thorac Oncol.	4	829-833	2009
3	Sanuki-Fujimoto, N., Ishikura, S, Hayakawa, K., Kubota, K., <u>Nishiwaki, Y.</u> , <u>Tamura, T.</u>	Radiotherapy quality assurance review in a multi-center randomized trial of limited-disease small cell lung cancer: the Japan Clinical Oncology Group (JCOG) trial 0202.	Radiat Oncol.	4	16	2009
4	Sanuki-Fujimoto, N., Sumi, M., Ito, Y., Imai, A., Kagami, Y., Sekine, I., Kunitoh, H., Ohe, Y., <u>Tamura, T.</u> , Ikeda, H.	Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses.	Radiother Oncol.	91(3)	433-437	2009
5	Kano, Y., <u>Mori, K.</u>	Schedule-dependent synergism and antagonism between pemetrexed and docetaxel in human lung cancer cell lines in vitro.	Cancer Chemo Pharm.	64	1129-1137	2009
6	Fujii, T., Kunikane, H., <u>Okamoto, H.</u> , Watanabe, K., Kunitoh, H., <u>Mori, K.</u> , <u>Yokoyama, A.</u> , Fukuda, H., <u>Tamura, T.</u> , <u>Saijo, N.</u>	A Phase II Study of Cisplatin and Irinotecan as Induction Chemotherapy Followed by Accelerated Hyperfractionated Thoracic Radiotherapy with Daily Low-dose Carboplatin in Unresectable Stage III Non-small Cell Lung Cancer: JCOG 9510.	Jpn J Clin Oncol.	39	784-790	2009

研究成果の刊行に関する一覧表

雑誌

7	Tomita, N., Kodaira, T., <u>Hida, T.</u> , Tachibana, H., Nakamura, T., Nakahara, R., Inokuchi, H.	The Impact of Radiation Dose and Fractionation on Outcomes for Limited-Stage Small-Cell Lung Cancer.	Int J Radiat Oncol Biol Phys.		in press	2009
8	Kunitoh, H., <u>Tamura, T.</u> , Shibata, T., <u>Nakagawa, K.</u> , Takeda, K., <u>Nishiwaki, Y.</u> , Osaki, Y., <u>Noda, K.</u> , <u>Yokoyama, A.</u> , <u>Saijo, N.</u> ; JCOG Lung Cancer Study Group, Tokyo, Japan.	A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9605).	Br J Cancer	101(9)	1549-1554	2009
9	Okamoto, K., Okamoto, I., Takezawa, K., Tachibana, I., Fukuoka, M., Nishimura, Y., <u>Nakagawa, K.</u>	Cisplatin and Etoposide Chemotherapy Combined with Early Concurrent Twice-daily Thoracic Radiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients.	Jpn J Clin Oncol.	40(1)	54-59	2009
10	Oze, I., Hotta, K., <u>Kiura, K.</u> , Ochi, N., Takigawa, N., Fujiwara, Y., Tabata, M., Tanimoto, M.	Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results.	PLoS One	4(11)	e7835	2009
11	Hotta, K., <u>Kiura, K.</u> , Fujiwara, Y., Takigawa, N., Oze, I., Ochi, N., Tabata, M., Tanimoto, M.	Association between incremental gains in the objective response rate and survival improvement in phase III trials of first-line chemotherapy for extensive disease small-cell lung cancer.	Ann Oncol.	20(5)	829-834	2009

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限局型小細胞肺癌に対する新たな標準的治療の確立に関する研究

研究成果の刊行物・別刷

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

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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

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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

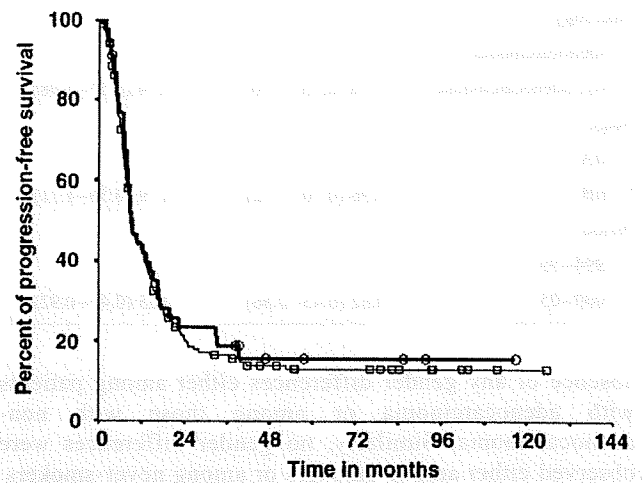


Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

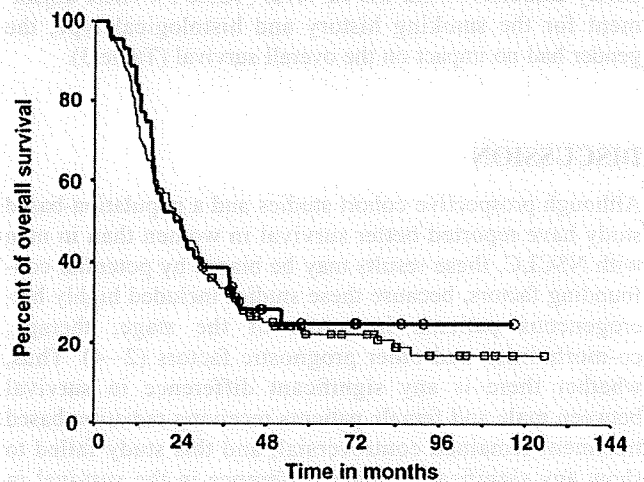


Figure 2. Overall survival by sex. Thick line, females; thin line, males.

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.

References

- Patel JD. Lung cancer in women. *J Clin Oncol* 2005;23:3212–8.
- Visbal AL, Williams BA, Nichols FC, 3rd, Marks RS, Jett JR, Aubry MC, et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. *Ann Thorac Surg* 2004;78:209–15; discussion 215.
- Blanchon F, Grivaux M, Asselain B, Lebas FX, Orlando JP, Piquet J, et al. 4-year mortality in patients with non-small-cell lung cancer: development and validation of a prognostic index. *Lancet Oncol* 2006;7:829–36.
- Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. *Ann Oncol* 2002;13:1087–93.
- Jeremic B, Shibamoto Y. Pre-treatment prognostic factors in patients with stage III non-small cell lung cancer treated with hyperfractionated radiation therapy with or without concurrent chemotherapy. *Lung Cancer* 1995;13:21–30.
- Werner-Wasik M, Scott C, Cox JD, Sause WT, Byhardt RW, Asbell S, et al. Recursive partitioning analysis of 1999 Radiation Therapy Oncology Group (RTOG) patients with locally-advanced non-small-cell lung cancer (LA-NSCLC): identification of five groups with different survival. *Int J Radiat Oncol Biol Phys* 2000;48:1475–82.
- Bradley JD, Ieumwananonthachai N, Purdy JA, Wasserman TH, Lockett MA, Graham MV, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2002;52:49–57.
- Chen M, Jiang GL, Fu XL, Wang LJ, Qian H, Zhao S, et al. Prognostic factors for local control in non-small-cell lung cancer treated with definitive radiation therapy. *Am J Clin Oncol* 2002;25:76–80.
- Bollmann A, Blankenburg T, Haerting J, Kuss O, Schutte W, Dunst J, et al. Survival of patients in clinical stages I-IIIb of non-small-cell lung cancer treated with radiation therapy alone. Results of a population-based study in Southern Saxony-Anhalt. *Strahlenther Onkol* 2004;180:488–96.
- Ademuyiwa FO, Johnson CS, White AS, Breen TE, Harvey J, Neubauer M, et al. Prognostic factors in stage III non-small-cell lung cancer. *Clin Lung Cancer* 2007;8:478–82.
- Travis W, Colby T, Corrin B, Shimamoto Y. *Histological Typing of Lung and Pleural Tumors (World Health Organization International Histological Classification of Tumors)*, 3rd edn. Berlin: Springer 1999.
- Therasse P, Arbuuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
- Armitage P, Berry G, Matthews J. Survival analysis. In: Armitage P, Berry G, Matthews J, editors. *Statistical Methods in Medical Research*, 4th edn. Oxford: Blackwell Science Ltd 2002;568–90.
- de Perrot M, Licker M, Bouchardy C, Usel M, Robert J, Spiliopoulos A. Sex differences in presentation, management, and prognosis of patients with non-small cell lung carcinoma. *J Thorac Cardiovasc Surg* 2000;119:21–6.
- Alexiou C, Onyeaka CV, Beggs D, Akar R, Beggs L, Salama FD, et al. Do women live longer following lung resection for carcinoma? *Eur J Cardiothorac Surg* 2002;21:319–25.
- Cerfolio RJ, Bryant AS, Scott E, Sharma M, Robert F, Spencer SA, et al. Women with pathologic stage I, II, and III non-small cell lung cancer have better survival than men. *Chest* 2006;130:1796–802.
- Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 2008;3:457–66.
- Hanagiri T, Sugio K, Uramoto H, So T, Ichiki Y, Sugaya M, et al. Gender difference as a prognostic factor in patients undergoing resection of non-small cell lung cancer. *Surg Today* 2007;37:546–51.
- Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. *J Clin Oncol* 1986;4:702–9.

20. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. *J Clin Oncol* 1991;9:1618-26.

21. Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J, et al. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. *J Clin Oncol* 1995;13:1221-30.

22. Wakelee HA, Wang W, Schiller JH, Langer CJ, Sandler AB, Belani CP, et al. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. *J Thorac Oncol* 2006;1:441-6.

23. Hoang T, Xu R, Schiller JH, Bonomi P, Johnson DH. Clinical model to predict survival in chemo-naive patients with advanced non-small-cell

lung cancer treated with third-generation chemotherapy regimens based on eastern cooperative oncology group data. *J Clin Oncol* 2005;23:175-83.

24. Mandrekar SJ, Schild SE, Hillman SL, Allen KL, Marks RS, Mailliard JA, et al. A prognostic model for advanced stage nonsmall cell lung cancer. Pooled analysis of North Central Cancer Treatment Group trials. *Cancer* 2006;107:781-92.

25. Yamamoto H, Sekine I, Yamada K, Nokihara H, Yamamoto N, Kunitoh H, et al. Gender differences in treatment outcomes among patients with non-small cell lung cancer given a combination of carboplatin and paclitaxel. *Oncology* 2008;75:169-74.

26. Sekine I, Sumi M, Ito Y, Nokihara H, Yamamoto N, Kunitoh H, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. *Radiother Oncol* 2006;80:93-7.

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

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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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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 United 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” benchmark¹⁶: 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.

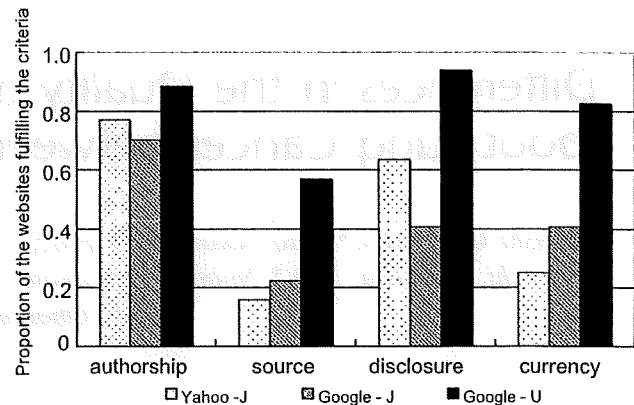


FIGURE 1. JAMA benchmark: Description of the JAMA benchmark¹⁶ is listed by the search engines; display of authorship (authors and contributors, their affiliations, and relevant credentials); attribution (references and sources for all content, and all relevant copyright information); disclosure (Web 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

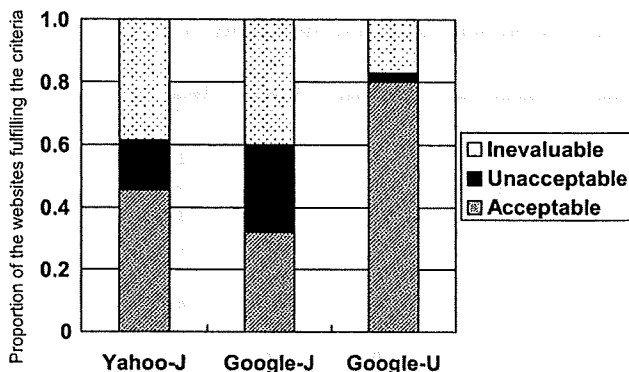


FIGURE 2. Evaluations of the treatment description in the Web sites: The treatment description is classified into three categories: acceptable (description of the systematic review such as guidelines from authorized facilities¹⁷⁻²⁰; links to systematic reviews; abstracts of systematic reviews), unacceptable (recommendation of alternative medicine or a generally unapproved treatment), and invaluable (lack of description).

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

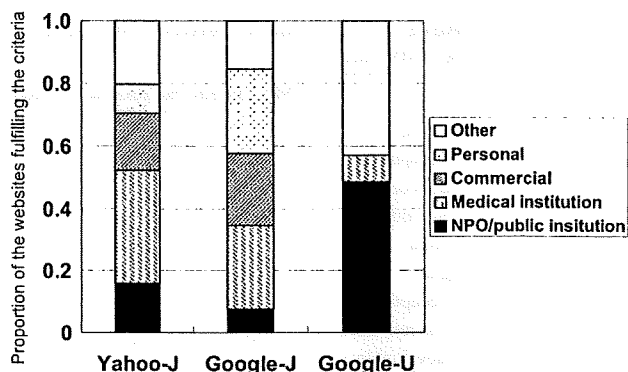


FIGURE 3. Administrators of the Web sites: Administrators were classified into five categories: NPO (nonprofit organization) or public institution, medical institution, commercial (for the specific treatments), personal (pages made by patients or their families), and others.

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.

REFERENCES

- Wilson P. How to find the good and avoid the bad or ugly: a short guide to tools for rating quality of health information on the internet. *BMJ* 2002;324:598–602.
- Bichakjian CK, Schwartz JL, Wang TS, Hall JM, Johnson TM, Biermann JS. Melanoma information on the internet: often incomplete—a public health opportunity? *J Clin Oncol* 2002;20:134–141.
- Meric F, Bernstam EV, Mirza NQ, et al. Breast cancer on the world wide web: cross sectional survey of quality of information and popularity of websites. *BMJ* 2002;324:577–581.
- Helft PR, Hlubocky F, Daugherty CK. American oncologists' views of internet use by cancer patients: a mail survey of American Society of Clinical Oncology members. *J Clin Oncol* 2003;21:942–947.
- Trumbo CW. Cancer information on the world wide Web: gross characteristics. *J Natl Cancer Inst* 2004;96:332–333.
- Helft PR, Eckles RE, Johnson-Calley CS, Daugherty CK. Use of the internet to obtain cancer information among cancer patients at an urban county hospital. *J Clin Oncol* 2005;23:4954–4962.
- Miniwatts Marketing Group. Internet Usage and Population in North America, November 30, 2007. Available at: <http://www.internetworldstats.com/stats14.htm>, Accessed on August 1, 2008. (Accessed at: <http://www.internetworldstats.com/stats14.htm>).
- Miniwatts Marketing Group. Asia Marketing Research, Internet Usage, Population Statistics and Information. July 5, 2008. Available at: <http://www.internetworldstats.com/asia.htm#jp>, Accessed on August 1, 2008.
- Most internet users start at a search engine when looking for health information online. Very few check the source and date of the information they find. October 29, 2006. Available at: http://www.pewinternet.org/pdfs/PIP_Online_Health_2006.pdf. Accessed on August 1, 2008. (Accessed at: http://www.pewinternet.org/pdfs/PIP_Online_Health_2006.pdf).
- Nemoto K, Tachikawa H, Sodeyama N, et al. Quality of Internet information referring to mental health and mental disorders in Japan. *Psychiatry Clin Neurosci* 2007;61:243–248.
- Tatsumi H, Mitani H, Haruki Y, Ogushi Y. Internet medical usage in Japan: current situation and issues. *J Med Inter Res* 2001;3:E12.
- Berland GK, Elliott MN, Morales LS, et al. Health information on the Internet: accessibility, quality, and readability in English and Spanish. *JAMA* 2001;285:2612–2621.
- Minino AM, Heron MP, Murphy SL, Kochanek KD. Deaths: final data for 2004. *Natl Vital Stat Rep* 2007;55:1–119.
- Kato H, Sobue T, Katanoda K. Cancer Statistics in Japan. November 11, 2006. Available at: <http://ganjoho.ncc.go.jp/public/statistics/backnumber/odjrh3000000o8is-att/preface.pdf>. Accessed August 1, 2008.
- Linszen C, Schook RM, The AM, Lammers E, Festen J, Postmus PE. A web site on lung cancer: who are the users and what are they looking for? *J Thorac Oncol* 2007;2:813–818.
- Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet: Caveat lector et viewer—Let the reader and viewer beware. *JAMA* 1997;277:1244–1245.
- Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
- Socinski MA, Morris DE, Masters GA, Lilenbaum R. Chemotherapeutic management of stage IV non-small cell lung cancer. *Chest* 2003;123:226S–243S.
- The Lung Cancer Disease Site Group. Lung Cancer Evidence-based Series (EBS) and Practice Guidelines (PG). May 7, 2008. Available at: <http://www.cancercares.on.ca/pdf/pebc7-2f.pdf>, Accessed on August 1, 2008.
- National Institute for Clinical Excellence. The Diagnosis and Treatment of Lung Cancer. February, 2005. Available at: <http://www.nice.org.uk/nicemedia/pdf/cg024fullguideline.pdf>. Accessed on August 1, 2008.
- Griffiths KM, Christensen H. Quality of web based information on treatment of depression: cross sectional survey. *BMJ* 2000;321:1511–1515.
- Borges AAH, Cervi PM, Arcaya MLTAd, Guardado G, Rabaza AR, Sosa AJ. Rate of compliance with the HON code of conduct versus number of inbound links as quality markers of pediatric web sites. In MEDNET2001;2001, Udine, Italy: Technology and Healthcare, IOS Press Amsterdam, 2001.
- comScore. Core Search Report September, 2007. Available at: <http://www.comscore.com/press/release.asp?press=1805>. Accessed on August 1, 2008.
- comScore. Top Japanese Web Rankings for September, 2007. Available at: <http://www.comscore.com/press/release.asp?press=1838>, Accessed on August 1, 2008.