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 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.

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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.

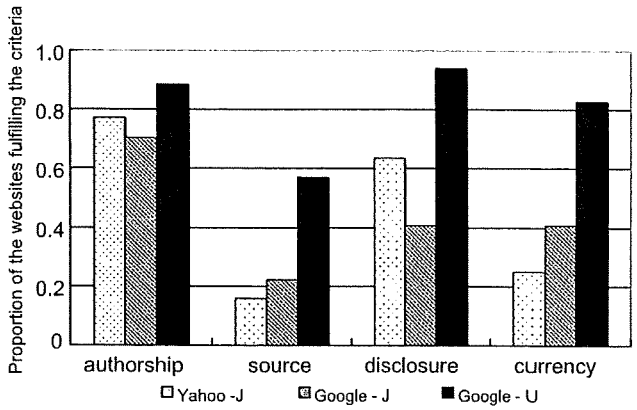

FIGURE 1. JAMA benchmark: Description of the JAMA benchmark[16] is listed by the search engines; display of authorship (authors and contributors, their affiliations, and relevant credentials); attribution (references and sources for all content, and all relevant copyright information); disclosure (Web 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

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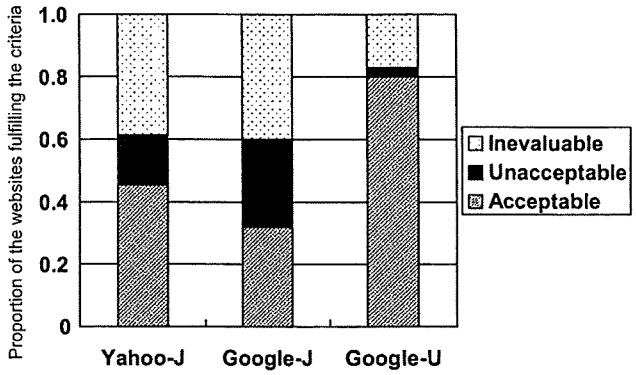

FIGURE 2. Evaluations of the treatment description in the Web sites: The treatment description is classified into three categories: acceptable (description of the systematic review such as guidelines from authorized facilities[17–20]; links to systematic reviews; abstracts of systematic reviews), unacceptable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

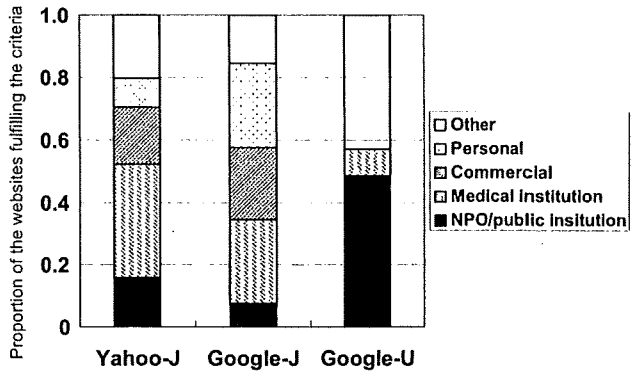

FIGURE 3. Administrators of the Web sites: Administrators were classified into five categories: NPO (nonprofit organization) or public institution, medical institution, commercial (for the specific treatments), personal (pages made by patients or their families), and others.

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

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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

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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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Lung cancer RT

Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses

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ABSTRACT

Introduction: The role of elective nodal irradiation of non-small-cell lung cancer (NSCLC) patients treated with radiotherapy remains unclear. We investigated the significance of treating clinically uninvolved lymph nodes by retrospectively analyzing the relationship between loco-regional failure and the irradiated volume.

Methods: Between 1998 and 2003, patients with IA–IIIB NSCLC were treated with radiotherapy. The eligibility criteria for this study were an irradiation dose of 60 Gy or more and a clinical response better than stable disease. Typical radiotherapy consisted of 40 Gy/20 fr to the tumor volumes (clinical target volume of the primary tumor [CTVp], of the metastatic lymph nodes [CTVn], and of the subclinical nodal region [CTVs]), followed by off-cord boost to CTVp+n to a total dose 60–68 Gy/30–34 fr. The relationship between the sites of recurrence and irradiated volumes was analyzed.

Results: A total of 127 patients fulfilled the eligibility criteria. Their median overall and progression-free survival times were 23.5 (range, 4.2–109.7) and 9.0 months (2.2–109.7), respectively. At a median follow-up time of 50.5 months (range, 14.2–83.0) for the surviving patients, the first treatment failure was observed in 95 patients (loco-regional; 41, distant; 42, both; 12). Among the patients with loco-regional failure, in-field recurrence occurred in 38 patients, and four CTVs recurrences associated with CTVp+n failure were observed. No isolated recurrence in CTVs was observed.

Conclusions: In-field loco-regional failure, as well as distant metastasis, was a major type of failure, and there was no isolated elective nodal failure. Radiation volume adequacy did not seem to affect elective nodal failure.

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Radiation therapy is an integral component of the multi-modal treatment of non-small-cell lung cancer (NSCLC). Recent phase III studies have demonstrated that concomitant chemoradiotherapy improves survival, and this has resulted in the general acceptance of concurrent chemoradiotherapy as one of the standard treatments for locally advanced NSCLC [1]. Despite the improved survival, however, most patients die from their disease as a result of local or distant failure.

Local failure remains a major challenge when treating NSCLC with radiotherapy. A number of studies of dose escalation to the gross tumor volume (GTV) have been conducted as a means of improving local control [2–5]. The conventional radiation fields for NSCLC typically encompass the entire mediastinum and ipsilateral hilum (elective nodal region) to deliver a dose of 40 Gy, even without evidence of disease in these areas, followed by a 20 Gy boost to the GTV. However, the conventional treatment has added considerable morbidity and can limit the dose escalation. In phase I–II dose escalation studies, there is a trend toward omitting the practice of elective nodal irradiation (ENI) after their experiences with toxicity, which is not based on direct evidence [2–5]. According to those studies, omitting ENI has not sacrificed treatment outcomes so far. They also analyzed patterns of recurrence in relation to irradiated volume in a dose escalation setting [6].

By contrast, the current literature provides limited information regarding patterns of failure when conventional fields and doses are used [7,8]. Since it is important to know whether loco-regional failure is within or outside the irradiation field, we retrospectively analyzed patterns of failure after radiation therapy for NSCLC, especially in regard to the relationship between local failure and irradiated volume.

Methods and materials

Patients

Between January 1998 and March 2003, 263 patients with newly diagnosed NSCLC were treated with thoracic radiation therapy,

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with or without chemotherapy, at the National Cancer Center Hospital. All tumors were cytologically or histologically confirmed NSCLC. Patients' disease was staged by the tumor-node-metastasis (TNM) staging system (UICC, version 6, 2002). The diagnostic workup included a bone scan, brain scan by computed tomography (CT) or magnetic resonance imaging, CT scan of the chest, and CT or ultrasound imaging of the abdomen. The criteria for inclusion in this study were irradiation with a dose of 60 Gy or more as a part of the initial treatment and a clinical response better than stable disease. After excluding patients with metastatic disease, whose primary tumor was located in the apex of the lung (superior sulcus), and whose post-treatment evaluation was inadequate, the remaining 127 patients served as the subjects of the analysis.

Details of treatment

Radiotherapy

Gross tumor volume (GTV) was defined as the demonstrable extent of the primary tumor and the metastatic lymph nodes, GTVp and GTVn, respectively. GTVn was defined as abnormally enlarged regional lymph nodes measuring over 1.0 cm along their short axis. Clinical target volume (CTV) consisted of the adjacent mediastinum and ipsilateral hilum (CTV of the subclinical nodal region, CTVs) as well as CTVp and CTVn which were assumed to be equal to GTVp and GTVn, respectively. A planning target volume (PTV) margin of 1–1.5 cm was drawn around each CTV.

External-beam radiotherapy with a 6, 10, or 15 MV photon beam was delivered using a linear accelerator. A majority of the patients were treated with anteroposterior opposing fields encompassing CTV to a dose of 40 Gy/20 fractions (2 Gy per fraction, 5 days per week), followed by an off-cord boost to the GTV by oblique opposing fields, to a total dose of 60–68 Gy/30–34 fractions. No attempt was made to encompass the supraclavicular areas in most patients; the supraclavicular areas were treated only electively. Initially, treatment planning was performed by using an X-ray simulator for the anteroposterior fields and a CT-port for the oblique opposing fields, but after the end of 1999, most treatment planning, especially to define the off-cord boost, was performed using a CT-based planning system (FOCUS, Computed Medical Systems).

The dose to the spinal cord was limited to 45–50 Gy. The size of the treatment fields was adjusted so that it did not exceed half of the hemithorax before introducing CT-based planning system, or so that the volume of normal lung tissue receiving a dose over 20 Gy would be less than 40%.

Chemotherapy

Systemic chemotherapy was used in 87 patients (68.5%), and the majority of the patients received platinum-based chemotherapy sequentially or concurrently with the radiation therapy. One of the representative regimens was 2–3 cycles of cisplatin 80 mg/sqm on day 1 and vinorelbine 25 mg/sqm on days 1 and 8 (or vindesine 3 mg/sqm on days 1, 8, and 15) in 21–28 days. The second most common regimen was cisplatin 80 mg/sqm on day 1, vindesine 3 mg/sqm on days 1 and 8, and mitomycin C 8 mg/sqm on day 1, in 21–28 days. The other regimens are summarized in Table 1.

Evaluation

Patients were followed at 4- to 6-week intervals for 6 months after treatment and at 3- to 6-month intervals thereafter. Chest X-ray and laboratory workups were performed at each post-treatment visit. Unless there were changes in the chest X-ray or in symptoms, a CT scan was performed about 2–3 months after the treatment for the assessment of the treatment response, and every 6–12 months thereafter. Follow-up information was obtained from the medical charts and death certificates.

Table 1
Baseline patient characteristics.

Characteristics	Patients	(%)
Median age (yr)	65 (36–83)	
Gender		
Male	106	83
Female	21	17
Performance status (WHO)		
0	12	9
1	109	86
2	6	5
Stage		
I (A/B)	5(1/4)	4
II (A/B)	12(3/9)	9
III (A/B)	110(59/51)	87
Histology		
Adenocarcinoma	64	50
Squamous cell carcinoma	39	31
Large cell carcinoma	4	3
NSCLC (not otherwise specified)	20	16
Chemotherapy (concurrent/sequential)	87(63/24)	69
Chemotherapy regimens		
Cisplatin + vindesine or vinorelbine	48	55
Carboplatin + paclitaxel	12	14
MVP (cisplatin + vindesine + mitomycin)	12	14
Nedaplatin or nedaplatin + paclitaxel	11	13
Others	4	5

When evaluating overall survival, an event was defined as death from any cause. When evaluating progression-free survival, an event was defined as documented tumor progression (loco-regional or distant) or death from any cause. Local or loco-regional failure was judged to have occurred if there was radiographic evidence of progressive disease. Absence of progression of residual disease for more than 6 months following treatment was considered evidence of loco-regional control. A recurrence in supraclavicular nodes was considered regional failure, not an elective nodal failure, because the supraclavicular regions are not routinely included within the radiation fields in our practice. Treatment failure was not always confirmed histologically. Elective nodal failure (ENF) was defined as recurrence in CTVs without evidence of local failure, as the first event or even after distant metastasis.

The adequacy of field borders was assessed in terms of CTVs coverage and PTV margin in patients with loco-regional failure. The failure patterns were analyzed to distinguish in-field recurrence from out-of-field recurrence; "in-field" included CTVs as well as CTVp and CTVn.

The Kaplan–Meier method was used from the start of the treatment to calculate the overall survival and progression-free survival of all the 127 patients.

Results

A total of 127 patients, median age 65 years (range, 36–83), met the criteria for evaluation in this study. The majority of patients had stage IIIA ($n = 59$) or IIIB ($n = 51$) disease. Other baseline characteristics of the patients and details of their treatment are summarized in Table 1.

At a median follow-up time of 50.5 months (range, 14.2–83.0) of the surviving patients, 95 had experienced treatment failure. Median survival time was 23.5 months (range, 4.2–109.7), and median time to progression was 9.0 months (range, 2.2–109.7). The 2-year cumulative survival rate and 2-year progression-free survival rate were 51.4% and 27.6%, respectively. The survival

curves are shown in Fig. 1. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Eighty-seven (69%) patients received chemotherapy concomitantly or sequentially with the radiotherapy. The overall survival time of the patients who received chemotherapy was 21.7 months (range, 7.6–33.9), as opposed to 19.1 months (range, 6.8–32.7) among those who did not receive chemotherapy, and the difference was not statistically significant ($p = 0.10$). There were no statistically significant differences in disease-free survival nor loco-regional control according to whether the patients had received chemotherapy. Concurrent use of chemoradiotherapy did not affect survival among the 87 patients who received chemotherapy (data not shown).

There were 53 patients with a first loco-regional failure, alone ($n = 41$) or with distant metastasis ($n = 12$), and the majority of the failures were in-field ($n = 38$, 72%). Nine (21%) patients had out-of-field recurrences in the form of supraclavicular node metastasis ($n = 5$) or pleural metastasis ($n = 4$), with or without local recurrence. There were no isolated ENFs (Table 2).

Four patients (7%) experienced nodal failure in CTVs simultaneously with local or distant failure. Three of them had received a prophylactic dose of 40 Gy to the CTVs, and the other had inadequate margin of the CTVs field. Other characteristics of these patients are shown in Table 3. There were no "marginal only" failures among in-field failures; all the failures at the field borders were associated with out-of-field failures.

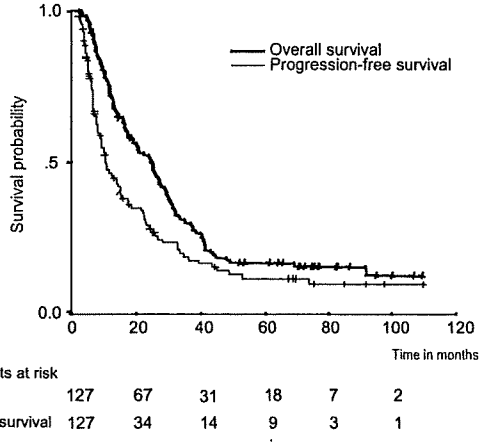

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

Types of event	Patients	%
Loco-regional alone	41	43%
In-field		
CTVpn	30	
CTVpn + CTVs[a]	2	
In-field + out-of-field		
CTVpn + pleural effusion	2	
CTVpn + supraclavicular nodes	2	
Out-of-field		
Supraclavicular nodes	3	
Pleural effusion[b]	2	
Loco-regional + distant	12	13%
In-field + out-of-field		
CTVpn + CTVs	2	
Distant alone	42	44%
All events	95	

[a] One also had concurrent failure in the contralateral hilum.
[b] One also had concurrent supraclavicular recurrence.

Conventional X-ray simulation was performed in 8 (6%) patients, while 70 (55%) had CT-based simulation and remaining 49 (39%) had both (initially with X-ray simulation, followed by CT-based simulation for off-cord boost). A majority ($n = 122$, 96%) of the patients were treated with anteroposterior opposing fields as elective nodal irradiation, followed by oblique opposing fields to the total dose.

ENI was incomplete ($n = 12$) or not performed ($n = 6$) in 18 of the 53 patients with loco-regional failure because of diminished pulmonary function or deteriorated performance status. All the incomplete ENIs were due to insufficient CTVs coverage. In 12 of the 18 patients, the failure was in the tumor volume, in 3 patients it was in the pleura, and in 2 patients it was in the supraclavicular nodes. Only 1 patient had recurrence in both the tumor volume and the uninvolved nodal area.

Discussion

In this series of NSCLC cases treated with conventional fields and doses, the loco-regional failures after radiotherapy mainly occurred in the tumor volumes, and there were no isolated ENFs.

There are several possible reasons for these results. First, micrometastasis in the CTVs may have been controlled by prophylactic delivery of 40 Gy to the region, and depending on the location of the primary tumor, the sites of occult metastasis may often have received additional unintentional radiation doses. Kepka et al. reported an isolated ENF rate of 9% in 185 patients treated with the ENI using 3-dimensional conformal radiotherapy (3D-CRT). Their analysis showed that the ENF occurred more frequently in the regions that received under 40 Gy than in the regions that received higher doses (69% vs. 31%, respectively, $p = 0.04$) [7]. However, despite the same ENF rate of 9% in 1705 patients in the four trials conducted by the Radiation Therapy Oncology Group (RTOG), a retrospective evaluation of in-field progression revealed that neither in-field progression nor survival was affected by the adequacy of ENI [8]. Field adequacy did not have any negative impact on regional control in our series either (Tables 3).

Second, the amount of micrometastasis in unenlarged mediastinal regional nodes may have been small enough to be controlled by chemotherapy, which has been shown to have activity that reduces the incidence of distant micrometastasis in advanced NSCLC. However, the degree of systemic and local efficacy of chemotherapy did not reach statistical significance in our series, probably because of the small number of patients and their heterogeneity (data not shown).

Third, since the failure sites in the majority of patients were distant, they would have died of their disease before the ENF became apparent. As a result, the loco-regional failure rates may have been lower than their true values because we did not investigate regional sites once a patient developed distant metastasis.

The therapeutic significance of treating subclinical nodal regions during and after surgery for NSCLC has been questioned. Some studies have established the presence of considerable microscopic nodal disease in clinically uninvolved lymph nodes [9,10], but the role of mediastinal lymphadenectomy remains controversial and has been limited to the precise staging of the disease [11–13]. A study by Izbicki et al. which compared systemic mediastinal lymphadenectomy with mediastinal lymph node sampling showed that radical systemic mediastinal lymphadenectomy had no effect on the disease-free or overall survival of patients with limited nodal involvement [13,14]. The role of adjuvant radiotherapy after complete resection also remains unclear [15–17]. A systemic

Table 3
Patients with CTVs failure.

	Patient #1	Patient #2	Patient #3	Patient #4
Age (yr)/Sex	45/Female	74/Female	61/Male	78/Male
Reason for inoperability	Unresectable	Unresectable	Decreased pulmonary function	Unresectable, age
Stage	IIIA	IIIA	IIB	IIIB
Primary location	Left lower lobe	Right upper lobe	Right lower lobe	Left upper lobe
Histology	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma
Chemotherapy	Yes	Yes	No	No
Response	Partial response	Partial response	Partial response	Partial response
Site of first failure	Distant and loco-regional	Distant and loco-regional	Loco-regional	Loco-regional
Field border adequacy	Yes	Yes	No	Yes
Dose to CTVs failure	40	40	0	40
Death	No	No	Yes	No

review and meta-analysis [18] showed that postoperative radiotherapy was detrimental to patients with early NSCLC, although there may have been some efficacy in patients with N2 tumors. These arguments also raise questions about the clear benefit of ENI in regard to survival.

In-field loco-regional failure was a major site of failure in the current study: all the recurrences in the CTVs were associated with failure in the gross tumor volume. Thus, more intensive treatment strategies are needed to enhance loco-regional control without sacrificing safety. One possible strategy is to reduce the ENI field in regard to the patients' risk factors while escalating the total dose. Such an attempt has already been made in regard to surgery: Asamura et al. retrospectively reviewed the prevalence of lymph node metastasis with respect to the location of the primary tumor or other characteristics to decide on the optimal lobe-specific extent of systematic lymph node dissection for NSCLC [19,20]. By using such predictors, including the location of the primary tumor, histology, or nodal stage [21–24], it is possible to identify the nodal areas at risk and to optimize the extent of ENI in radiation therapy as well. On the other hand, more precise diagnosis by novel technology, such as positron emission tomography [25], may enable the omission of ENI and avoid unnecessary irradiation to areas at low risk for subclinical disease.

In terms of the technical feasibility of dose escalation, Grills et al. found that intensity-modulated radiation therapy without ENI for NSCLC increased the deliverable mean target dose in node-positive patients by 25–30% over 3D-CRT and by 130–140% over traditional ENI [26].

Because omitting ENI is likely to leave microscopic disease untreated, there is concern that it may result in increased failure in these areas. However, the preliminary results of dose escalation trials have shown that isolated ENF outside the irradiated volume occurred in fewer than 6% of the cases and that omission of ENI did not seem to sacrifice outcome [2–5,27]. There is insufficient evidence to support the use of ENI for any patient with localized NSCLC (Stages I–III), irrespective of whether chemotherapy is administered [28]. There has been only one randomized trial that compared high-dose thoracic radiotherapy without ENI and standard dose radiotherapy with ENI, and it showed a survival benefit of high-dose thoracic radiotherapy without ENI [29]. One possible explanation for this finding is that incidental doses to elective nodal areas may contribute to the eradication of the subclinical disease. The pattern of ENF according to nodal regions was described by Rosenzweig et al., who implemented the use of involved-field radiation therapy with dose escalation in 524 patients [6]. Since the majority of the 42 ENFs that were observed occurred in the areas that received less than 45 Gy, the incidental doses to elective nodal areas may have been substantial despite the attempt not to treat these regions in their study. In addition, Zhao et al. reported that involved-field radiation therapy with a dose escalated to 70 Gy delivered a considerable dose to CTVs, and when the primary tumor was large or centrally located, the percentages of CTVs in the lower paratracheal region, subcarinal region and ipsilateral hilar region receiving over 40 Gy were 33%, 39%, and 98%, respectively [30].

Because of the retrospective nature of our study, no conclusions about the value of ENI for NSCLC can be drawn. However, the finding that in-field loco-regional failure, as well as distant metastasis, was a major type of failure with the standard field and dose of thoracic radiotherapy confirmed the need for more intensive treatment.

Further investigation to verify the true significance of ENI or to identify best candidates for ENI is necessary before it is abandoned in the context of dose escalation.

Conclusion

The loco-regional failures after radiotherapy in this series of NSCLC cases treated with conventional fields and doses mainly occurred in the tumor volumes, and there were no isolated ENFs. The results confirmed the need for more intense treatment to improve local control.

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Review

Problems with Registration-Directed Clinical Trials for Lung Cancer in Japan

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SEKINE, I., NOKIHARA, H., YAMAMOTO, N., KUNITOH, H., OHE, Y., SAIJO, N. and TAMURA, T. *Problems with Registration-Directed Clinical Trials for Lung Cancer in Japan.* Tohoku J. Exp. Med., 2007, **213** (1), 17-23 —— New anticancer agents against lung cancer are needed because efficacy of chemotherapy is limited. The long time required, low quality, and considerable costs of registration-directed clinical trials in Japan ("Chiken") have been pointed out. The quality of 24 phase I and 41 phase II trials of an anticancer drug for lung cancer were analyzed according to the approval year of the drug. The human resources and infrastructure to support oncology clinical practice and clinical trials were compared between Japan and the USA. A maximum tolerated dose was not defined in any of seven phase I trials before 1989, and was determined in two of six trials between 1989 and 1996 and in seven of 10 trials thereafter. Before 1989, 29 (20%) of 142 patients registered in two trials were ineligible, and the number of ineligible patients was not reported in the five trials. Sample size calculations were not performed in any of seven phase II trials before 1989 and were performed in only four of 10 trials between 1989 and 1996 and in all 23 trials conducted thereafter. The shortage of human resources, including medical oncologists, oncology nurse practitioners and clinical research coordinators, is serious and acute. The infrastructure to support clinical trials also remains insufficient in Japan. In conclusion, registration-directed clinical trials of anticancer agents have advanced significantly during last three decades but remain unsatisfactory. The development of infrastructure and human resources is an urgent task to ensure high-quality clinical trials without unnecessary delays. ——— clinical trials; medical oncologists; nurse practitioners; lung cancer; anticancer agents

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Lung cancer is one of the most common malignancies and the leading cause of cancer-related deaths in many countries. In the year 2000, the annual number of deaths from lung cancer was estimated to be 1.1 million worldwide, and global lung caner incidence is increasing at a rate of 0.5% per year (Schottenfeld and Searle 2005). About 80% of patients with lung cancer have already developed distant metastases or pleural effusion, either by the time of the initial

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diagnosis or by the time recurrence is detected after surgery for local disease. These patients can be treated with systemic chemotherapy, but the efficacy of currently available anticancer agents is limited to the extent that patients with advanced disease rarely live long. Therefore, new chemotherapeutic agents continue to be developed against lung cancer (Sekine and Saijo 2000).

The Japanese Pharmaceutical Affairs Law (PAL) was enacted in 1948, and was first amended in 1960 to provide for regulations to ensure the maintenance of the quality, efficacy, and safety of drugs and medical devices, and to promote research and development of these medical and pharmaceutical products. Good Clinical Practice (GCP) was enforced by the Bureau Notification of the Ministry of Health and Welfare of Japan ("Kyokuchou-Tsuuchi") in 1989 (the former GCP). In 1996, the PAL and its related laws were amended to strengthen GCP (the new GCP), Good Laboratory Practice, Good Post-Marketing Surveillance Practice, and standard compliance reviews, conforming to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. In contrast to the laws prevailing in the US and EU, marketing approval for anticancer agents in Japan has been granted based on reports of the anti-tumor effects of the new agents in phase II trials (Fujiwara and Kobayashi 2002).

Under this Japanese drug approval system regulated by the PAL, 23 anticancer drugs have been approved for use against lung cancer during the last five decades (Fig. 1). Of these, 9 drugs are original to Japan, some of which are routinely used all over the world. Several problems, however, have been pointed out in registration-directed clinical trials in Japan ("Chiken"), including the long time required, low quality, and considerable cost (The Ministry of Health, Labour and Welfare of Japan 2002; The Ministry of Education, Science and Culture and the Ministry of Health, Labour and Welfare 2003). As a result, Japanese cancer patients must wait for a long time

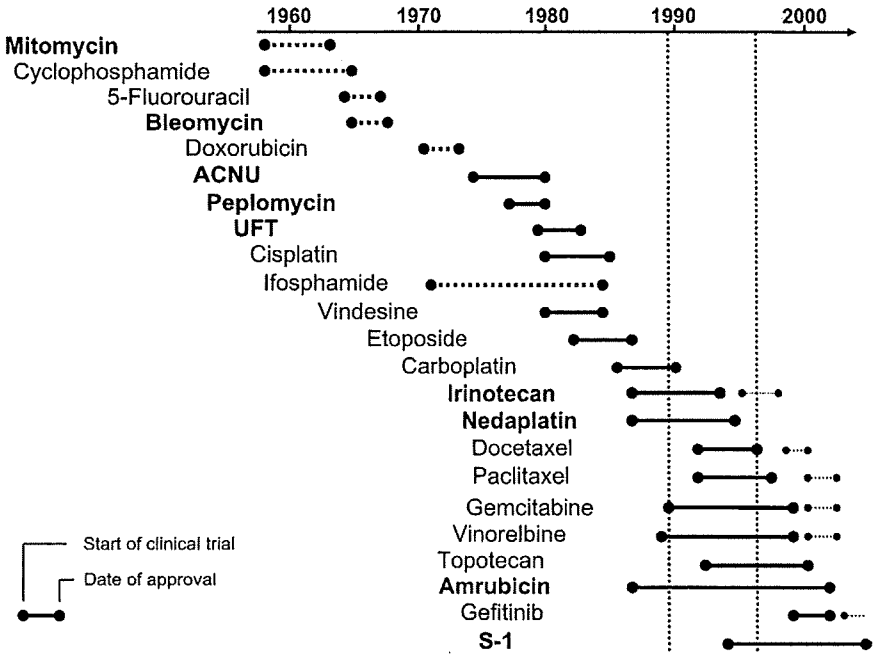

Fig. 1. Anticancer drugs approved for lung cancer in Japan.
Bold: original to Japan. Dotted line: case series studies, solid thick line: investigational new drug phase I-II trials for approval, and dotted thin line: post-marketing sponsored phase III trials. Vertical dotted lines indicate the year when the former and new GCP were issued.

until they receive new anticancer drugs which have been approved long before in other countries (The Ministry of Health, Labour and Welfare of Japan 2005). We discuss the aspects and issues of registration-directed trials in Japan by reviewing such trials for the 23 anticancer drugs.

Review of registration-directed clinical trials for the 23 anticancer drugs

A total of 65 phase I and II trials of an anticancer drug for approval were reviewed in terms of definition of eligibility criteria, maximum tolerated dose (MTD), sample size, response criteria, and extramural review for tumor responses. The MTD is the dose associated with seriouis but reversible toxicities in a sizeable proportion of patients and the one that offers the best chance for a favorable therapeutic ratio (Piantadosi 1997). The number of patients accrued in a trial, percentage of ineligible patients, number of participant hospitals in a trial, and the study period defined as the months between the first and last patient accrual were also analyzed. They were obtained from a published paper for 53 trials, from a meeting abstract and in-company resource for one trial, and from in-company resource alone for the remaining 11 trials. The clinical developmental period of an anticancer drug was defined as years between the start month of the first phase I trial and the month of the approval for lung cancer. These parameters are compared according to the approval year of the drug. We categorized three periods of approval: 1) before 1989, 2) between 1989 and 1996, and 3) between 1997 and 2004, because the former GCP was enforced in 1989, and the new GCP in 1997 (Fujiwara et al. 2002).

Of the 23 anticancer drugs, six drugs whose clinical development started before 1974 were approved on the basis of the clinical experience of the use of the drug without clinical trials (Fig. 1). A total of 24 phase I trials were identified (Table 1). The MTD was not defined in the protocol of any trials before 1989, but was defined in 33% of trials between 1989 and 1996, and in 70% of trials after 1996. Instead of the MTD, maximum acceptable dose, defined as the dose associated with grade 2 or severer toxicity in two thirds or more patients, was used in a trial after 1996. About twice more patients were registered in a trial before 1989 than thereafter, but 20% of the registered patients before 1989 were ineligible. The study period of a phase I trial got longer as the number of participant hospitals decreased, from 7 months and 11 hospitals before 1989 to 13 months and 4 hospitals after 1996, respectively.

In this review, 41 phase II trials for approval were analyzed (Table 2). Calculation of the sample size was not made in any trials before 1989, was seen in 40% of trials between 1989 and 1996, and in all trials thereafter. Response criteria were

TABLE 1. Investigational new drug phase I trials for approval.

	Before 1989	1989-1996	1997 or thereafter
Total number of trials	7	6	11
Defined, number (%) of trials			
Eligibility criteria	4 (57)	6 (100)	11 (100)
Maximum tolerated dose*	0 (0)	2 (33)	7 (70) ‡
Results of trials, median (range)			
Number of patients**	61 (32-170)	24 (18-54)	29 (9-43)
% of ineligible patients	20 (20-21) †	8 (0-33)	6 (0-22)
Number of hospitals	11 (1-21)	9 (1-18)	4 (1-17)
Study period in months	7 (5-30)	10 (5-11)	13 (8-24)

*Statistically significant difference obtained ($p = 0.014$ by the chi-square test); **Statistically significant difference obtained ($p < 0.01$ by the Kruskal Wallis test); †Data were available in 2 trials only; ‡Data were available in 10 trials only.

TABLE 2. Investigational new drug phase II trials for approval.

	Before 1989	1989-1996	1997 or thereafter
Total number of trials	7	11	23
Defined, number (%) of trials			
Eligibility criteria	4 (57)	11 (100)	23 (100)
Sample size calculation*	0 (0)	4 (40) ‡	23 (100)
Response criteria	6 (86)	11 (100)	23 (100)
Extramural review	3 (43)	9 (82)	23 (100)
Results of trials, median (range)			
Number of patients	71 (10-127)	68 (18-153)	61 (11-102)
% of ineligible patients	18 (0-29) †	3 (0-22)	3 (0-12)
Number of hospitals	27 (3-103)	17 (1-30)	20 (5-46)
Study period in months	18 (12-36)	12 (6-34)	26 (4-48) §

*Statistically significant difference obtained ($p < 0.01$ by the chi-square test); †Data were available in 5 trials only; ‡Data were available in 10 trials only; §Data were available in 22 trials only.

defined in almost all studies, but an extramural review was conducted only after 1989. The median number of registered patients in a trial was constant through the three periods, but the percentage of ineligible patients was high in trials conducted before 1989. The number of patients in a trial, and the number of hospitals in a trial were similar regardless of the year. The median study period in recent trials was 26 months.

The clinical development period was evaluated in the 23 drugs. Cisplatin was approved for germ cell tumors in 1983 and additionally approved for non-small cell lung cancer (NSCLC) in 1986. S-1 was firstly approved for gastric cancer in 1999, and additionally approved for NSCLC in 2004. The other drugs were approved for lung cancer for the first time. The median (range) clinical development period was 5.2 (3.2-14.5) years before 1989, 6.0 (4.8-9.1) years between 1989 and 1996, and 9.0 (3.9-15.4) years in 1997 or thereafter.

Development and recent problems of phase I and phase II trials in Japan

The concept of the "clinical trial" was not widely followed in Japan until 1974, when a phase I trial of nimustine hydrochloride (ACNU) was launched as one part of the United States-Japan Cooperation Cancer Research Program on the basis of the agreement between the National Cancer Institute and Japan Society for the Promotion of Science (Sugano 1982; Niitani 1999). Phase I trials before 1989 required the accrual of many patients, because 1) the maximum tolerated dose was not defined, 2) many patients were treated at unnecessary dose levels because the modified Fibonacci dose escalation schedule was not applied, and 3) the percentage of ineligible patients was high. Some of these issues were improved in 1997 or thereafter, but the maximum tolerated dose is still not defined in as many as 40% of trials. Recently, oncology phase I trials came to be conducted among fewer hospitals than before, as more participants were recruited in each hospital. This facilitated communication among phase I investigators, which is important to complete phase I trials safely.

Phase II trials play the central role in anticancer agent approval in Japan, because the approval can be granted based on the response rate in these trials. The quality of protocols for phase II trials suggested by eligibility criteria, sample size calculation, response criteria, and extramural review has been improved significantly. The study period of phase II trials, however, was and is still too long, as long as 4 years in recent trials. To increase participant hospitals, however, is not necessarily a desirable solution,

because a certain number of patients per hospital are needed to maintain the quality of trials by training doctors in the application of a new drug. Thus, enhancing patient recruitment in each hospital participating in the trial is the most important consideration.

A high standard of oncology clinical practice as the basis for clinical trials

Since a high standard of clinical practice is the basis for all clinical trials, the infrastructure for oncological clinical practice should be promptly advanced. The shortage of human resources including medical oncologists and oncology nurse practitioners in Japan is serious and acute. In the United States, medical oncology was established as a separate discipline by the American Board of Internal Medicine in 1971, and approximately 8,000 certified internists as of 2003 have been further certified by the Board in the subspecialty of medical oncology (Holland et al. 2003). In contrast, medical oncology has not been established as an academic unit or a regular university course in many medical schools in Japan. The Japanese Society of Medical Oncology was launched as an association in 1993, and framed the system of cancer medical specialists in 2003. A total of 1,479 doctors were certified as a tentative medical oncology supervisor between 2003 and 2005, and 47 doctors as a medical oncology specialist in 2005 (Table 3) (Japanese Society of Medical Oncology 2005).

To deal with complex cancer care, oncology nurse practitioners in the United States have become an integral part of the multidisciplinary team in the care of patients. As of 2002, more than 19,000 oncology nurse practitioners have been certified by the Oncology Nursing Society in the United States (Rieger 2003). In contrast, the number of oncology nurse practitioners registered in the Japanese Nursing Association was only 44 as of 2005 (Table 3) (Japanese Nursing Association 2005). Introduction of oncology nurse practitioners in clinical practice should lessen the burden on oncologists significantly and help them to have the incentive to take part in registration-directed clinical trials.

The infrastructure and human resources to support clinical trials

The infrastructure to support in-house clinical trials remains insufficient and even lacking in almost all institutes in Japan, while it has been advanced systematically in the United States. In the 1960s, General Clinical Research Centers were founded with the support of National Institutes of Health in 80 universities and academic institutions to provide the primary resources and optimal environment necessary for investigators to conduct clinical research. They include experienced nursing, laboratory, computer system, and biostatistical staff (Robertson and Tung 2001; General Clinical Research Centers 2005). To carry out a multicenter trial, a central data center

TABLE 3. Medical oncology professionals in Japan and the USA.

Professionals	*n* of medical oncology professionals	
	Japan	USA
Medical oncologists	47 [1]	8,000 [2]
Oncology nurse practitioners	44 [3]	19,000 < [4]
Clinical research coordinators	335 [5]	10,723 [6]

[1] Certified by the Japanese Society of Medical Oncology in 2005.
[2] Certified by the American Board of Internal Medicine as of 2003.
[3] Certified by the Japanese Nursing Association as of 2005.
[4] Certified by the Oncology Nursing Society as of 2002.
[5] Certified by the Japanese Society of Clinical Pharmacology and Therapeutics as of 2005.
[6] Certified by the Association of Clinical Research Professionals as of 2005.

is needed to deal with the increased administrative difficulties and quality assurance problems associated with this type of trial (Pollock 1994). The quality control and quality assurance system of the Japan Clinical Oncology Group has been significantly developed during the last two decades (Japan Clinical Oncology Group 2005). Using Internet resources may facilitate developing national and regional networks for clinical trials by reducing the burden associated with the extensive research time and considerable cost of all these processes (Paul et al. 2005).

The new GCP demands more of the clinical researchers in time, resources and money to enhance the science, credibility, and ethics of clinical trials for approval (Sweatman 2003). The clinical research coordinator (CRC) plays a key role in the clinical trial process by supporting investigators. The CRCs are involved in every aspect of registration-directed clinical trials, including protocol development, checking eligibility criteria, informed consent, organizing study schedules, checking clinical tests, filling in case report forms, and providing support for monitoring and auditing the trials (Rico-Villademoros et al. 2004; Sakamoto 2004). Association of Clinical Research Professionals in the USA has offered the CRC certification since 1992, and there are 10,723 CRCs to date (Association of Clinical Research Professionals 2006). The Japanese Society of Clinical Pharmacology and Therapeutics launched the certified CRC system in 2003, and there were 335 certified CRCs as of 2005 (Table 3) (The Japanese Society of Clinical Pharmacology and Therapeutics 2005).

In conclusion, clinical trials of anticancer agents for approval have been developing significantly, but still remain at an unsatisfactory level. Development of the infrastructure and human resources for clinical trials is an urgent task to complete good quality clinical trials for approval without delay.

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Bodyweight change during the first 5 days of chemotherapy as an indicator of cisplatin renal toxicity

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To determine whether bodyweight (BW) loss, daily urine volume (UV) or furosemide use are associated with cisplatin nephrotoxicity, performance status, serum chemistries before treatment, average daily UV, maximum BW loss and use of furosemide on days 1–5 of chemotherapy were evaluated retrospectively in chemotherapy-naive patients with thoracic malignancies who had received 80 mg/m² cisplatin. Associations between these parameters and the worst serum creatinine levels (group 1, grade 0–1; and group 2, grade 2–3) during the first cycle were evaluated. Of the 417 patients (327 men and 90 women; median age, 59 years), 390 were categorized into group 1 and 27 were categorized into group 2. More women and older patients were observed in group 2 than in group 1 (11.1 *vs* 5.2%, $P = 0.044$, and 65 *vs* 59 years, $P = 0.041$, respectively). The median average daily UV was 3902 mL in group 1 and 3600 mL in group 2 ($P = 0.021$). A maximum BW loss ≥2.1 kg was noted in 4.4% of patients in group 1 and 18.5% of patients in group 2 ($P = 0.006$). Furosemide was used in 206 (49.4%) patients. The median total dose of furosemide in groups 1 and 2 were 0 mg and 26 mg, respectively ($P = 0.024$). A multivariate analysis showed that a maximum BW loss ≥2.1 kg and the total furosemide dose were significantly associated with group category. In conclusion, BW loss and total furosemide dose were associated with cisplatin nephrotoxicity. (*Cancer Sci* 2007; 98: 1408–1412)

Cisplatin alone or in combination with other chemotherapeutic agents has been the most frequently used chemotherapy regimen against a variety of solid tumors for 30 years because of its significant therapeutic effects.[1] In spite of intensive efforts to devise platinum analogs and the successful development of carboplatin, cisplatin remains a key agent in the treatment of germ cell tumors, head and neck cancer and bladder cancer, as shown in several randomized controlled trials comparing the two platinum agents.[2] In addition, cisplatin has a significant role in the treatment of lung and ovarian cancers, although carboplatin is becoming increasingly used against these cancers as an alternative chemotherapeutic agent.[3,4]

Cisplatin nephrotoxicity has been a major dose-limiting toxicity for this drug in most drug administration schedules.[5] Although the exact mechanism is unclear, high concentrations of platinum and widespread necrosis were observed in the proximal tubules of the kidney. This tubular impairment secondarily leads to a reduction in renal blood flow and glomerular filtration rate, potentiating primary tubular damage. This vicious circle causes a delayed deterioration in renal function, as an increase in the serum creatinine level typically appears 6–7 days after cisplatin administration in humans.[5,6] The standard prophylaxis for cisplatin nephrotoxicity is a normal saline infusion of 1–4 L with osmotic diuresis on the day of cisplatin administration.[5] Although this vigorous hydration diminishes life-threatening renal toxicity, 7–40% of patients still develop a mild to moderate increase in their serum creatinine levels, which influences subsequent cisplatin therapy.[7,8] For the prevention of cisplatin nephrotoxicity, the maintenance of good renal hemodynamics may be necessary for a week or longer after cisplatin administration, although indicators of hydration management on day 2 of chemotherapy and thereafter have not been reported. The purpose of this retrospective study was to evaluate bodyweight (BW) changes, daily urine volumes (UV) and use of furosemide on days 1–5 of chemotherapy as well as pretreatment patient characteristics in the hope of finding an association between these factors and nephrotoxicity during the first cycle of cisplatin-based chemotherapy.

Patients and Methods

Patient selection. Patients were selected retrospectively for the present study according to the following criteria: (1) a histological or cytological diagnosis of thoracic malignancy; (2) no prior chemotherapy; (3) a chemotherapy treatment regimen that included 80 mg/m² of cisplatin; and (4) treatment as an in-patient at the National Cancer Center Hospital. Patients were excluded if: (1) their pretreatment serum creatinine level was abnormal; or (2) no record of BW or daily UV on days 1–5 of chemotherapy was available.

Treatment. Cisplatin at a dose of 80 mg/m² was administered intravenously over 60 min on day 1 in combination with other chemotherapeutic agents. Hydration just before cisplatin administration consisted of 500 mL normal saline, 500 mL 5% glucose and 10 mL KCl over 4 h. Hydration just after cisplatin infusion consisted of 500 mL normal saline with 40 g mannitol over 2 h, followed by 500 mL normal saline, 1000 mL 5% glucose and 15 mL KCl over 6 h. On days 2–5, 1000 mL normal saline, 1000 mL 5% glucose and 20 mL KCl were administered over 8 h. Antiemetic prophylaxis consisted of a $5HT_3$ antagonist and 16 mg dexamethasone on day 1 followed by 8 mg dexamethasone on days 2 and 3, 4 mg on day 4 and 2 mg on day 5. Furosemide was given orally or intravenously if fluid retention was suspected based on an increased BW or a decreased UV. These treatments were repeated every 3–4 weeks.

Data collection and statistical analyses. The patients' baseline characteristics, including age, sex and performance status as well as serum albumin, Na, K, Ca and fasting blood sugar levels were analyzed. The modified Ca level was calculated using the following formula:

$$\text{modified Ca (mg/dL)} = \text{serum Ca (mg/dL)} + 4 - \text{serum albumin (g/dL)}.$$

The daily UV and BW at 0800 hours (before breakfast) and at 1600 hours (before dinner) were measured once a day on days

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Table 1. Patient demographics and pretreatment blood chemistry tests in groups categorized according to worst creatinine grade

		Group 1 (n = 390)		Group 2 (n = 27)		P-value
		n	%	n	%	
Sex	Male	310	94.8	17	5.2	0.044
	Female	80	88.9	10	11.1	
Age (years)	Median	59	(Range 18–77)	65	(Range 38–74)	0.041
Performance status	0	169	92.3	14	7.7	0.82
	1	218	94.3	13	5.6	
	2–3	3	100	0	0	
Serum albumin	≥3.7 g/dL	319	94.1	20	5.9	0.32
	≤3.6 g/dL	71	91.0	7	9.0	
Serum Na	≥138 mEq/L	341	93.2	25	6.8	0.43
	≤137 mEq/L	49	96.1	2	3.9	
Serum K	≤4.9 mEq/L	373	93.7	25	6.3	0.46
	≥5.0 mEq/L	17	89.5	2	10.5	
Modified Ca†	≤10.4 mg/dL	376	93.3	27	6.7	0.31
	≥10.5 mg/dL	14	100	0	0	
Fasting blood sugar	≤125 mg/dL	322	92.8	25	7.2	0.36
	≥126 mg/dL	54	96.4	2	3.6	
	Not done	14	100	0	0	

†Calculated using the equation: modified Ca (mg/dL) = serum Ca (mg/dL) + 4 − serum albumin (g/dL). Groups 1 and 2 were patients with worst creatinine grades of 0–1 and 2–3, respectively.

1–5 of the chemotherapy regimens. The BW at 0800 hours on day 1 was used as the baseline BW. During the chemotherapy course, blood chemistry was analyzed at least once a week. Data on furosemide use and the BW gain just before furosemide use during the first course of chemotherapy were obtained from medical charts.

The worst serum creatinine level during the first course of chemotherapy was graded (WCG) according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0. The patients were categorized into two groups according to their WCG: patients with WCG_{0-1} (group 1) and patients with WCG_{2-3} (group 2). The daily UV and BW changes, compared with the baseline BW, on days 2–5 of the chemotherapy regimens were noted, and differences in the averages of these measures between groups 1 and 2 were evaluated using repeated measures analyses of variance. Correlations between daily UV and BW changes were assessed using scatter diagrams and Pearson correlation coefficients.

The daily UV on days 1–5 and the maximum BW loss during days 1–5 of the first chemotherapy course were calculated for each patient. These parameters, the pretreatment parameters, the use of furosemide, and their associations with the two group categories were evaluated using χ-tests for categorical variables, Mann–Whitney tests for continuous variables, and logistic regression analyses for both types of variables. The total furosemide dose was calculated using the following formula:[9]

$$\text{total furosemide dose (mg)} = \text{intravenous dose (mg)} + 0.65 \times \text{oral dose (mg)}.$$

The Dr SPSS II 11.0 for Windows software package (SPSS Japan, Tokyo, Japan) was used for the statistical analyses.

Results

Between November 2000 and May 2006, 427 patients met the four inclusion criteria. Of these, six patients were excluded because their pretreatment serum creatinine levels were elevated, and four patients were excluded because no data on their daily UV or BW were available. Thus, a total of 417 patients were analyzed in the present study. The subjects comprised 327 men and 90 women, with a median age of 59 years (range 18–78 years) (Table 1). Non-small cell lung cancer was the most common tumor type, noted in 338 patients, followed by small cell lung cancer in 71 patients, thymic cancer in four patients, malignant mesothelioma in three patients, and tracheal cancer in one patient. Thirty-two patients with stage I–II diseases received chemotherapy as an adjuvant therapy after surgery. The remaining 385 patients with stage III–IV diseases or postoperative recurrent diseases received chemotherapy for the treatment of locally advanced or metastatic diseases.

All of the patients received cisplatin at a dose of 80 mg/m^2 in combination with other agents. The chemotherapy regimens were cisplatin and vinorelbine (n = 200), cisplatin and etoposide (n = 77), cisplatin, vindesine and mitomycin (n = 48), cisplatin and irinotecan (n = 41), cisplatin and gemcitabine (n = 41), and cisplatin and docetaxel (n = 10). The WCG was evaluated in all of the patients, with 390 patients categorized into group 1 and 27 patients categorized into group 2.

The average daily UV during days 1–5 of the chemotherapy regimens showed that the UV on day 1 did not differ between groups 1 and 2, but the daily UV on days 2–5 in group 2 were lower than those in group 1 (Fig. 1A, P = 0.042). The average changes in BW on days 2–5 showed that patients gained BW on days 2–3 and lost BW on days 4–5 (Fig. 1B). The line plotting the changes in BW in group 2 was always below that for group 1 (P = 0.036). Thus, the patients in group 2 retained less water than the patients in group 1. Furthermore, the patients in group 2 may have developed dehydration on day 5, as their average BW dropped to below the baseline level (Fig. 1B). Scatter diagrams comparing the average UV on days 1–2 and the BW change on day 3, and the average UV on days 1–4 and the BW change on day 5 showed no correlation between the UV and BW changes (data not shown), suggesting that the reduction in fluid intake may have caused the BW loss.

The development of renal toxicity was associated with some patient demographics. The percentage of women was higher in group 2 than in group 1 (11.1 *vs* 5.2%, P = 0.04). The median age of the patients in group 1 was 59 years (range 18–77 years), whereas that for group 2 was 65 years (range 38–74 years) (P = 0.041). None of the pretreatment chemistry parameters differed between the groups (Table 1). The frequency of renal toxicity did not differ according to chemotherapy regimen but was associated with a decreased average daily UV during days

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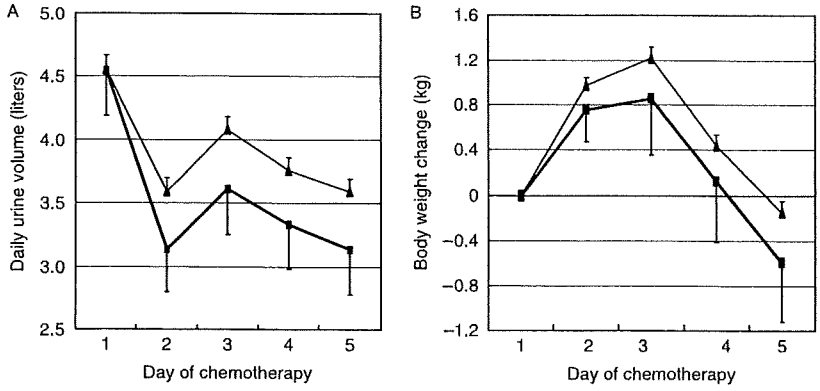

Fig. 1. (A) Average daily urine volumes during days 1–5 of chemotherapy. The differences were statistically significant ($P = 0.042$, repeated measures analysis of variance). (B) Average bodyweight changes on days 1–5 of chemotherapy. The differences were statistically significant ($P = 0.036$, repeated measures analysis of variance). Thin line with closed triangles: group 1, patients with a worst creatinine grade of 0–1 ($n = 390$); thick line with closed squares: group 2, patients with a worst creatinine grade of 2–3 ($n = 27$). Error bars show the 95% confidence intervals.

Table 2. Treatment-related parameters and groups categorized according to worst creatinine grade

		Group 1 ($n = 390$)		Group 2 ($n = 27$)		*P*-value
		n	%	*n*	%	
Agents combined with cisplatin	Vinorelbine	184	92.0	16	8.0	0.83
	Etoposide	74	96.1	3	3.9	
	Vindesine + mitomycin	45	93.8	3	6.2	
	Gemcitabine	39	95.1	2	4.9	
	Irinotecan	39	95.1	2	4.9	
	Docetaxel	9	90.0	1	10.0	
Average daily urine volume (mL)†	Median	3902	(Range 2058–6680)	3600	(Range 1700–5020)	0.021
	≤3000	41	87.2	6	12.8	0.054
	3001–4000	185	92.5	15	7.5	
	≥4001	164	96.5	6	3.5	
Maximum bodyweight loss (kg)‡	Median	0.2	(Range 0–3.9)	0.4	(Range 0–4.6)	0.11
	0	172	95.0	9	5.0	0.006
	0.1–2.0	201	93.9	13	6.1	
	≥2.1	17	77.3	5	22.7	
Total furosemide dose§	Median	0	(Range 0–160)	26	(Range 0–360)	0.024
	0	201	95.2	10	4.7	0.015
	1–30	87	94.6	5	5.4	
	31–60	70	93.3	5	6.7	
	61–90	11	91.7	1	8.3	
	≥91	21	77.8	6	22.2	

†The average daily urine volume on days 1–5 of chemotherapy. ‡Maximum body weight loss during days 1–5 of chemotherapy. §Total furosemide dose (mg) = intravenous dose (mg) + 0.65 × oral dose (mg). Groups 1 and 2 were patients with worst creatinine grades of 0–1 and 2–3, respectively.

1–5 of the chemotherapy regimens (Table 2). In addition, only 5–6% of the patients with a maximum BW loss of 2 kg or less were classified as WCG_{2-3}, whereas 23% of the patients with a maximum BW loss of more than 2 kg were classified as WCG_{2-3} ($P = 0.006$). Furosemide was administered to 206 of the 417 patients (49.4%). Of these patients, 198 did not complain of any symptoms whereas eight developed mild edema in the lower extremities or face, which disappeared after a few days. The difference in the frequencies of renal toxicity among patients who received furosemide and those who did not (8.3 *vs* 4.7%, respectively; $P = 0.14$) was not large enough to be statistically significant. Administration route (intravenous or oral), day of use (day 1, day 2 or days 3–8), or BW gain just before use of furosemide (0–1.4, 1.5–2.9 or ≥3.0 kg) did not influence the frequency of renal toxicity. The total dose of furosemide, however, differed between groups 1 and 2 (median, 0 mg; range, 0–160 mg *vs* median, 26 mg; range, 0–360 mg, respectively; $P = 0.024$). In particular, 22% of the patients who received more than 90 mg of furosemide were classified as WCG_{2-3} (Table 2).

A multivariate analysis showed that the maximum BW loss (odds ratio, 1.77; 95% confidence interval, 1.08–2.90) and the total furosemide dose (odds ratio, 1.21; 95% confidence interval, 1.11–1.33) were significantly associated with the WCG_{2-3} category. Associations with sex and the daily UV were marginally significant (Table 3).

Discussion

The present study showed that the maximum BW loss during days 1–5 of chemotherapy was associated with the development of cisplatin renal toxicity. In particular, 23% of patients with a maximum BW loss of more than 2 kg were classified as WCG_{2-3}. Because dehydration amounting to as little as a 2% loss in BW results in impaired physiological and performance responses,[10] the BW loss and dehydration observed in the present study may be enough to aggravate cisplatin nephrotoxicity. No correlation was noted between the UV and BW changes, suggesting that the dehydration was attributable to a reduced oral intake by patients as a result of cisplatin-induced emesis. BW measurements are

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