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ORIGINAL REPORT

# Nationwide Survey on Complementary and Alternative Medicine in Cancer Patients in Japan

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## ABSTRACT

**Purpose**
To determine the prevalence of use of complementary and alternative medicine (CAM) by patients with cancer in Japan, and to compare the characteristics of CAM users and CAM nonusers.

**Patients and Methods**
A questionnaire on cancer CAM and the Hospital Anxiety and Depression Scale were delivered to 6,607 patients who were treated in 16 cancer centers and 40 palliative care units.

**Results**
There were 3,461 available replies for a response rate of 52.4%. The prevalence of CAM use was 44.6% (1,382 of 3,100) in cancer patients and 25.5% (92 of 361) in noncancer patients with benign tumors. Multiple logistic regression analysis determined that history of chemotherapy, institute (palliative care units), higher education, an altered outlook on life after cancer diagnosis, primary cancer site, and younger age were strongly associated with CAM use in cancer patients. Most of the CAM users with cancer (96.2%) used products such as mushrooms, herbs, and shark cartilage. The motivation for most CAM use was recommendation from family members or friends (77.7%) rather than personal choice (23.3%). Positive effects were experienced by 24.3% of CAM users with cancer, although all of them received conventional cancer therapy concurrently. Adverse reactions were reported by 5.3% of cancer patients. CAM products were used without sufficient information by 57.3% of users with cancer and without a consultation with a doctor by 60.7% of users.

**Conclusion**
This survey revealed a high prevalence of CAM use among cancer patients, without sufficient information or consultation with their physicians. Oncologists should not ignore the CAM products used by their patients because of a lack of proven efficacy and safety.

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## INTRODUCTION

The WHO defines complementary and alternative medicine (CAM), or so-called traditional medicine, as follows: "a comprehensive term used to refer both to traditional medical systems such as traditional Chinese medicine, Indian ayurveda and Arabic unani medicine, and to various forms of indigenous medicine."[1] CAM therapies include medication therapies (which involve the use of herbal medicine, animal parts, and/or minerals) and nonmedication therapies carried out primarily without the use of medication (such as acupuncture or manual therapy). Populations throughout Africa, Asia, and Latin America use traditional medicine to help meet their primary health care needs. In addition to being accessible and affordable, traditional medicine is also often part of a wider belief system, and is considered integral to everyday life and well-being. In Europe and North America, CAM is increasingly being used in parallel to

allopathic medicine, particularly for treating and managing chronic disease. Concerns about the adverse effects of chemical medicines, a desire for more personalized health care, and greater public access to health information fuel the increasing use of CAM in many industrialized countries.[2-5]

The widespread use of a variety of nutritional, psychological, and natural medical approaches as CAM has been well documented.[2,6-8] Recent surveys demonstrate that more than 50% of US cancer patients use CAM therapies at some point after their diagnosis.[3,6,7] Despite extensive use, there is a paucity of data available to indicate whether these practices are efficacious and safe.[9-11] Therefore, serious research efforts are underway to determine the scope of CAM use by patients and their motivations for its use.[6-10] CAM in cancer medicine seems to be widely available in Japan as well as in the Western countries. We performed a preliminary survey on cancer CAM in a single cancer center in 1999. This survey revealed that 32% of cancer patients used CAM, and the most frequently used CAM involved natural products, such as mushrooms, shark cartilage, and beeswax-pollen mixtures.[12] The most pressing and significant problems associated with these products were commonly held but incorrect assumptions and the absence of any regulatory oversight. In addition, interactions between herbs and drugs may increase or decrease the pharmacologic or toxicologic effects of either component. For example, St John's wort has recently been reported to dramatically reduce plasma levels of SN-38 (the active metabolite of irinotecan, a key oncologic drug), which may have a deleterious impact on treatment outcome.[13]

An enormous amount of unreliable information on cancer CAM is available from the Internet and other media sources. It is often the case that cancer patients and their relatives are at a loss about how to deal with such information and have a difficult time choosing what kind of CAM they should adopt. However, there have been no large-scale surveys of this sort in Asia, and the actual state of CAM use in cancer patients is still unclear. Therefore, we performed a nationwide cross-sectional survey to evaluate the prevalence of CAM use in cancer patients and their perceptions of cancer CAM, especially of CAM products used in Japan.

## PATIENTS AND METHODS

### Participants

Before initiation of this survey, the study protocol was examined by the institutional review boards of cancer centers and related hospitals (CCs) joining the nationwide association of medical centers for cancer and adult diseases in Japan, and hospice and palliative care units (PCUs) joining the Japanese association of palliative care. Sixteen of 29 CCs and 40 of 88 PCUs approved the survey. All participating institutions agreed not to treat patients systematically with any CAM. The total number of questionnaires that would be distributed to the patients was predicted by the responsible physician working for each collaborating institute, and this information was provided in advance to the National Shikoku Cancer Center. Questionnaires on cancer CAM were then sent to the responsible collaborating physicians in the CCs and PCUs from October 2001 to March 2002. The day on which the questionnaires were distributed to the patients was determined voluntarily by each institute within 2 weeks of receipt. Questionnaires were distributed to the patients by the medical staff (physicians, nurses, clerks, and so on) at each collaborating institute after exclusion of those with an Eastern Cooperative Oncology Group performance status of 4 and those who underwent surgery that day. Replies were sent back to the National Shikoku Cancer Center directly from each patient. Questionnaires were marked in advance to identify the type of clinic the patients were attending (ie, CCs or PCUs, and inpatient or outpatient). Returned questionnaires were coded with an identification number to ensure confidentiality.

### Questionnaire

We had previously evaluated a questionnaire about cancer CAM in 219 cancer patients who were admitted to the National Shikoku Cancer Center as a preliminary study.[12] In the present study, we used a modified version of that questionnaire after testing several samples. Some additional questions were quoted from previously published articles.[6-8] The original questionnaire we used was written in Japanese. The attached questionnaire (Appendix) has been translated into English. The questionnaire was developed through a systematic literature review and discussions by two experienced medical oncologists, a psychiatrist, a pharmacist, a basic scientist, and a research assistant. On the cover page of the questionnaire, CAM was clearly defined as follows: "any therapy not included in the orthodox biomedical framework of care for patients. CAM means remedies that are used without the approval of the relevant government authorities, such as the Ministry of Health and Welfare in Japan, that approve new drugs after peer review of preclinical experiments and clinical trials regulated by law. CAM usually skips these steps and is offered directly to the public. Health insurance does not usually cover the cost of CAM, and patients will be liable for the whole expense incurred by any CAM. CAM includes natural products from mushrooms, herbs, green tea, shark cartilage, other special foods, megavitamins, acupuncture, aromatherapy, massage, meditation, and so on."

The questionnaire was composed of the following two parts: background of the patients (disease, onset, age, sex, daily living activity level, educational level, religion, cancer treatment, changes of outlook on life, satisfaction with receiving conventional medicine, and use of cancer CAM; questions 1 to 12) and users' perception of cancer CAM (initiation time, kinds of CAM used, reason for starting CAM, method of obtaining information about the CAM used, expectations for CAM use, effectiveness or ineffectiveness, adverse effects, average expense per month, whether a history of CAM use was provided to the physician in charge, whether the physician in charge was consulted, response of physician, reason for not consulting physician, and concurrent use of anticancer drugs and CAM products that are sold over the counter; questions 13 to 28).

### Hospital Anxiety and Depression Scale

A brief scale, the Hospital Anxiety and Depression Scale (HADS), was used in this study to clarify the relationship between emotional state and CAM preference. The HADS has 14 items in two question groups, one each on anxiety and depression, and each question is rated from 0 to 3. The validity and reliability of the Japanese version of HADS have been confirmed previously.[14,15] From previous articles, including the original one and studies in the Japanese population, we adopted 10 points as the cutoff above which anxiety and depression would be scored as high.[14-16] The patients in the high group were considered to have an adjustment disorder or more severe condition. The HADS was delivered to patients along with the questionnaire on CAM.

### Statistical Analysis

Differences of CAM use within categories of selected demographic and clinical variables (age, sex, disease sites, daily living activity level, patient's desire, changes of outlook on life, institute, education, and religion) were assessed by the $\chi^2$ test. The factors predicting CAM use were analyzed by univariate analysis and then multiple logistic regression analysis was performed using all significant predictor variables ($P < .05$). The analysis provided an odds ratio and 95% CI for each variable while simultaneously controlling for the effects of other variables. Variables not contributing substantially to the model were systematically removed in a backward stepwise regression process using the likelihood ratio test as the criterion for removal. The Hosmer-Lemeshow $\chi^2$ test was used to assess the goodness of fit between the observed and predicted number of outcomes for the final model, with $P > .05$ indicating a good fit. All analyses were performed using SPSS Base and Regression models 11.0J (SPSS Japan Inc, Tokyo, Japan)

## RESULTS

### Response Rate to Questionnaire and CAM User Rates

A total of 6,607 questionnaires on cancer CAM were sent to collaborating CCs and PCUs according to the required number estimated by the primary investigators at those institutes. As a result, questionnaires were delivered to 6,074 patients who were treated in CCs (2,688 inpatients and 3,386 outpatients) and to 533 patients who were treated in PCUs (367 inpatients and 166 outpatients). A total of 3,733 questionnaires were returned to our center, of which 3,461 were valid with useable answers. The remaining 272 returned questionnaires were invalid because of a critical lack of major answers, such as unwritten diagnosis or no response to CAM use. Consequently, the rate of valid replies was 52.4%. Of the valid replies, 3,100 were from cancer patients and 361 were from noncancer patients with benign tumors. The flow diagram of the study population is indicated in Figure 1.

The prevalence of CAM use in cancer patients was 44.6% (1,382 of 3,100) and that in noncancer patients was 25.5% (92 of 361). In terms of background differences, noncancer patients were younger, had less impaired daily activity, and were much more likely to be in CCs than cancer patients. The rate of use among cancer patients was significantly higher than that for noncancer patients ($P < .0001$). All of the 3,100 replies from cancer patients were subject to analysis. Many users (86.7%) started CAM after their diagnosis of cancer and 73.3% of users were continuing it at the time of the survey.

### Backgrounds of Patients and CAM Users

The backgrounds of all the cancer patients and CAM users with cancer are summarized in Table 1. The prevalence of CAM use was significantly higher in patients who were younger than 61 years old ($P < .0001$), female ($P < .0001$), patients with a lower daily activity level ($P < .0001$), patients with higher education ($P < .0001$), patients who received chemotherapy ($P < .0001$), patients with a change of outlook on life ($P < .0001$), patients who were dissatisfied with conventional treatments ($P = .0001$), patients in PCUs ($P < .0001$), and patients with a low HADS anxiety score

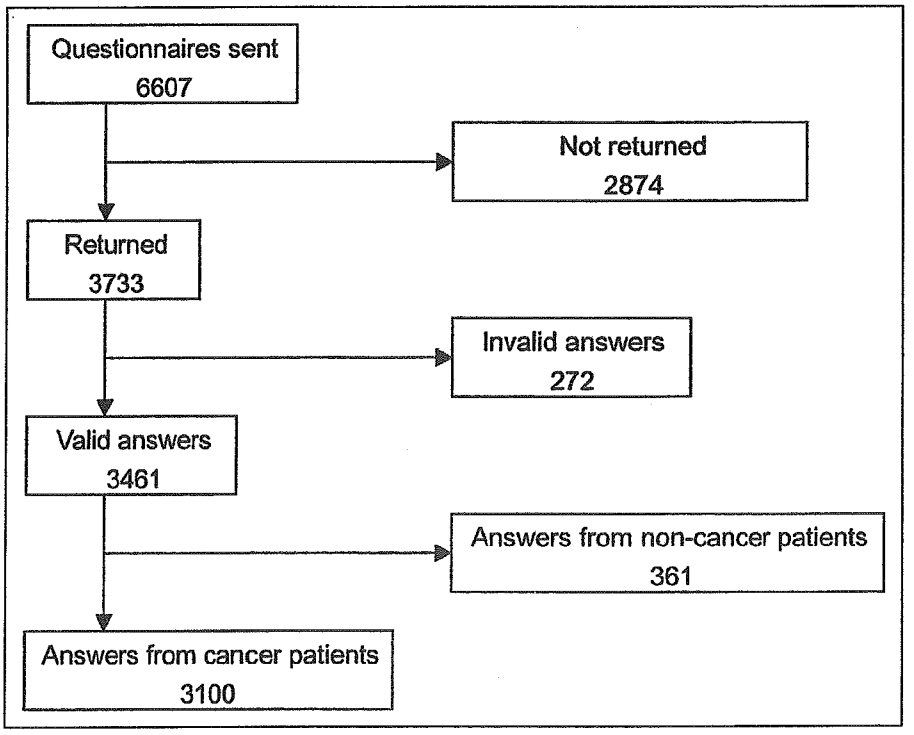


**Fig 1.** Flow diagram of the study population.

**Table 1.** Background and CAM Usage

| Background | No. of Patients | No. of Users | % | $P$ ($\chi^2$ test) |
|---|---|---|---|---|
| Total | 3,100 | 1,382 | 44.6 | |
| Age, years | | | | |
| > 60 | 1,603 | 625 | 39.0 | |
| ≤ 60 | 1,485 | 752 | 50.6 | < .0001 |
| Sex | | | | |
| Male | 1,484 | 586 | 39.5 | |
| Female | 1,614 | 796 | 49.3 | < .0001 |
| Activity of daily living | | | | |
| Free or somewhat limited | 2,293 | 1,002 | 43.7 | |
| Bed rest (≥ 50% of each day) | 726 | 348 | 47.9 | < .0001 |
| Education | | | | |
| High school | 1,721 | 719 | 41.8 | |
| Post-high school | 879 | 464 | 52.8 | < .0001 |
| Practicing religion | | | | |
| No | 2,140 | 945 | 44.2 | |
| Yes | 593 | 281 | 47.5 | .1660 |
| Conventional treatment | | | | |
| Chemotherapy | 1,839 | 968 | 52.6 | |
| Nonchemotherapy | 1,260 | 414 | 32.9 | < .0001 |
| Change in outlook on life | | | | |
| No | 1,381 | 509 | 36.9 | |
| Yes | 1,558 | 793 | 50.9 | < .0001 |
| Treatment met patient's needs | | | | |
| No | 1,212 | 591 | 48.8 | |
| Yes | 1,830 | 762 | 41.7 | .0001 |
| Institute | | | | |
| Cancer centers | 2,811 | 1,203 | 42.8 | |
| Palliative care units | 289 | 179 | 61.9 | < .0001 |
| Treatment place | | | | |
| Inpatient ward | 1,665 | 717 | 43.1 | |
| Outpatient clinic | 1,434 | 665 | 46.4 | .0699 |
| HADS | | | | |
| High anxiety score (≥ 11) | 1,915 | 852 | 44.5 | |
| Low anxiety score (< 11) | 741 | 378 | 51.0 | .0029 |
| High depression score (≥ 11) | 1,018 | 510 | 50.0 | |
| Low depression score (< 11) | 1,652 | 734 | 44.4 | .0049 |
| Cancer | | | | |
| Lung | 380 | 203 | 53.4 | |
| Breast | 532 | 273 | 51.3 | |
| Hepatobiliary | 256 | 129 | 50.4 | |
| Genitourinary | 445 | 196 | 43.9 | |
| Gastrointestinal | 708 | 278 | 39.3 | |
| Head and neck | 266 | 82 | 30.8 | |
| Other | 513 | 222 | 43.3 | < .0001 |

Abbreviations: CAM, complementary and alternative medicine; HADS, Hospital Anxiety and Depression Scale.

($P = .0029$) and a high HADS depression score ($P = .0049$). In terms of disease sites, the rate of use was higher in patients with lung, breast, and hepatobiliary cancers than in those with other cancers ($P < .0001$). The prevalence of CAM use in inpatient wards of CCs and that in outpatient clinics of CCs was 40.6% and 45.3%, respectively. The prevalence of CAM users in inpatient wards of PCUs and that in outpatient clinics of PCUs was 61.0% and 64.3%, respectively. The prevalence of CAM use in PCUs was significantly higher than that in CCs in outpatient clinics ($P < .0001$), as well as inpatient wards ($P < .0001$). Similarly, the prevalence of CAM use in inpatient wards was significantly higher than that in outpatient clinics in both CCs ($P < .0001$) and PCUs ($P < .0001$).

### *Predictors of Cancer CAM Use*

Multivariate logistic regression analysis was performed to detect the factors predictive of CAM use, using the variables with a significantly different rate among users. The institutional review board of one CC did not permit the questions about education and religion, and 500 questionnaires in which those two questions were deleted were sent to that center. As the result, the rate of reply on education and religion was apparently low. Given that the anxiety and depression scores of HADS could not be calculated if one of each of seven questions was not answered, the number of available replies was also decreased relative to the other questions. For these reasons we performed two analyses of

the relevant variables separating the two patient populations: analysis 1 included the significant variables other than education and HADS, and analysis 2 included all significant variables as shown in Table 2. Patients who received chemotherapy; patients in PCUs; patients whose outlook on life had changed; patients with lung, breast, or hepatobiliary cancer; patients younger than 61 years old; and female patients were more likely to use CAM in both sets of analysis. In analysis 2, higher education was determined as a potent predictive factor, and dissatisfaction with conventional treatments was a weak predictive factor.

### Types of CAM

The types of CAM used are listed in Table 3. The majority of CAM users (96.2%) relied on CAM products as opposed to nonmedical therapies. The most frequently used CAM product was mushrooms (Agaricus 60.6% and active hexose correlated compound [AHCC] 8.4%). Agaricus is extracted from a particular type of mushroom, *Agaricus blazei Murill.* It is purported to be an interferon inducer. AHCC is thought to act as an immunomodulator. Other CAM products were propolis (28.8%), Chinese herbs (7.1%), chitosan (7.1%), and shark cartilage (6.7%). Propolis is a beeswax-pollen mixture. Chitosan is an extract from crustaceans, such as crabs and lobsters. These are claimed to be enhancers of the immune system. Shark cartilage is known to be an inhibitor of tumor angiogenesis.[17] Chinese herbs (easily bought over the counter, but not prescribed by physicians) were used by 7.1% of patients. The rate of use of traditional Chinese medicine (qigong, moxibustion, and acupuncture) was less than 4%.

### Perceptions and Attitudes Toward CAM

As shown in Table 3, 77.7% of the patients started using CAM on recommendation from family members or friends. Only 23.3% of the patients decided to use CAM on the basis of their own will. Patients expected the following effects from CAM: suppression of tumor growth (67.1%), cure (44.5%), symptom relief (27.1%), and complementary effects to conventional therapy (20.7%). In terms of the effectiveness of CAM, 24.3% of the patients experienced positive effects, such as tumor shrinkage, inhibition of tumor growth, pain relief, fewer adverse effects from anticancer drugs, and feeling better. However, at the same time, all of the patients were treated with conventional therapies such as surgery, chemotherapy, hormonal therapy, and/or radiation. The effects were not related to the use of any specific CAM product. Almost two thirds of the patients did not know if the CAM really worked or not. Conversely, only 5.3% of the patients experienced adverse effects, such as nausea, diarrhea, constipation, skin eruption, and liver dysfunction. No adverse effects were experienced by 62.2% of the patients. Patients who were uncertain about adverse effects comprised 32.6% of respondents.

More than half of the patients (57.3%) started CAM without obtaining enough information on it. Most of the patients (84.5%) had not been asked about CAM use by their physician or other health professionals. Nearly two thirds of the patients (60.7%) have never consulted their physicians on CAM use. When the patients consulted their physicians, 60.3% of the patients were told that they were free to use it or not. Patients who were told to continue using CAM and those who were told to cease use comprised 10.5% (8.5% in CCs and 19.5% in PCUs) and 11.3% (12.2% in CCs and 7.3% in PCUs) of CAM users, respectively. The main reason (56.1%) given for why they were not willing to ask their physicians about CAM was that their physicians did not ask about CAM use. The prevalence of patients who thought the physicians would not understand CAM and who thought they would prohibit CAM use was 19.4% and 8.7%, respectively.

The prevalence of concurrent use of anticancer drugs and CAM products was 61.8% in CAM users. The average monthly expenditure for CAM was 57,000 yen (approximately US $500; range, 0 to 1200,000 yen).

**Table 2.** Analysis of CAM Use With Multivariate Logistic Regression

| Variable (reference) | Analysis 1 (n = 2,810)* | | | Analysis 2 (n = 2,020)† | | |
|---|---|---|---|---|---|---|
| | Odds Ratio | 95% CI | *P* | Odds Ratio | 95% CI | *P* |
| Used chemotherapy (*v* did not) | 2.06 | 1.76 to 2.43 | < .0001 | 2.24 | 1.85 to 2.73 | < .0001 |
| Seen at a palliative care unit (*v* a cancer center) | 2.29 | 1.73 to 3.03 | < .0001 | 2.22 | 1.59 to 3.10 | < .0001 |
| Experienced a change in outlook on life (*v* did not) | 1.47 | 1.26 to 1.73 | < .0001 | 1.40 | 1.15 to 1.70 | .0007 |
| Lung, breast, hepatobiliary cancer (*v* other cancers) | 1.47 | 1.25 to 1.73 | < .0001 | 1.34 | 1.10 to 1.62 | .0031 |
| ≤ 60 years of age (*v* > 60 years) | 1.39 | 1.18 to 1.64 | < .0001 | 1.32 | 1.08 to 1.61 | .0063 |
| Symptomatic (*v* asymptomatic) | 1.16 | 0.98 to 1.36 | .074 | 1.23 | 1.01 to 1.49 | .0373 |
| Did not meet patient's needs (*v* met them) | 1.21 | 1.03 to 1.42 | .0234 | 1.22 | 1.00 to 1.48 | .047 |
| Female (*v* male) | 1.17 | 0.98 to 1.40 | .0764 | 1.16 | 0.94 to 1.43 | .174 |
| More educated (*v* less educated) | — | — | — | 1.61 | 1.32 to 1.95 | < .0001 |
| Low HADS score for anxiety (*v* high score) | — | — | — | 1.11 | 0.90 to 1.38 | .3227 |
| High HADS score for depression (*v* low score) | — | — | — | 1.02 | 0.84 to 1.25 | .8447 |

Abbreviation: HADS, Hospital Anxiety and Depression Scale.
*Analysis 1 was performed with all variables except for education and HADS because there were fewer responses for these variables.
†Analysis 2 was performed with all variables listed.

**Table 3.** Types of CAM Used and Perceptions and Attitudes of 1,382 CAM Users

| Characteristic | % |
|---|---|
| Type of CAM used* | |
| CAM products (Chinese herbs, mushrooms, shark cartilage, vitamins, and so on) | 96.2 |
| Qigong† | 3.8 |
| Moxibustion | 3.7 |
| Acupuncture | 3.6 |
| Motive for starting CAM | |
| Recommendation from family or friends | 77.7 |
| Will of patients themselves | 23.3 |
| Expectations for CAM use* | |
| Suppress cancer growth | 67.1 |
| Cure | 44.5 |
| Symptom relief | 27.1 |
| Complementary effects to conventional therapy | 20.7 |
| Positive effects | |
| Yes | 24.3 |
| No | 6.2 |
| Unclear | 69.5 |
| Adverse effects | |
| Yes | 5.3 |
| No | 62.2 |
| Unclear | 32.6 |
| Obtained enough information on CAM | |
| Yes | 42.7 |
| No | 57.3 |
| Heard about CAM use from health professionals | |
| Yes | 15.5 |
| No | 84.5 |
| Consulted with doctors about CAM use | |
| Yes | 39.3 |
| No | 60.7 |

NOTE. Unanswered rates were less than 10% in all categories.
*Questions in which multiple selections of answers were allowed.
†Component of traditional Chinese medicine that combines movement, meditation, and regulation of breathing to enhance the flow of vital energy (qi) in the body to improve circulation and enhance immune function.

## DISCUSSION

The surveyed cancer population in this study used complementary but not alternative therapies because they were simultaneously treated in conventional medical facilities. However, we could not completely rule out the possibility that they had previously used alternative medicine. Therefore, we used the term CAM in this study.

Although we received more than 3,000 replies, the response rate (52.4%) was a little lower than in previous studies.[3,6,18,19] This may have introduced bias into our study. However, the patients' privacy was completely preserved and our survey method was the easiest way for the patients to reply to the questionnaire without feeling any pressure. We believe that our survey is helpful for assessing regional research priorities and for comparing the current status of CAM use in studies using a similar mailed-questionnaire method in other countries.

The prevalence of CAM use in cancer patients was significantly higher than that in noncancer patients. Most of the noncancer patients in this study had benign tumors and attended the cancer centers. Therefore, the noncancer patients in our study represent neither the general healthy population nor patients with benign chronic disease. Indeed, the rate of CAM use in the general population of people suffering from disease in our country was reported to be higher than that of our noncancer patients.[20] The prevalence of CAM use in cancer patients was 44.6%. This rate was slightly higher than that found in our previous study (32%) of a single cancer center survey.[12] The prevalence appears to increase each year in our country, as in the Western countries.[2] CAM user rates were significantly higher in patients undergoing chemotherapy and in patients in PCUs, and these associations were confirmed by multivariate analysis. Chemotherapy is usually delivered to inoperable, advanced, or metastatic cancers with a palliative intent but not a curative intent. In PCUs, there were no conventional treatments with tumor shrinkage as the expected outcome. Patients' relatives or friends often recommended that the patient use CAM products in that situation. In general, medical professionals in PCUs are rather generous in accepting the use of CAM. The percentage of patients whose CAM use had been recommended was approximately two-fold higher in PCUs (19.5%) compared with that in CCs (8.5%). These are probably the primary reasons for the high rate of CAM use in patients undergoing chemotherapy and in PCUs. The multivariate analysis also revealed a close association between CAM use and high educational status, changes in outlook on life, primary cancer site, and younger age. The patients' perception of received conventional treatments and female sex were marginal predictors in our study. Predictors of CAM use have been reported in many previous studies,[7,8,19] and our data support that these predictors are similar to those in developed countries. With few exceptions, the literature indicates that highly educated patients and younger patients tend to use CAM.

Different predictors are associated with the different types of CAM used. In our surveyed population, the most frequently used CAM was natural products. Oral intake of medications is more likely in patients with lung, breast, and hepatobiliary cancers than in patients with head and neck, GI, and urogenital cancers, taking the sites of disease and the manners of progression into consideration. This is likely to be closely related to the use of CAM products because all of these are oral supplements. The predictors chemotherapy and disease site would therefore be related to the type of CAM used (ie, CAM products). Indeed, this hypothesis was suggested in a previous report in which predictors shifted to include chemotherapy after spirituality and psychotherapy or support groups were excluded from the types of CAM used.[7] Supplements (herbs or vitamins) were the main types of CAM used by the patients of that limited analysis. Unexpectedly, psychological factors such as anxiety and depression showed no relation to the use of CAM. However, these factors frequently fluctuate during the disease course, as we observed in the process of informed consent.[15] If the HADS had been administered when the patients initiated CAM use, the results would likely be different.

The majority of CAM users in this study took products such as mushrooms, herbs, and shark cartilage. Mushrooms (Agaricus and AHCC) were the most frequently used among the products. This was characteristic of our CAM users. The popular types of CAM in Western countries, such as spiritual practice, mind and body therapy, vitamins and special diet, and homeopathy, were rarely used in our country. Such mushrooms are sold in Japan as diet supplements. The providers emphasize their effects on boosting the immune system based on basic experimental findings using cultured human tumor cells, and advertise in many magazines or through the Internet with anecdotal reports of users. No reliable, well-designed clinical trials in cancer patients have been performed with these mushrooms. Nonetheless, many cancer patients used such products hoping for tumor growth suppression (67.1%) and cure (44.5%) rather than complementary effects (20.7%). These mushrooms and other similar natural products are generally expensive. This contributed to the high expenditure on CAM among our users (US $500 per month on average), compared with that in the Western countries (US $50 to $70 per month on average).[6] The main motive for CAM use was the recommendation of family members or friends. The population of patients who were willing to seek out CAM on their own was unexpectedly small, about one fourth of the users. It has been reported that support group dynamics influence individuals to be more likely to use CAM among breast cancer survivors.[6] In our study, many patients seemed to be motivated to use CAM by the recommendations of relatives. Friends also offered recommendations on CAM use.

Approximately one fourth of the users experienced positive effects from CAM, even though they all received conventional therapies previously or concurrently. Although it was unclear whether the positive effects were due to the CAM products or the conventional treatments, they nonetheless believed that the CAM was effective. In retrospect, we should have added a question to our questionnaire about the effectiveness of the conventional treatments received. Conversely, most patients reported no adverse reactions to CAM. However, the potential for harmful drug–CAM product interactions exists.[21-23] Herbs or vitamins can mask or distort the effects of conventional drugs.

This survey revealed that approximately 60% of users started CAM without obtaining enough information about it, and without informing their doctors. This proportion was similar to that in our previous survey.[12] The same issues have been pointed out in many reports from the United States and Europe.[7,24,25] In our survey, when patients consulted their physicians, 60.3% of the patients were told that they were free to continue using CAM or to stop, whereas 10.5% of the patients were told to continue using CAM and 11.3% of the patients were told to stop. These figures were also similar to the results in our previous study of clinical oncologists.[26] When oncologists were asked, 74% of them neither recommended nor prohibited the use of the products. Twelve percent of them encouraged their patients to use CAM products, and 6% told their patients to stop. It appears that a difficult situation for many oncologists emerges because of the lack of scientific information on CAM. However, physicians should acknowledge that the main reason (56.1%) patients did not inform their physicians of their CAM use was that the physicians did not ask them about it. These results indicate that better patient-physician communication and more reliable information on CAM products are needed. The prevalence of concurrent use of anticancer drugs and CAM products was considerably high (61.8%) in the present study. In our previous survey of oncologists, 83.9% of oncologists had administered anticancer drugs concurrently with CAM products.[12] Nevertheless, our present knowledge of interactions is incomplete, especially regarding anticancer drugs.[22,23] More research is urgently needed. Oncologists should be aware of these facts, and the use of CAM products should be determined before initiating chemotherapy, especially when using new investigational drugs.

A few limitations of this study must be acknowledged. First, the response rate was somewhat low compared with that of other studies, although it was greater than 50%, as discussed previously. Second, there is no definite evidence that our study population is representative of cancer patients in Japan. It seems impossible to select cancer patients randomly from throughout the entire country. We used the associations of CCs and PCUs in Japan as our survey source. Otherwise, such a large-scale survey could not be performed. These limitations have also been reported in the previous literature,[7,8] and unfortunately, inconsistencies in measures of CAM and differing patient populations and methodologies (ie, interviews *v* mailed surveys) limit the generalization of studies on CAM use.[3,4] Third, two questions were deleted from the questionnaire sent to one of the CCs. As a result, about 500 replies on education and religion were lacking. However, the analyses with or without the data from that center achieved similar results. Therefore, this did not significantly affect our conclusions.

Many cancer patients continue receiving oncologic care with standard therapies while pursuing CAM methods. A recent survey regarding the impact of the media and the Internet on cancer patients revealed that 71% of cancer patients actively searched for information, and 50% used the Internet.[27] The survey concluded that strategic efforts were needed to provide guidance for patients to help them better interpret such medical information. Oncologists need to be aware of the importance of this issue and of the rationale used to promote CAM. A great need for public and professional education regarding this subject is evident.

### Acknowledgment

We thank all of the physicians and patients who participated in this survey.

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

## *Appendix*

1. What is your disease?

_____

2. When was your disease diagnosed?

Year _____ month _____

3. How old are you?

_____ Years old

4. Please indicate your sex.

Male/Female

5. What about your present daily activity? Please tick the number below.

1) not limited at all, 2) somewhat limited with slight symptoms

3) bed rest more than 50% of the day, 4) bed rest all day

6. Please indicate your level of education.

1) junior high school, 2) high school, 3) college, 4) university, 5) other ( )

7. Are you committed to any religion?

Yes / No

8. Please indicate all treatments that you have received.

1) surgery, 2) chemotherapy, 3) hormonal therapy, 4) radiation, 5) palliative care

6) others ( )

9. Please indicate all treatments that you are currently receiving or will receive.

1) surgery, 2) chemotherapy, 3) hormonal therapy, 4) radiation, 5) palliative care

6) others ( )

10. Has your outlook on life been changed by suffering from this disease?

Yes / No (if yes, how? )

11. Did (Do) the treatments you received meet your needs?

Yes / No

12. Have you ever used complementary and alternative medicines (CAM)?

(*CAM includes various therapies as follows: Chinese herbal medicine, other CAM products such as Agaricus, Propolis, Chitosan, and shark cartilage, acupuncture, chiropractic, aromatherapy, homeopathy, imagery, yoga, thalassotherapy, hypnosis, etc.)

Yes / No

If 'yes', please continue to answer the questions below.

If 'no', the questions are finished here. Thank you very much for your cooperation.

---

13. When did you start CAM?

Year _____ month _____

14. Are you using CAM now?

Yes / No (if no, when did you stop? Year _____ month _____ )

15. What kind of CAM do (did) you use?

(continued on following page)

## *Appendix (continued)*

Please state all the names of cancer CAM you use (used), referring to cancer CAM notes*.

1. _____ 2. _____

3. _____ 4. _____

5. _____ 6. _____

16. Why did you start CAM? Please tick the number below.

1) recommended by family members or friends, 2) your own free will,

3) recommended from a physician, 4) other ( )

17. Did you obtain enough information about the efficacy and safety of CAM before you started it?

Yes / No

18. What did (do) you expect by using CAM? Multiple choices are allowed in this question.

1) cure, 2) suppress the progression, 3) improve the symptoms, 4) complementary effects to the present medicine, 5) other ( )

19. Did it work?

Yes / No / difficult to judge

20. If 'yes', how effective was it?

_____

21. Did you experience any detrimental effects from CAM?

Yes / No / difficult to judge

22. If 'yes', how detrimental was it?

_____

23. What was the cost to you? Please indicate the mean expenditure per month.

_____ Yen

24. Did your doctor or other medical professionals ask about CAM use?

Yes / No

25. Have you mentioned CAM use to your doctor?

Yes / No

26. If 'yes', how did your doctor respond?

1) encouraged you to continue using, 2) advised you to stop using,

3) was neutral about using (neither encouraged nor discouraged),

4) other ( )

27. If 'no', why did you not mention it to your doctor?

1) Because my doctor never asked me about the topic, 2) Because I thought my doctor would not understand, 3) Because I thought my doctor would disapprove of CAM use, 4) other ( )

28. Please answer the next question, if you have received or are receiving chemotherapy.

Have you ever used CAM products and anticancer drugs at the same time? CAM products include Chinese herbs, mushrooms, shark cartilage, etc. which are sold over the counter.

Yes / No

Thank you very much for your cooperation.

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# 各種がん検診から学ぶ精度管理—肺癌

中山富雄[1]・楠　洋子[1]・鈴木隆一郎[1]

**要旨**——我が国の市町村で行われている肺癌検診は，年間700万人以上が受診しているが，肺癌発見数は3600人弱（発見率51/10万人）で，受診者の増加に伴っていない．都道府県別にみると発見率は最大111.5，最小18.5でその差は最大6.2倍とバラツキは大きかった．市町村別に見ると，精検受診率や精検完了率が30%を下回る市町村も認められ，受診者数5000人以上の市町村の6.3%で過去2年間肺癌は1例も発見されていなかった．肺癌検診は外的精度管理の枠組みがないまま，急速に普及していった．市町村事業と位置づけられてからは，実施数や費用のみが問題とされており，精度については検討されておらず，受診者にも精度に関する情報は提供されていない．今後は対象者や精度管理指標の基準値を盛り込んだ運用指針の見直しと，第3者機関による検診成績の情報公開が必要である．（肺癌．2005;45:183-187）

**索引用語**——精度管理，肺癌，検診

# Quality Control in Lung Cancer Screening in Japan

*Tomio Nakayama*[1]*; Yoko Kusunoki*[1]*; Takaichiro Suzuki*[1]

***ABSTRACT*** —— The number of people screened for lung cancer has been increasing and now exceeds 7000000 per year in Japan, but the number of detected lung cancer is only about 3600 cases（detection rate; 0.051%）and has not been increasing. When detection rates were compared according to prefectures, in the detection rate varied by a factor of as much of 6.2 as large. In some municipalities, the rate of compliance and completion of diagnostic work-up fell below 30%. None of the lung cancer cases had been detected in the past two years in 6.3% of municipalities with 5000 or more screened people. Lung cancer screening has spread rapidly, though there is no framework for external quality control in Japan. Therefore, only the number of screening participants and the cost of screening are managed, the level of accuracy of the screening is not controlled in each municipalities offering the screening program. Thus screening participants are not offered a uniformly accurate of screening program. It is necessary to innovate guidelines including a quality control index, and to disclose information of the screening result by a central coordinative organization. (*JJLC.* 2005;45:183-187)

***KEY WORDS*** —— Quality control, Lung cancer, Screening

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我が国では，住民を対象とした肺癌検診は，すでに普及していた結核検診で撮影されたフィルムを利用し，高危険群に対して喀痰細胞診を併用する形で，昭和58年より開始された．喀痰細胞診については，日本臨床細胞学会からの資格認定を受けた細胞検査士と指導医が従事することが義務づけられた．しかしX線撮影と読影に関し

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**Table 1.** Quality Control Index of Lung Cancer Screening by a Screening System

| | Total | Hospital-based | Population-based |
|---|---|---|---|
| Positive rate | 2.7% | 3.2% | 2.6% |
| The rate of compliance of diagnostic work-up | 87.0% | 81.9% | 88.5% |
| The rate of completion of diagnostic work-up | 76.4% | 61.5% | 80.7% |
| Detection rates * | 48.0 | 51.6 | 47.2 |

*; per 100000 population.

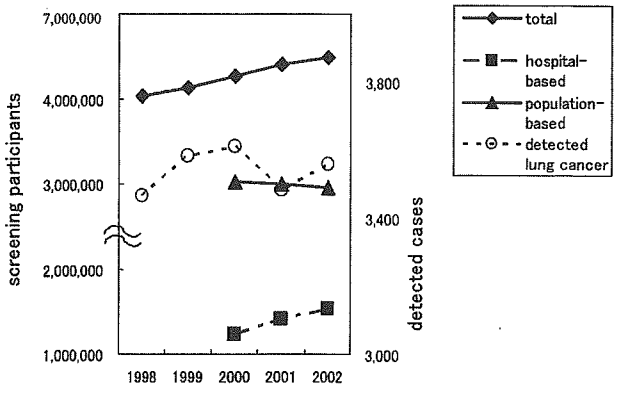


**Figure 1.** Changes in the numbers of participants in lung cancer screening and detected lung cancer.

ては，資格認定がなされないまま，全国的に普及し，現在にいたっている．

現状での肺癌検診の精度管理は，診療放射線技師や細胞検査士による内的精度管理の色彩が濃く，またその努力が対外的には評価されていない．一方外的精度管理の枠組みはなく，実施する市町村や，受診者に相当する一般の人たちにも，自らの身を守るための検診の精度を容易に知るすべはない．

今回，全国の市町村の検診実施成績が集計されている地域保健・老人保健事業報告を用いて，肺癌検診の精度の評価を試みた．

## 方　法

平成10～14年の地域保健・老人保健事業報告を用い，全国・都道府県別・市町村別に集計を行った．老人保健事業報告は，厚生労働省統計情報部の統計表データベースシステム（http://wwwdbtk.mhlw.go.jp/IPPAN/ipcart/sko_K_Nyuuryoku）よりダウンロードして，使用した．集団方式と個別方式の分離集計は，平成12年度から掲載されているため，過去3年分を利用した．都道府県別の発見率の比較には5年間の平均値を用いた．市町村別の集計は13年度から掲載されているので，過去2年分を使用した．市町村合併がこの2年間の間に行われているものは，合併後の市町村単位で集計した．

## 結　果

### 1. 全国集計での解析

肺癌検診の全受診者数は約700万人で，平成10～14年の5年間にかけても，約50万人の増加を認めているが，発見肺癌数は変動はあるものの，受診者の増加に伴っていない（Figure 1）．検診方式別に平成12年からの3年間の受診者数を比較すると集団方式はほぼ一定であったが，個別検診の増加が著しい．この3年間の平均の精度管理指標を見ると，要精検率2.7%，精検受診率87.0%，完了率76.4%，肺癌発見率は10万人あたり48.0人であった（Table 1）．個別方式では，発見率が51.6と若干集団方式よりも高いが，精検受診率が81.9%と低く，精検完了率は61.5%にすぎなかった．

性・年齢階級別に見ると，40歳代の女性受診者が約70万人存在するが，発見数は50人に満たなかった（Figure 2）．50歳代では受診者の4分の3が女性であった．60歳代から男性受診者数が増加し，発見数も男性が女性を上回った．要精検率は，胸部X線では男女とも年齢とともに増加し，発見率も増加した．一方喀痰細胞診の要精検率は年齢に全く関係なく，男性では肺癌の発見率が65歳以上で急増したが，女性では全年齢を通じてほとんど喀痰からは発見されていない．

### 2. 都道府県単位の解析

都道府県別の過去5年間の受診者数の推移を見ると，東日本では千葉・埼玉など東京のベッドタウンでの受診者数の急増が著しいが，西日本では漸減している府県も見られた．肺癌発見率を都道府県別に比較すると，最低で10万対20を切る府県と，最高で100を越える府県があり，その格差は6.2倍であった（Figure 3）．

個別方式と集団方式との間で，発見率を比較すると，集団方式の発見率は，各府県間であまり差がなかったが，個別方式では格差が極めて大きかった．

また要精検率とがん発見率を比較すると，個別方式では相関があり，集団方式では相関は全くなかった．精検受診率は個別方式で大きくバラツキがあり，集団方式ではほぼ全国一定であった．

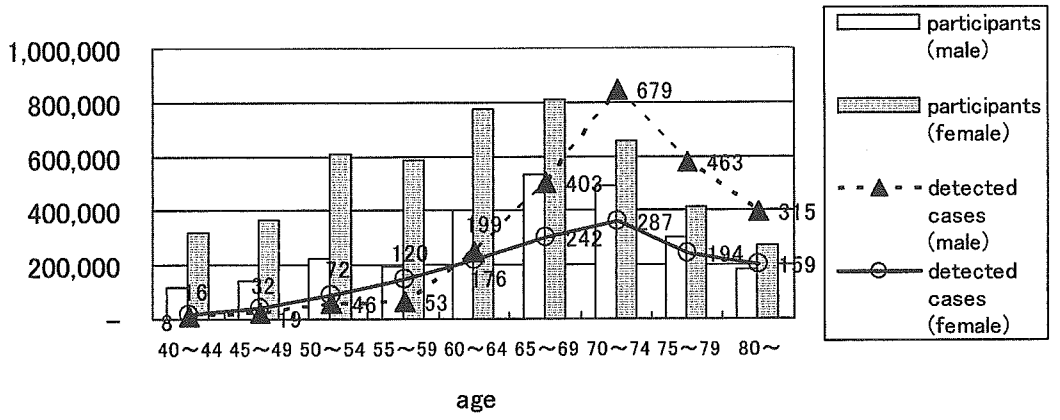


**Figure 2.** The number of screening participants and detected lung cancer by gender and age group.

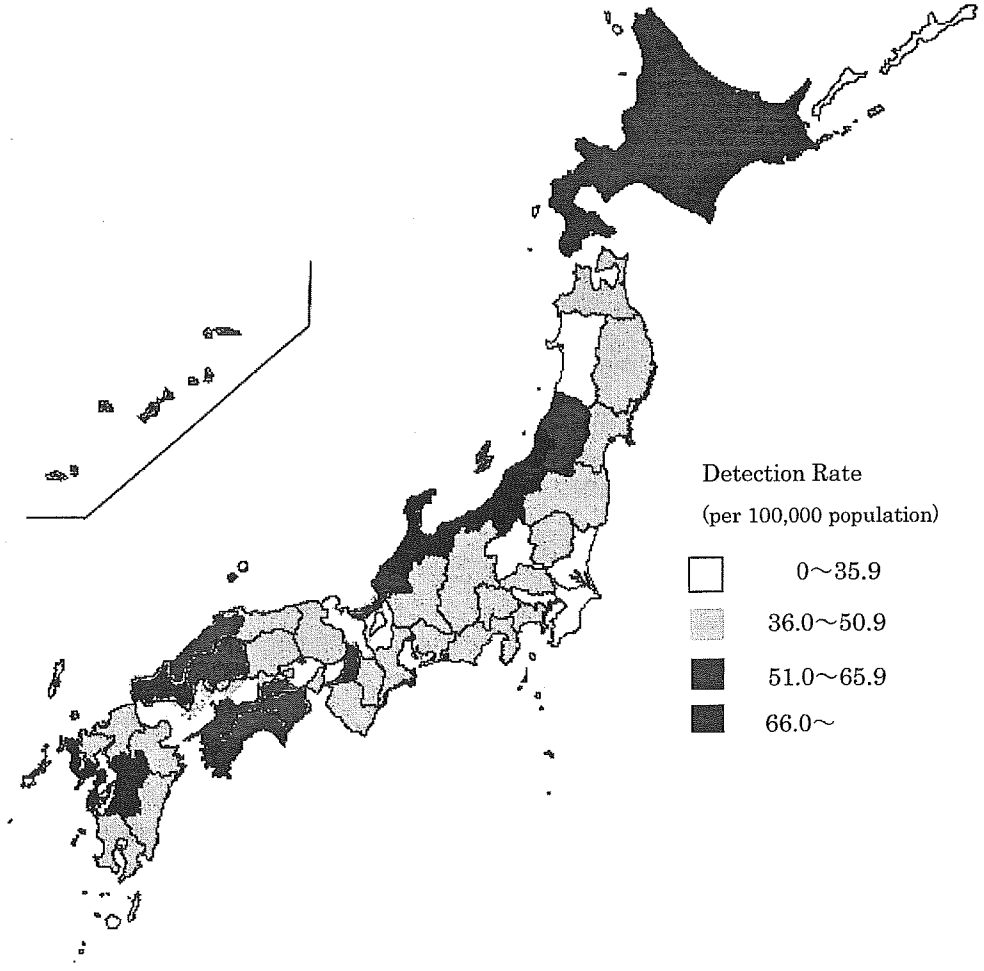


**Figure 3.** Detection rate of lung cancer by prefectures.

### 3. 市町村別集計

胸部X線の要精検率が0.5%を下回るあるいは，20%を上回る市町村が併せて6.4%存在した(Table 2)．精検受診率はおおむね80%を上回っていたが，30%を下回る市町村も存在し，10%を下回る市町村もわずかながら存在した．精検完了率は30%を下回る市町村が60市町村以上もあった．年間の平均受診者数を1000～5000人未満と5000人以上に分けて比較すると，5000人未満では

**Table 2.** Quality Control Index of Lung Cancer Screening by Municipalities

| Positive rate | | (%) | The rate of compliance of diagnostic work-up | | (%) | The rate of completion of diagnostic work-up | | (%) |
|---|---|---|---|---|---|---|---|---|
| 0- 0.4 | 173 | 5.7 | 0- 9.9 | 7 | 0.2 | 0- 9.9 | 27 | 0.9 |
| 0.5- 0.9 | 219 | 7.2 | 10.0-29.9 | 7 | 0.2 | 10.0-29.9 | 34 | 1.1 |
| 1.0- 4.9 | 2201 | 72.3 | 30.0-49.9 | 38 | 1.3 | 30.0-49.9 | 115 | 3.8 |
| 5.0- 9.9 | 369 | 12.1 | 50.0-79.9 | 534 | 17.8 | 50.0-79.9 | 1026 | 34.2 |
| 10.0-19.9 | 60 | 2.0 | 80.0-99.9 | 1767 | 58.9 | 80.0-99.9 | 1541 | 51.3 |
| 20.0- | 20 | 0.7 | 100.0 | 648 | 21.6 | 100.0 | 258 | 8.6 |

**Table 3.** Detection Rate of Lung Cancer Cases by the Number of Participants of Lung Cancer Screening in Each Municipalities

| Detection rate * | Participants (1000-4999) | (%) | Participants (5000-) | (%) |
|---|---|---|---|---|
| 0 | 392 | 25.3 | 18 | 6.3 |
| 1.0-29.9 | 214 | 13.8 | 78 | 27.2 |
| 30.0-49.9 | 353 | 22.8 | 77 | 26.8 |
| 50.0-69.9 | 167 | 10.8 | 57 | 19.9 |
| 70.0-99.9 | 216 | 13.9 | 41 | 14.3 |
| 100- | 207 | 13.3 | 16 | 5.6 |

*; per 100000 population.

**Table 4.** The Rate of Sputum Cytology Screening Participants in Chest X-ray Screening Participants in Each Municipalities

| | Male | (%) | Female | (%) |
|---|---|---|---|---|
| 0- 4.9 | 680 | 22.4 | 2669 | 88.2 |
| 5.0- 9.9 | 684 | 22.6 | 140 | 4.6 |
| 10.0-14.9 | 553 | 18.3 | 65 | 2.1 |
| 15.0-29.9 | 798 | 26.4 | 45 | 1.5 |
| 30.0-49.9 | 191 | 6.3 | 34 | 1.1 |
| 50.0-99.9 | 106 | 3.5 | 61 | 2.0 |
| 100- | 13 | 0.4 | 11 | 0.4 |

4分の1の市町村，5000人以上でも6.3%の市町村において過去2年間の肺癌発見率は0であった(Table 3)．また発見率100を越える市町村は，受診者数5000未満の市町村の13.3%を占めたが，5000以上の市町村では5.6%にすぎなかった．受診規模の小さい市町村で，発見率の高い精度の高い検診が行われていることが示された．

また喀痰細胞診を，女性受診者の50%以上に行っている市町村が72 (2.4%) あった (Table 4)．女性の喫煙率はせいぜい15%にすぎず，この実施率は喀痰細胞診の対象を受診者も市町村も理解していないものと考えられる．

## 考　察

現状の肺癌検診の精度の問題点はあまりにも多い．

他のがん検診に比べて，機材が普及しており，処理能力が高く，安価であることなどから，本検診は急速に普及した．しかし直近5年の成績では受診者は増加を続けながらも肝心の肺癌発見数が伴われていない．すなわち，内容（精度）が吟味されないまま，ただ漫然と事業が拡大されているにすぎない．平成10年以降，がん検診は一般財源化され，市町村の“事業”として位置づけられている．市町村では，緊縮財政と市町村合併の動きの中で，全事業の見直しが行われている．がん検診事業については，予算や実施数という面ではなく，精度という面での見直しが行われるべきであり，精度が確保できない検診に公費をつぎ込んで漫然と継続していくことは大いに問題である．日本肺癌学会編集の「肺癌取扱い規約」の「肺癌集団検診の手引き」には，肺癌検診の対象者が定義されている．しかし喀痰細胞診に関しては，受診者のほぼ全数に行われている市町村がいまだに存在し，学会編集の手引きが守られていない．胸部X線での見落としを喀痰細胞診で拾い上げることを目的としていると善意に解釈することも可能であるが，残念ながらほとんどがんは発見されていない．また対象者として「肺癌取扱い規約」に定義されていても，若年女性の受診者が多いことは，効率性の観点から問題である．40歳代の女性受診者における肺癌発見率は10万人あたり10人を下回っている．「肺癌集団検診の手引き」は，老健法導入時から20年間判定基準をのぞけばほとんど改訂されておらず，現状に即したものとは言い難い．

検診の方式については，受診者の利便性を鑑み，各種がん検診において集団方式から個別方式への転換が図られている．しかし今回の検討で明らかなように，肺癌検診においては，個別検診は精度のバラツキが大きすぎる．専門医療機関と提携し，精度管理委員会を設けて，熱心に個別方式を行っている一部の地区医師会のように，すぐれた精度を報告している地区も見られるが，ほとんど肺癌が発見されていない地区も多く見られる．読影医側の問題ももちろんあるが，医師会や市区町村に集計や精度管理を行う機能がないため，実際は肺癌が発見されていても，集計もれが生じるという問題も大きい．個別検診に関しては，担当医師会での事務局機能の整備を行っていただきたい．また集団方式に関しては，精度は全国ほぼ一定であったが，要精検率と発見率は相関していなかった．標準化発見比ではないため，正確な評価が難しいが，間接X線での限界ではないかと考えられる．

さて，これら肺癌検診に関わる様々な問題を生み出す原因は，肺癌検診を管理する指針や組織がないことに起因する．欧米では乳癌のマンモグラフィー検診や，子宮頸がん検診など有効性が確立された検診に関しては，法律を設け，中央で精度を管理したorganized screeningが行われ，高い受診率と精度が維持されている．しかし，日本では多種類の検診が市町村の自由裁量で行われ，希望する受診者に野放図に提供されており，結果として低い受診率と低い精度のまま放置されているのが現状である．各府県におかれた成人病管理指導協議会の部会が，その責務を担っているはずであるが，現在では，年1回(もしくは数年に1回)形式上開かれるだけのものになっている．その報告は，知事に対して行われているのであって，一般の住民に対してはほとんど公開されていない．現状の肺癌検診の精度に問題があることが，社会問題化されていないことから，協議会を主催する行政側もドラスティックな変化を起こしたくないのであろうが，透明性を確保するという現在の流れには全く即していない．

今後，肺癌検診の精度向上の対策としては，検診を管理するための運用指針を，国として新たに検討し，作成することが現実的な選択であろう．20年前に定められた現行の指針（肺癌集団検診の手引き）には，問題があることは，今回の検討で明らかであり，また市町村の現場では決して遵守されていないことも事実である．適切な対象者の選択や，精度管理指標の基準値，などを盛り込んだものを，作成することが必要であろう．また情報の徹底した公開を第3者機関で行うべきである．現状では老人保健事業報告という形で，実施成績は報告されており，厚生労働省統計情報部のデータベースからは市町村単位での成績もダウンロードすることは可能ではある．しかしその存在を知らない人が容易に探しだせる状況にはなく，また要精検率や発見率さえ計算されていない単純集計表のままである．このようなものではなく，専門家の解釈・解説付きの集計結果を，一般の住民が容易にアクセスし，理解できるものが必要である．

一般医療や行政サービスのすべての面で，見直しや情報公開が急速に進んでいる．肺癌検診は開始後約20年が経過したものの，いまだ検診黎明期と同じ様相で行われている．今後速やかな運営の見直しと情報公開が進むことを期待する．

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ORIGINAL REPORT

# Phase II Study of Radiotherapy Employing Proton Beam for Hepatocellular Carcinoma

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## ABSTRACT

### Purpose
To evaluate the safety and efficacy of proton beam radiotherapy (PRT) for hepatocellular carcinoma.

### Patients and Methods
Eligibility criteria for this study were: solitary hepatocellular carcinoma (HCC); no indication for surgery or local ablation therapy; no ascites; age ≥ 20 years; Zubrod performance status of 0 to 2; no serious comorbidities other than liver cirrhosis; written informed consent. PRT was administered in doses of 76 cobalt gray equivalent in 20 fractions for 5 weeks. No patients received transarterial chemoembolization or local ablation in combination with PRT.

### Results
Thirty patients were enrolled between May 1999 and February 2003. There were 20 male and 10 female patients, with a median age of 70 years. Maximum tumor diameter ranged from 25 to 82 mm (median, 45 mm). All patients had liver cirrhosis, the degree of which was Child-Pugh class A in 20, and class B in 10 patients. Acute reactions of PRT were well tolerated, and PRT was completed as planned in all patients. Four patients died of hepatic insufficiency without tumor recurrence at 6 to 9 months. Three of these four patients had pretreatment indocyanine green retention rate at 15 minutes of more than 50%. After a median follow-up period of 31 months (16 to 54 months), only one patient experienced recurrence of the primary tumor, and 2-year actuarial local progression-free rate was 96% (95% CI, 88% to 100%). Actuarial overall survival rate at 2 years was 66% (48% to 84%).

### Conclusion
PRT showed excellent control of the primary tumor, with minimal acute toxicity. Further study is warranted to scrutinize adequate patient selection in order to maximize survival benefit of this promising modality.

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## INTRODUCTION

Cirrhosis is found in more than 80% of patients with hepatocellular carcinoma (HCC). This precludes more than 70% of the patients from receiving potentially curative treatments, and also contributes eventually to fatal hepatic insufficiency and multifocal tumorigenesis.[1,2] Approximately 50% to 70% and 30% to 50% of 5-year overall survival was achieved with surgery including liver transplantation[3-6] and percutaneous local ablation,[7-9] respectively, for an adequately selected population of patients. However, no standard strategy has been established for patients with unresectable HCC at present.

Partial liver irradiation for HCC using 50 to 70 Gy of megavoltage x-ray with or without transarterial chemoembolizaztion (TACE) for 5 to 7 weeks has been widely applied during the last two decades. This resulted in response rates of 33% to 67%, with a median survival period of 13 to 19

months and 10% to 25% overall survival at 3 years.[10-12] Since 1985, proton radiotherapy (PRT) administered at a median dose of 72 cobalt gray equivalent ($Gy_E$) in16 fractions during 3 weeks with or without TACE, had been applied in more than 160 patients with HCC at the University of Tsukuba, resulting in a more than 80% local progression-free survival rate with 45% and 25% overall survival at 3 and 5 years, respectively.[13,14] The excellent depth-dose profile of the proton beam enabled us to embark on an aggressive dose escalation while keeping a certain volume of the noncancerous portion of the liver free from receiving any dose of irradiation. This single-institutional, single-arm, prospective study was conducted to confirm encouraging retrospective results of PRT for HCC using our newly installed proton therapy equipment.

## PATIENTS AND METHODS

### Patient Population

Patients were required to have uni- or bidimensionally measurable solitary HCC of $\leq$ 10 cm in maximum diameter on computed tomography (CT) and/or magnetic resonance (MRI) imaging. In addition, the following eligibility criteria were required: no history of radiotherapy for the abdominal area; no previous treatment for HCC within 4 weeks of inclusion; no evidence of extrahepatic spread of HCC; age $\geq$ 20 years; Zubrod performance status (PS) of 0 to 2; WBC count $\geq$ 2,000/$mm^3$; hemoglobin level $\geq$ 7.5 g/dL; platelet count $\geq$ 25,000/$mm^3$; and adequate hepatic function (total bilirubin $\leq$ 3.0 mg/dL; AST and ALT $<$ 5.0$\times$ upper limit of normal; no ascites). Patients who had multicentric HCCs were not considered as candidates for this study, except for those with the following two conditions: (1) multinodular aggregating HCC that could be encompassed by single clinical target volume; (2) lesions other than targeted tumor that were judged as controlled with prior surgery and/or local ablation therapy. Because a planned total dose would result in a significant likelihood of serious bowel complications, patients who had tumors abutting or invading the stomach or intestinal loop were excluded. The protocol was approved by our institutional ethics committee, and written informed consent was obtained from all patients.

### Pretreatment Evaluation

All patients underwent indocyanine green clearance test, and the retention rate at 15 minutes (ICG R15) was measured for the purpose of quantitative assessment of hepatic functional reserve. CBC, biochemical profile including total protein, albumin, total cholesterol, electrolytes, kidney and liver function tests, and serological testing for hepatitis B surface antigen and antihepatitis C antibody were done. C-reactive protein and tumor markers including alpha feto-protein and carcinoembryonic antigen were also measured. Chest x-ray was required to exclude lung metastasis. All patients were judged as unresectable by expert hepatobiliary surgeons in our institution, based on their serum bilirubin level, ICG R15, and expected volume of resected liver.[15] Gastrointestinal endoscopy was done to exclude active ulcer and/or inflammatory disease located at the stomach and the duodenum. All patients underwent abdominal ultrasonography, triphasic CT or MRI, CT during arteriography and arterial portography.[16] Diagnosis of HCC was based on radiographic findings on triphasic CT/MRI. Radiologic criteria for HCC definition were as follows: tumor showing high attenuation during hepatic arterial and portal venous phase indicating hypervascular tumor; tumor showing low attenuation during delayed phase indicating rapid wash-out of contrast media. Confirmatory percutaneous fine-needle biopsies were required for all patients unless they had radiologically compatible, postsurgical recurrent HCC. Tumors that broadly abut on the vena cava, portal vein, or hepatic vein that were associated with caliber changes and/or filling defects of these vessels, were tentatively defined as positive for macroscopic vascular invasion. One patient had visible tumor on fluoroscopy because of residual iodized oil contrast medium used in previous TACE. For the other 29 patients, one or two metallic markers (inactive Au grain of which the diameter and length were 1.1 mm and 3.0 mm, respectively) were inserted percutaneously at the periphery of the target tumor.

### Treatment Planning

PRT was performed with the Proton Therapy System (Sumitomo Heavy Industries Ltd, Tokyo, Japan), and treatment planning, with the PT-PLAN/NDOSE System (Sumitomo Heavy Industries Ltd). In this system, the proton beam was generated with Cyclotron C235 with an energy of 235 MV at the exit. Gross tumor volume (GTV) was defined using a treatment planning CT scan using X Vision Real CT scanner (Toshiba Co Ltd, Tokyo, Japan), and clinical target volume (CTV) and planning target volume (PTV) were defined as follows: CTV = GTV + 5 mm, and PTV = CTV + 3 mm of lateral, craniocaudal, and anteroposterior margins. Proton beam was delivered with two-beam arrangement to minimize irradiated volume of noncancerous liver using our rotating gantry system. The beam energy and spread-out Bragg peak[13] were fine-tuned so that 90% isodose volume of prescribed dose encompassed PTV. To evaluate the risk of radiation-inducing hepatic insufficiency, dose-volume histogram (DVH) was calculated for all patients.[17]

Scanning of CT images for both treatment planning and irradiation of proton beam were done during the exhalation phase using a Respiration-Gated Irradiation System (ReGIS). Our ReGIS during this study period was composed in the following manner: strain gauge, which converts tension of the abdominal wall into electrical respiratory signal, was put on the abdominal skin of the patient; gating signal triggering CT scanning or proton beam was generated during the exhalation phase.

### Treatment

The fractionation and dosage in this study were based on the results of a retrospective study at the University of Tsukuba. A total dose ranging from 50 $Gy_E$ in 10 fractions to 87.5 $Gy_E$ in 30 fractions (median, 72 $Gy_E$ in16 fractions) was administered without serious acute and late adverse events. All patients received PRT to a total dose of 76 $Gy_E$ for 5 weeks in 3.8-$Gy_E$ once-daily fractions, four fractions in a week using 150 to 190 MV proton beam. Relative biologic effectiveness of our proton beam was defined as 1.1. No concomitant treatment (eg, TACE, local ablation, systemic chemotherapy) was allowed during and after the PRT, unless a treatment failure was detected. Verification of patient set-up was done in each fraction using a digital radiography subtraction system. In this system, fluoroscopic images obtained at daily set-up were subtracted by the original image that was taken at the time of treatment planning. Position of the patient couch was adjusted to overlap the diaphragm, inserted metallic markers, and bone landmarks on the original position at the end of the exhalation phase.

PRT was administered 4 days a week, mainly Monday to Thursday, and Friday was reserved for maintenance of the PRT system. Predefined adverse reaction of PRT was dermatitis, pneumonitis, hepatic insufficiency, and gastrointestinal ulcer and/or bleeding. If one of these reactions of grade 3 or higher, or unexpected reactions of grade 4 or higher were observed in three patients, further accrual of patients was defined to be stopped. No further PRT was allowed when grade 4 hematologic toxicity or any of the toxicities of grade 3 or higher were observed at the digestive tract or lung. PRT was delayed up to 2 weeks until recovery when an acute nonhematologic toxicity of grade 3 or higher, other than that described above, was observed. However, when only an elevation of liver enzymes was observed without manifestation of clinically significant signs and symptoms, PRT was allowed to be continued according to the physician's judgment.

### Outcomes

It has been reported that the tumor, although achieving a complete response, persisted over a long period, ranging from 3 weeks to 12+ months after the completion of PRT.[18] Therefore, a local progression-free survival rate at 4 weeks after the end of PRT was adopted as the primary end point of this study, where an event was defined as progression of the primary tumor with size increase of more than 25%, in order to facilitate an interim analysis as described in the Statistical Design section below. Assessment of primary tumor response using CT and/or MRI was performed 4 weeks after the completion of PRT. Overall survival and disease-free survival rates were also evaluated as secondary end points. Death of any cause was defined as an event in calculation of overall survival, whereas tumor recurrences at any sites or patient deaths were defined as events for disease-free survival. Adverse events were reviewed weekly during the PRT by means of physical examination, CBC, liver function test, and the other biochemical profiles as indicated. The severity of adverse events was assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. After completion of PRT, reviews monitoring disease status, including CT and/or MRI examinations and long-term toxicity were done at a minimum frequency of once every 3 months.

### Statistical Design

The null hypothesis of a true local progression-free rate of 50% or lower was based on average results of photon radiotherapy reported from Japan, in which each study accumulated approximately 20 patients.[11,12] This was tested against the alternative hypothesis of a true rate of 80% or higher with an $\alpha$ level of 5% and a power of 80%, which required 30 patients according to the method by Makuch and Simon.[19] If fewer than five patients experienced local progression-free status within 4 weeks postirradiation at the end of first nine enrollments, the trial would be stopped. Otherwise, if more than 24 patients remained locally progression-free among the total of 30 patients, this would be sufficient to reject the null hypothesis and conclude that PRT warrants further study. Time-to-event analyses were done using Kaplan-Meier estimates, and 95% CIs were calculated. The difference of time-to-event curve was evaluated with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model.

## RESULTS

### Patients

Thirty patients were enrolled between May 1999 and February 2003. Patient characteristics at the start of PRT are

**Table 1.** Characteristics of 30 Enrolled Patients

| Characteristic | Patients No. | Patients % |
|---|---|---|
| Age, years | | |
| Median | 70 | |
| Range | 48-87 | |
| Sex | | |
| Male | 20 | 67 |
| Female | 10 | 33 |
| ECOG performance status | | |
| 0-1 | 29 | 97 |
| 2 | 1 | 3 |
| Clinical stage (2) | | |
| I | 9 | 30 |
| II | 19 | 63 |
| III | 2 | 7 |
| Positive viral markers | | |
| Hepatitis B virus | 3 | 10 |
| Hepatitis C virus | 26 | 87 |
| Both | 1 | 3 |
| Child-Pugh classification | | |
| A | 20 | 67 |
| B | 10 | 33 |
| C | 0 | 0 |
| Pretreatment indocyanine green clearance at 15 minutes, % | | |
| < 15 | 0 | 0 |
| 15-40 | 21 | 70 |
| 40-50 | 5 | 17 |
| > 50 | 4 | 13 |
| Tumor size, mm | | |
| Median | 45 | |
| Range | 25-82 | |
| 20-50 | 19* | 63 |
| > 50 | 11 | 37 |
| Macroscopic vascular invasion | | |
| Yes | 12 | 40 |
| No | 18 | 60 |
| Morphology of primary tumor | | |
| Single nodular | 26 | 87 |
| Multinodular, aggregating | 1 | 3 |
| Diffuse | 2 | 7 |
| Portal vein tumor thrombosis | 1* | 3 |
| Serum alpha-fetoprotein level, ng/mL | | |
| < 300 | 21 | 70 |
| ≥ 300 | 9 | 30 |
| Histology | | |
| Well-differentiated | 10 | 33 |
| Moderately differentiated | 14† | 47 |
| Poorly differentiated | 2 | 7 |
| Differentiation not specified | 3 | 10 |
| Negative (radiologic diagnosis only) | 1 | 3 |
| Prior treatment | | |
| No | 13 | 43 |
| Recurrence | 6 | 20 |
| Local ablation/TACE | 11 | 37 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization.
*Includes one patient whose gross target volume was tumor thrombosis at the posterior branch of right portal vein as a result of postsurgical recurrence.
†Includes two patients with histological diagnoses that were defined in previous surgery.

listed in Table 1. All patients had underlying liver cirrhosis with an initial ICG R15 value of ≥ 15%. Thirteen patients received PRT as a first treatment for their HCC. Six patients had postsurgical recurrences, and 11 received unsuccessful local ablation and/or TACE to the targeted tumor before PRT. Histologic confirmation was not obtained in one patient who had tumor with typical radiographic features compatible with HCC. Vascular invasion was diagnosed as positive in 12 patients. Three patients had HCC of ≤ 3 cm in diameter; however, they were not considered as candidates for local ablation therapy because of tumor locations that were in close proximity to the great vessels or the lung.

### Adverse Events

All patients completed the treatment plan and received 76 $Gy_E$ in 20 fractions of PRT with a median duration of 35 days (range, 30 to 64 days). Prolongation of overall treatment time of more than 1 week occurred in four patients: three were due to availability of the proton beam, and one because of fever associated with grade 3 elevation of total bilirubin that spontaneously resolved within 1 week. Adverse events within 90 days from commencement of PRT are listed in Table 2. Decrease of blood cell count was observed most frequently. A total of 10 patients experienced transient grade 3 leukopenia and/or thrombocytopenia without infection or bleeding necessitating treatment. Of note, eight of them already had leuko- and/or thrombocytopenia, which could be ascribable to portal hypertension, before commencement of PRT corresponding to grade 2 in terms of the NCI-CTC criteria. Because none of the five patients experiencing grade 3 elevation of transaminases showed clinical manifestation of hepatic insufficiency and maintained good performance status, PRT was not discontinued. Nevertheless, these events spontaneously resolved within 1 to 2 weeks.

Development of hepatic insufficiency within 6 months after completion of PRT was defined as proton-inducing hepatic insufficiency (PHI), and this was observed in eight patients. Causal relationship between PHI and several factors are described separately below. One patient developed transient skin erosion at 4 months that spontaneously resolved within 2 months. Another patient developed painful subcutaneous fibrosis at 6 months that required nonsteroidal analgesics for approximately 12 months thereafter. Both of these skin changes developed at the area receiving ≥ 90% of the prescribed dose because the targeted tumors were located at the surface of the liver adjacent to the skin. However, they remained free from refractory ulcer, bleeding, or rib fracture.

There were no observations made of gastrointestinal or pulmonary toxicity of grade 2 or greater in all patients. In addition, after percutaneous insertion of metallic markers, no serious adverse events, including bleeding or tumor seeding along the needle tracts, were observed.

**Table 2.** Adverse Events Within 90 Days From the Start of Proton Beam Radiotherapy

| Grade | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Leukopenia | 7 | 2 | 13 | 8 | 0 |
| Thrombocytopenia | 2 | 6 | 15 | 7 | 0 |
| Total bilirubin | 20 | 2 | 7 | 1 | 0 |
| Transaminases | 4 | 8 | 13 | 5 | 0 |
| Nausea/anorexia | 23 | 7 | 0 | 0 | 0 |
| Overall (maximum grade) | 0 | 4 | 14 | 12 | 0 |

### Tumor Control and Survival

At the time of analysis on November 2003, 12 patients had already died because of intrahepatic recurrence of HCC in seven, distant metastasis in two, and hepatic insufficiency without recurrence in three. Eleven of these 12 patients had been free from local progression until death; the durations ranged from 6 to 41 months (median, 8 months). One patient who had a single nodular tumor of 4.2 cm in diameter experienced local recurrence at 5 months and subsequently died of multifocal intrahepatic HCC recurrence. Otherwise, 18 patients were alive at 16 to 54 months (median, 31 months) without local progression. A total of 24 patients achieved complete disappearance of the primary tumor at 5 to 20 months (median, 8 months) post-PRT. Five had residual tumor mass on CT and MRI images for 3 to 35 months (median, 12 months) until the time of death (n = 4) or until last follow-up at 16 months (n = 1). As a whole, 29 of 30 enrolled patients were free from local progression until death or last follow-up, and the local progression-free rate at 2 years was 96% (95% CI, 88% to 100%). Tumor regression was associated with gradual atrophy of the surrounding noncancerous portion of the liver that initially suffered from radiation hepatitis,[20] as shown in Figure 1.

A total of 18 patients developed intrahepatic tumor recurrences that were outside of the PTV at 3 to 35 months (median, 18 months) post-PRT. Five of these occurred within the same segment of the primary tumor. Eight patients received TACE, and four received radiofrequency ablation for recurrent tumors; however, six did not receive any further treatment because of poor general condition in three and refusal in three. Five died without intrahepatic recurrence. Seven patients remained recurrence-free at 16 to 39 months (median, 35 months). Actuarial overall survival rates were 77% (95% CI, 61% to 92%), 66% (95% CI, 48% to 84%), and 62% (95% CI, 44% to 80%), and disease-free survival rates were 60% (95% CI, 42% to 78%), 38% (95% CI, 20% to 56%), and 16% (95% CI, 1% to 31%) at 1, 2, and 3 years, respectively (Fig 2).

### Correlation of Survival With Prognostic Factors

Overall survival was evaluated according to 10 factors as listed in Table 3. Univariate analyses revealed that factors

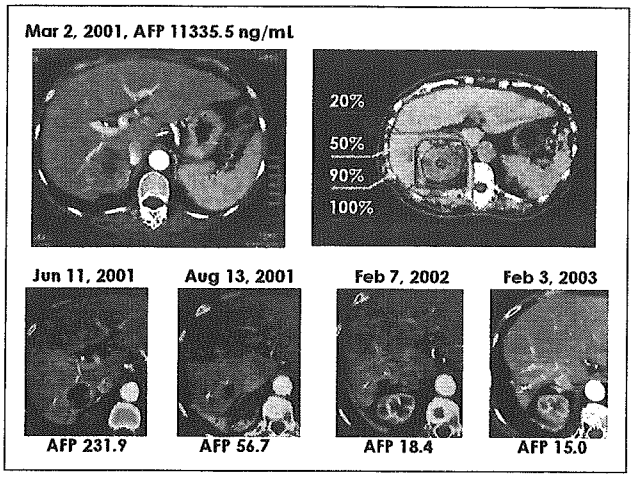


**Fig 1.** Case presentation: 70-year-old woman who received proton radiotherapy of 76 Gy in 20 fractions for 37 days from April 2, 2001, for her tumor located at the right posterior segment of the liver (left upper panel). Dose distribution was demonstrated in the right upper panel. Two portals from posterior and right lateral directions were used.

related to functional reserve of the liver and tumor size had significant influences on overall survival ($P < .05$). Liver function was the only independent and significant prognostic factor by multivariate analysis, as presented in Table 3. When clinical stage or Child-Pugh classification was substituted for ICG R15 as a covariate for liver function, the results of multivariate analyses were unchanged (data not shown). Overall survival according to pretreatment ICG R15 is shown in Figure 3.

### *Estimation of the Risk of Proton-Inducing Hepatic Insufficiency by Dose-Volume Histogram Analysis*

Eight patients developed PHI and presented with ascites and/or asterixis at 1 to 4 months after completion of PRT, without elevation of serum bilirubin and transaminases in the range of more than 3× the upper limit of normal. Of these, four died without evidence of intrahepatic tumor recurrence at 6 to 9 months; three died with recurrences of HCC at 4, 8, and 22 months; and one was alive at 41 months without tumor recurrence. DVH for hepatic noncancerous portions (entire liver volume minus gross tumor volume) was drawn according to pretreatment ICG R15 values (Fig 4A to C). The results showed that all of the nine patients with ICG R15 less than 20% were free from PHI and alive at 14 to 54 months. Three of the four patients with pretreatment ICG R15 ≥ 50% experienced fatal PHI without evidence of HCC recurrence, and another patient died of PHI with intrahepatic and systemic dissemination of HCC at 4 months. Among patients whose ICG R15 values ranged from 20% to 50%, all of the four patients whose percentage of hepatic noncancerous portions receiving ≥ 30 $Gy_E$ ($V_{30}$%) exceeded 25% developed PHI. On the other hand, none of the patients whose $V_{30}$% was less than 25% experienced PHI, as shown in Figure 4B ($P = .044$, Mann-Whitney $U$ test). Three-year overall survival for patients with either the $V_{30}$% ≥ 25% or ICG R15 ≥ 50% (n = 9) was 22% (95% CI, 0% to 50%), whereas it was 79% (95% CI, 60% to 98%) for the remaining 21 patients with favorable risk ($P = .001$).

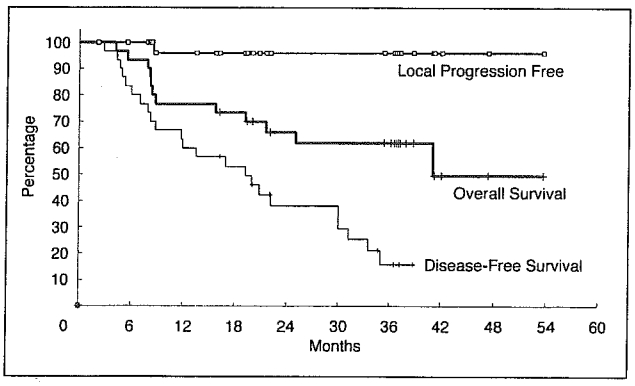


**Fig 2.** Kaplan-Meier estimate of local progression-free, overall, and disease-free survival rates for all 30 patients enrolled.

## DISCUSSION

The principal advantage of PRT lies in its possibility of aggressive dose escalation without prolongation of treatment duration in order to improve local control rate. The liver will be the most appropriate organ for this approach because it has a unique characteristic of developing compensatory hypertrophy when a part of this organ suffers from permanent damage. This study showed that the local control rate of PRT alone for patients with advanced HCC was consistent, as previously reported.[14] Slow regression of tumor volumes associated with gradual atrophy of surrounding noncancerous liver tissue was also in agreement with a previous report.[20] No serious gastrointestinal toxicity occurred, with careful patient selection performed in order to exclude these structures from PTV receiving high PRT dose. Eligibility criteria as to blood cell count in this study were eased up considerably in order to test the safety of PRT for patients with cirrhosis associated with portal hypertension. Nevertheless, no patients experienced serious sequelae relating to leukopenia or thrombocytopenia, which were the most frequently observed adverse events during PRT. All patients were able to complete their PRT basically in an outpatient clinic. Therefore we submit that the safety, accuracy, and efficacy of PRT administering 76 $Gy_E$/5 weeks using our newly installed Proton Therapy System and ReGIS for selected patients with advanced HCC has been confirmed.

Multivariate analysis suggested that the the functional reserve of the liver had significant influence on overall survival. Recent prospective series of untreated patients with