14. Thor AD, Edgerton SM, Jones FE. Subcellular localization of the HER4 intracellular domain, 4ICD, identifies distinct prognostic outcomes for breast cancer patients. Am J Pathol 2009; 175: 1802–1809.
15. Naresh A, Long W, Vidal GA et al. The ERBB4/HER4 intracellular domain 4ICD is a BH3-only protein promoting apoptosis of breast cancer cells. Cancer Res 2006; 66: 6412–6420.
16. Eralp Y, Derin D, Ozluk Y et al. MAPK overexpression is associated with anthracycline resistance and increased risk for recurrence in patients with triple-negative breast cancer. Ann Oncol 2008; 19: 669–674.
17. Ellis MJ, Lin L, Crowder R et al. Phosphatidyl-inositol-3-kinase alpha catalytic subunit mutation and response to neoadjuvant endocrine therapy for estrogen receptor positive breast cancer. Breast Cancer Res Treat 2010; 119: 379–390.
18. Ginestier C, Hur MH, Charafe-Jauffret E et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 2007; 1: 555–567.
19. Fu P, Ibusuki M, Yamamoto Y et al. Insulin-like growth factor-1 receptor gene expression is associated with survival in breast cancer: a comprehensive analysis of gene copy number, mRNA and protein expression. Breast Cancer Res Treat 2011; 130: 307–317.
20. Derin D, Eralp Y, Ozluk Y et al. Lower level of MAPK expression is associated with anthracycline resistance and decreased survival in patients with hormone receptor negative breast cancer. Cancer Invest 2008; 26: 671–679.
21. Aleskandarany MA, Rakha EA, Ahmed MA et al. Clinicopathologic and molecular significance of phospho-Akt expression in early invasive breast cancer. Breast Cancer Res Treat 2011; 127: 407–416.

*Annals of Oncology* 25: 1979–1987, 2014
doi:10.1093/annonc/mdu364
Published online 28 July 2014



# Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study

X. Pivot[1]*, J. Gligorov[2,3], V. Müller[4], G. Curigliano[5], A. Knoop[6], S. Verma[7], V. Jenkins[8], N. Scotto[9], S. Osborne[9] & L. Fallowfield[8] on behalf of the PrefHer Study Group

[1]*Department of Medical Oncology, University Hospital Jean Minjoz, Besançon;* [2]*Medical Oncology Department, APHP Hôpital Tenon, Paris;* [3]*UPMC, Institut Universitaire de Cancérologie, Paris, France;* [4]*Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [5]*Early Drug Development for Innovative Therapies Division, European Institute of Oncology, Milan, Italy;* [6]*Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark;* [7]*Division of Medical Oncology, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada;* [8]*Sussex Health Outcomes Research & Education in Cancer (SHORE-C), Brighton and Sussex Medical School, University of Sussex, Falmer, UK;* [9]*Global Medical Affairs, F. Hoffmann-La Roche Ltd, Basel, Switzerland*

*Received 10 May 2014; revised 16 July 2014; accepted 24 July 2014*

**Background:** Patients with HER2-positive early breast cancer (EBC) preferred subcutaneous (s.c.) trastuzumab, delivered via single-use injection device (SID), over the intravenous (i.v.) formulation (Cohort 1 of the PrefHer study: NCT01401166). Here, we report patient preference, healthcare professional satisfaction, and safety data pooled from Cohort 1 and also Cohort 2, where s.c. trastuzumab was delivered via hand-held syringe.

**Patients and methods:** Patients were randomized to receive four adjuvant cycles of 600 mg fixed-dose s.c. trastuzumab followed by four cycles of standard i.v. trastuzumab, or vice versa. The primary endpoint was overall preference proportions for s.c. or i.v., assessed by patient interviews in the evaluable ITT population.

**Results:** A total of 245 patients were randomized to receive s.c. followed by i.v. and 243 received i.v. followed by s.c. (evaluable ITT populations: 235 and 232 patients, respectively). s.c. was preferred by 415/467 [88.9%; 95% confidence interval (CI) 85.7–91.6; $P < 0.0001$; two-sided test against null hypothesis of 65% s.c. preference]; 45/467 preferred i.v. (9.6%; 95% CI 7–13); 7/467 indicated no preference (1.5%; 95% CI 1–3). Clinician-reported adverse events occurred in 292/479 (61.0%) and 245/478 (51.3%) patients during the pooled s.c. and i.v. periods, respectively ($P < 0.05$; $2 \times 2\ \chi^2$); 16 patients (3.3%) in each period experienced grade 3 events; none were grade 4/5.

*Correspondence to:* Prof. Xavier Pivot, Department of Medical Oncology, University Hospital Jean Minjoz, 1 Boulevard Fleming, Besançon Cedex 03, 25030 France. Tel: +33-381-669-212; Fax: +33-381-668-858; E-mail: xavier.pivot@univ-fcomte.fr

JJCO Japanese Journal of Clinical Oncology

*Jpn J Clin Oncol 2014;44(7)632–640*
*doi:10.1093/jjco/hyu059*
Advance Access Publication 12 May 2014

# Current Status of Medical Oncology in Japan—Reality Gleaned from a Questionnaire Sent to Designated Cancer Care Hospitals†

**Yuichi Takiguchi[1,*], Ikuo Sekine[1], Shunichiro Iwasawa[1], Ryota Kurimoto[1], Emiko Sakaida[2] and Kenji Tamura[3]**

[1]Department of Medical Oncology, Graduated School of Medicine, Chiba University, Chiba, [2]Department of Hematology, Graduated School of Medicine, Chiba University, Chiba and [3]Department of Medical Oncology, Chuo Hospital, National Cancer Center, Tokyo, Japan

*For reprints and all correspondence: Yuichi Takiguchi, Department of Medical Oncology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8670, Japan. E-mail: takiguchi@faculty.chiba-u.jp
†The work was performed at Department of Medical Oncology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8670, Japan

Received March 10, 2014; accepted April 10, 2014

**Objective:** Medical oncology in Japan has a relatively short history, with specialist certification starting in 2006, resulting in 867 certified medical oncologists as of 2014. Although the national government has appointed 397 Designated Cancer Care Hospitals, little is known about the actual situations of medical oncology services at these institutions.
**Methods:** Questionnaires regarding the presence of a medical oncology department, the number of physicians in the department, the presence of certified medical oncologists and the degree of the medical oncologists' responsibilities for drug therapies in adults with solid cancers were sent to all 397 institutions between 21 January and 1 May 2013.
**Results:** The response rate was 68.0%. Among the responses, 39.4% of the institutions had medical oncology departments with a median of three physicians. Most of the medical oncology departments were primarily responsible, as evaluated according to patient number, for the treatment of limited disease categories. The medical oncologists were significantly more responsible for molecular-targeted therapy than for chemotherapy in head and neck cancer or for cytokine therapy in renal cell carcinoma. The wide variety of adverse events associated with molecular-targeted therapy might have enhanced the roles of medical oncologists. As the proportion of hospitals with a medical oncology department increased according to the number of certified medical oncologists working at the institution, cultivating medical oncologists seems to be an urgent task for advancing medical oncology in Japan.
**Conclusions:** The present study provides fundamental data for the future development of medical oncology in Japan. The present study is to uncover the current situation of medical oncology in Japan.

*Key words: medical oncology – drug therapy – Designated Cancer Care Hospital – questionnaire – board certification*

## INTRODUCTION

Medical oncologists specialize in the diagnosis of cancer and its treatment using drug therapies, including chemotherapy, hormonal therapy, biological therapy and molecular-targeted therapy, whereas an update definition is still proposed (1). This medical field was established in the USA with the foundation of the American Society of Clinical Oncology in 1964, followed by the start of board certification in 1973. Many of the European countries have also developed medical oncology in similar styles with the emphasis on multidisciplinary team

healthcare professionals (2,3). On the other hand, the Japanese Society of Medical Oncology (JSMO) was founded in 2002 and began certifying medical oncologists in 2006, resulting in the certification of 867 medical oncologists throughout Japan as of February 2014. Certificates are issued after the completion of training in medical oncology for at least 5 years, including the completion of a 2-year training course complying with the original or revised ASCO/ESMO program (4–6), followed by document screening, including case reports for 50 patients undergoing drug therapy as well as paper and oral examinations; the average pass rate is ~60%. Because of its short history, however, the majority of currently certified medical oncologists have transferred from other fields of specialty, such as pulmonology, gastrointestinal medicine or hematology. Therefore, although certified medical oncologists are, in principal capable of using drug therapy for the treatment of patients with any type of cancer, the reality of practice in this field may differ from the ideology.

On the other hand, the government implemented the Cancer Control Act in 2006, followed by the enforcement of a more concrete act, the Basic Plans to Promote Cancer Control, to facilitate cancer control in Japan in response to an urgent nationwide petition addressed to the government (7). During these processes, each local prefectural government reviewed applications from institutions and recommended several of these hospitals to the Ministry of Health, Labor and Welfare; the Ministry finally appointed 397 hospitals that met the defined conditions of a Designated Cancer Care Hospital. Although these hospitals are obliged to provide comprehensive medical care for patients with cancer and for their families, their specialty is not necessarily limited to cancer. These hospitals are distributed nationwide to provide cancer control throughout Japan. Designated Cancer Care Hospitals are key institutions in overcoming cancer and are expected to have a medical oncology department with chemotherapy specialists, ideally JSMO-certified medical oncologists, who are capable of treating patients with any type of cancer. However, little is known about the actual situations of medical oncology departments in Designated Cancer Care Hospitals. Therefore, a questionnaire-based investigation was conducted to elucidate the current situations of medical oncology departments in Designated Cancer Care Hospitals in Japan.

## PATIENTS AND METHODS

A three-page questionnaire, along with a cover letter describing the purpose of the present study, was sent to all 397 Designated Cancer Care Hospitals. The questionnaire was addressed to the 'principal person in charge of cancer practice' at each institution. The first mailing was performed on 21 January 2013, with returns obtained from 203 institutions as of 26 March 2013, at which time the second mailing was performed for the remaining institutions. Finally, 270 institutions had returned their answers as of 1 May 2013, resulting in a response rate of 68.0%.

The questionnaire asked questions regarding the presence of a Department of Medical Oncology in the hospital, the number of staff-physicians in the department if present, the presence of JSMO-certified medical oncologists along with their number, and the primarily, secondarily and tertiarily responsible departments, in terms of patient number, for the use of chemotherapy, molecular-targeted therapy, hormonal therapy and cytokine therapy for each of 21 specific cancers. In the cover letter and questionnaire sheet, the Department of Medical Oncology was defined as an internal medical department responsible for the cross-sectional management of non-organ-specific cancers. Also in the cover letter and questionnaire, only data exclusively limited to adult solid cancers were requested. All replies were requested to include the name of the institution and the responding person. At the time of the questionnaire, the use of bevacizumab for glioblastoma and ovarian cancer was available without government approval, whereas immunotherapy and molecular-targeted therapy for melanoma were not available. The use of pazopanib for soft-tissue sarcoma was approved in November 2012 in Japan.

The data analysis used to uncover the role of medical oncology departments was conducted using two methods. First, the proportion of institutions in which a given department of the institution was primarily, secondarily and tertiarily responsible, in terms of patient number, for the use of a given therapeutic modality for each disease was calculated. The proportions of institutions in which the medical oncology department was primarily responsible for different therapeutic modalities, that is, cytotoxic, molecular-targeted, hormonal or cytokine therapies, for a given disease were then compared using a Student *t*-test, and differences with a $P$ value of $<0.05$ (two-tailed) were judged as significant. Second, 18 out of 21 diseases (excluding extragonadal germ cell tumors, cancers of unknown primary site and soft-tissue sarcoma) were further classified into nine groups: (i) malignant brain tumors, (ii) head and neck cancers, (iii) gastrointestinal and hepatobiliary cancers (including esophageal, gastric, colorectal, pancreatic and hepatobiliary cancers), (iv) lung cancers, (v) breast cancer, (vi) gynecological cancers (including uterine cancers consisting of cervical and endometrial cancers and ovarian cancers), (vii) urological cancers (including renal, bladder, prostate and testis cancers), (viii) skin melanoma and (ix) hematological cancers (including lymphomas and myeloma). Then, the numbers of categorized groups to which the medical oncology department in a given institution was primarily responsible, in terms of patient number, for the use of chemotherapy or molecular-targeted therapy were analyzed.

## RESULTS

### Presence of Medical Oncology Departments and JSMO-certified Medical Oncologists

Overall, 107 of the 270 institutions (39.4%) had medical oncology departments, with a median of three physicians

working in the department (ranging from 1 to 35). The distribution of the number of physicians working in the department is shown in Fig. 1. Overall, 156 of the 267 institutions (58.4%; three institutions did not answer this specific question) responded that they had currently employed JSMO-certified medical oncologists, with a median of one certified medical oncologist working in the department (ranging from 0 to 24). When limited to institutions with medical oncology departments, 92 of the 107 institutions (86.0%) had employed JSMO-certified medical oncologists, with a median number of 2 (ranging from 0 to 24). The proportions of institutions with medical oncology departments according to the number of JSMO-certified medical oncologists are shown in Fig. 2.

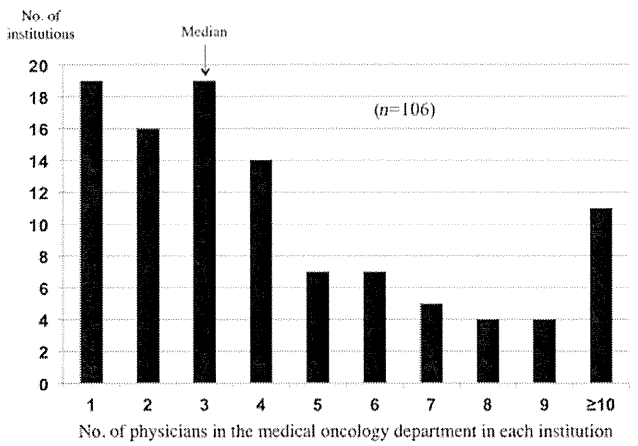



**Figure 1.** Distribution of the number of physicians in medical oncology departments in Designated Cancer Care Hospitals in Japan. Among 397 hospitals, 270 hospitals responded to the questionnaire; 107 of these hospitals answered that they had a medical oncology department. One institution did not disclose the number of physicians in the department.

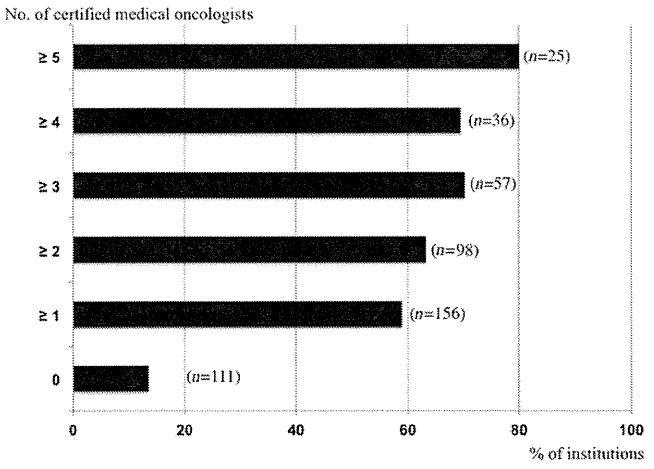


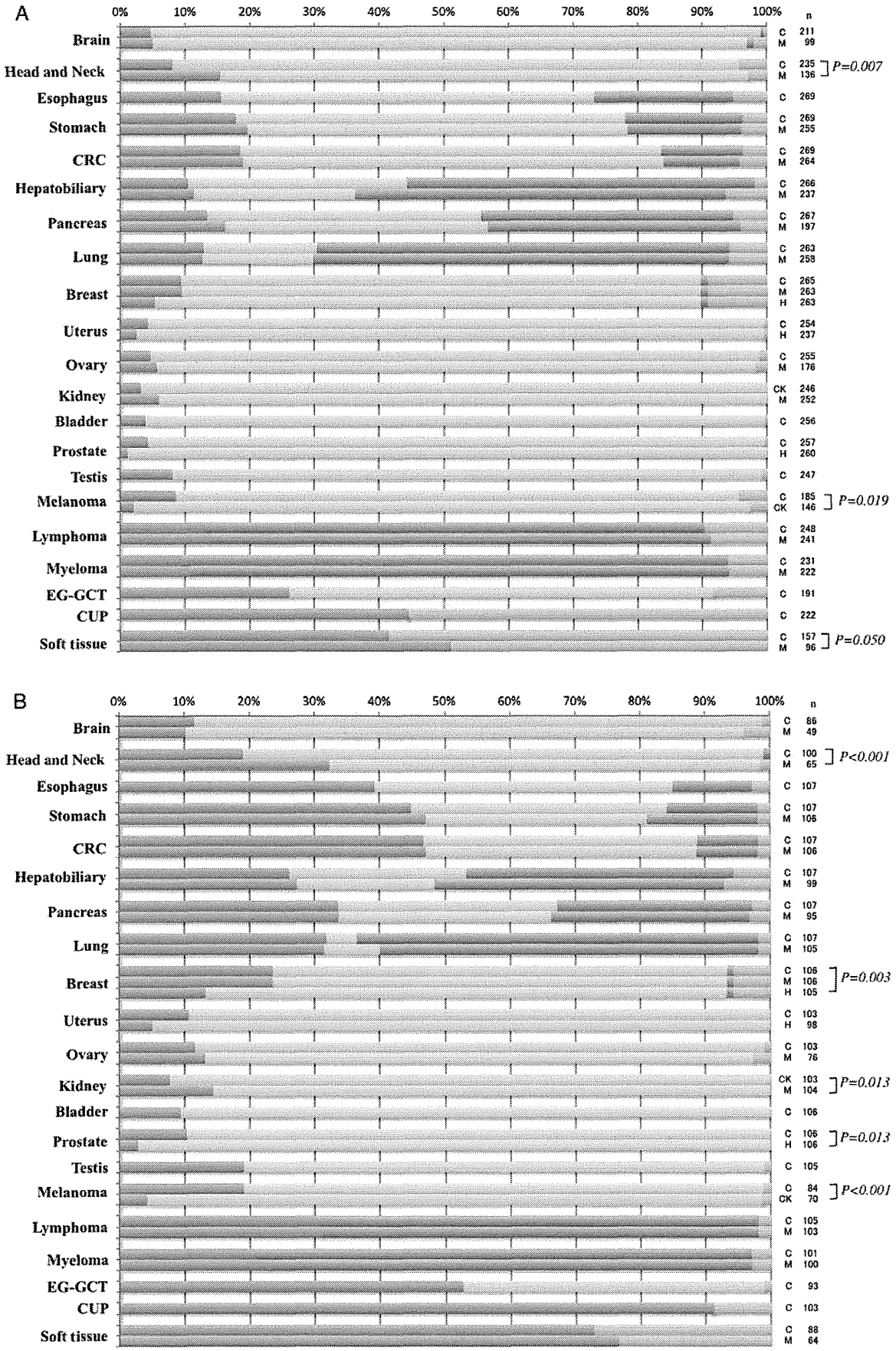

**Figure 2.** Percentages of institutions with medical oncology departments according to the number of JSMO-certified medical oncologists.

### Responsibility of Medical Oncology Departments for Cancer Drug Therapy

The responsibility, in terms of patient number, of a given department for providing a given therapy for a specific disease is summarized in Supplementary data, Table S1. In this table, the percentage of institutions in which a given department of the institution was primarily, secondarily, or tertiarily responsible for providing a given therapy for a specific disease is presented in each column, compared with all the institutions that responded to the questionnaire as well as all the institutions that have a medical oncology department.

Figure 3A and B illustrate the proportions of institutions in which a given department of the institution was primarily responsible, in terms of patient number, for a given drug therapy for each disease among all the institutions that responded to the questionnaire (3A) and among all the institutions with a medical oncology department (3B). In Fig. 3A containing data for all the institutions, the medical oncology departments were primarily responsible for molecular-targeted therapy more often than for chemotherapy for the treatment of head and neck cancers and soft-tissue sarcoma, while they were less often primarily responsible for cytokine therapy than for chemotherapy for the treatment of skin melanoma, with statistically significant differences. In Fig. 3B containing data for all the institutions with a medical oncology department, the medical oncology departments were primarily responsible for molecular-targeted therapy more often than for chemotherapy for the treatment of head and neck cancer, and they were primarily responsible for molecular-targeted therapy more often than for cytokine therapy for the treatment of renal cell carcinoma, with statistically significant differences. In contrast, they were less often primarily responsible for hormonal therapy than for chemotherapy for the treatment of breast and prostate cancers. In addition, they were less often primarily responsible for cytokine therapy than for chemotherapy for the treatment of skin melanoma.

Table 1 shows the percentages and accumulated percentages of institutions according to the number of disease groups (out of nine categories) in which the medical oncology department was primarily responsible for providing cytotoxic chemotherapy or molecular-targeted therapy. While the maximal number of disease groups was nine for cytotoxic chemotherapy, the maximal number of disease groups was eight for molecular targeted because molecular-targeted therapy is not available for the treatment of skin melanoma in Japan. In as many as 19.6 and 20.6% of the institutions, the medical oncology department failed to have primary responsibility, in terms of patient number, for providing cytotoxic chemotherapy and molecular-targeted therapy, respectively, to any disease group. In as many as 28.0 and 31.8% of the institutions, the medical oncology department was primarily responsible for providing cytotoxic chemotherapy and molecular-targeted therapy to only a single disease group. Consequently, approximately half of the medical oncology departments were primarily responsible for providing both



cytotoxic chemotherapy and molecular-targeted therapy to no more than two of the disease groups.

Table 2 shows the roles of medical oncology departments outside of the nine groups, that is, for extragonadal germ cell tumors, cancers of unknown primary site and soft-tissue sarcoma. The medical oncology departments generally play major roles in the treatment of these three diseases.

## DISCUSSION

The present study is the first to uncover the current state of medical oncology in Japan. As the questionnaire respondents were limited to Designated Cancer Care Hospitals, representing relatively high-ranked institutions for cancer care, the results are thought to reflect the standard of care in Japan. For instance, these hospitals reportedly account for 50.0% of all radiotherapy facilities in Japan (8). In addition, the response rate for the questionnaire was reasonably high, with 68% of the 397 Designated Cancer Care Hospitals throughout Japan providing a response.

In contrast to their roles expected by the JMSO, only 39.4% of the Designated Cancer Care Hospitals that responded to the questionnaire had medical oncology departments. In addition, these departments were generally rather small, with a median staff number of three. The percentage of institutions that employed JSMO-certified medical oncologists was only 58.4%, which is not high enough. Among the institutions with medical oncology departments, however, 86.0% employ JSMO-certified oncologists. Therefore, approximately one-third of the Designated Cancer Care Hospitals in Japan have both medical oncology departments and certified medical oncologists.

As the percentage of institutions with medical oncology departments was unexpectedly low, further analyses were conducted among the institutions with medical oncology departments and among the institutions overall. The analyses of all the institutions that responded suggested that medical oncology departments play somewhat limited roles in drug therapies for most cancers, with the exceptions of extragonadal germ cell tumor, cancer of unknown primary site and soft-tissue sarcoma; specifically, the medical oncology departments were primarily responsible, in terms of patient number, for the treatments of other diseases in no more than 20% of the institutions. When the analyses were limited to institutions with medical oncology departments, the medical oncology departments were found to be primarily responsible for providing drug therapies for gastrointestinal tract cancers in 40–50% of the institutions, for head and neck cancer, hepatobiliary cancer, pancreas cancer, lung cancer, breast cancer, lymphoma and myeloma in 20–35% of the institutions, and for much lower percentages of cases for other cancers. Accordingly, the majority of medical oncology departments are primarily responsible for a limited number of oncology fields.

Interestingly, the responsibilities of the medical oncology departments differed slightly with regard to providing chemotherapy, molecular-targeted therapy, hormonal therapy and cytokine therapy for the same diseases. That is, they were more often responsible for providing molecular-targeted therapy than for providing chemotherapy for the treatment of head and neck cancer and for providing cytokine therapy for the treatment of renal cell carcinoma. Conversely, they were less often responsible for providing hormonal therapy than for providing chemotherapy for the treatment of breast and prostate cancers and they were also less often responsible for providing cytokine therapy than for providing chemotherapy for the treatment of skin melanoma. These facts suggest that medical oncology departments are more often responsible for providing newly developed drug therapy, than for providing conventional therapy, in some specific fields. It should be noted that many molecular-targeted agents have a wider variety of adverse effects than chemotherapeutic agents, including rash, diarrhea, hand–foot syndrome, hypertension, proteinuria and endocrine dysfunctions, leading to more requirements for specialized care. It should also be noted that immunotherapy and molecular-targeted therapy for melanoma have not been approved and that cytokine therapy, including the use of interferon and interleukins, was still a treatment option for melanoma in Japan during the study period.

Japan adopted Western medicine exclusively from Holland until the mid-19th century, then mainly from Germany thereafter, followed by extensive development in Japan itself (9,10), resulting in a medical system based on organ specificities. In this system, for example, pulmonary medicine departments are responsible for all pulmonary diseases, including lung cancer, mediastinal malignancies and pleural mesothelioma. JSMO, the Japan Society of Clinical Oncology and the Japan Cancer Association collaborated and established the Japanese Board of Cancer Therapy at 2007 and started certifying clinical

**Figure 3.** Percentages of institutions in which a given department of the institution was primarily responsible, in terms of patient number, for providing a given therapy for a specific disease among all the institutions that responded to the questionnaire (A) and among all the institutions with a medical oncology department (B). The red, green, purple and sky-blue bars represent medical oncology department, sub-departments of surgery specific to the corresponding organ system, sub-departments of internal medicine specific to the corresponding organ system and others, respectively (for the specific department names, see Supplementary data, Table S1). Because the availability of services for each therapy varied from institution to institution, the sample sizes are different for each column. For example, chemotherapy for brain tumors was available at most of the institutions ($n = 211$), whereas molecular-targeted therapy for brain tumors was only provided at a limited number of institutions ($n = 99$) because bevacizumab was not approved in Japan for use in patients with brain tumors until the end of the study period. Statistically significant differences ($P < 0.05$) are shown for the percentages of institution in which medical oncology departments were primarily responsible for different therapies for the same disease. C, M, H and CK represent cytotoxic chemotherapy, molecular-targeted therapy, hormonal therapy and cytokine therapy, respectively. CRC, EG-GCT and CUP represent colorectal cancer, extragonadal germ cell tumors and cancers of unknown primary site, respectively.

**Table 1.** Rates and accumulated rates of institutions ($n = 107$) according to the number of disease groups for which the medical oncology departments were primarily responsible for providing cytotoxic chemotherapy or molecular-targeted therapy

| No. of groups[a] | Chemotherapy | | Molecular-targeted therapy | |
|---|---|---|---|---|
| | Rate (%) | Accumulated rate (%) | Rate (%) | Accumulated rate (%) |
| 0 | 19.6 | 19.6 | 20.6 | 20.6 |
| 1 | 28.0 | 47.6 | 31.8 | 52.4 |
| 2 | 21.5 | 69.1 | 25.2 | 77.6 |
| 3 | 10.3 | 79.4 | 5.6 | 83.2 |
| 4 | 6.5 | 85.9 | 5.6 | 88.8 |
| 5 | 3.7 | 89.6 | 8.4 | 97.2 |
| 6 | 3.7 | 93.3 | 2.8 | 100.0 |
| 7 | 4.7 | 98.0 | 0.0 | 100.0 |
| 8 | 0.0 | 98.0 | 0.0 | 100.0 |
| 9 | 1.9 | 100.0 | Not applicable | Not applicable |

[a]Eighteen out of 21 diseases (excluding extragonadal germ cell tumors, cancers of unknown primary site and soft-tissue sarcoma) were further classified into nine groups. See Patients and Methods for details.

**Table 2.** Numbers and percentages (in parentheses) of institutions according to the order of responsibility, in terms of patient number, of medical oncology departments in providing drug therapy for three specific diseases

| $n = 107$ | Primarily responsible | Secondarily responsible | Tertiarily responsible | No service[a] |
|---|---|---|---|---|
| Extragonadal germ cell tumor | 51 (47.7) | 9 (8.4) | 0 (0.0) | 13 (12.1) |
| Cancer of unknown primary site | 96 (89.7) | 1 (0.9) | 0 (0.0) | 4 (3.7) |
| Soft-tissue sarcoma | 66 (61.7) | 8 (7.5) | 0 (0.0) | 19 (17.8) |

[a]No service provided for the specific given disease.

oncologists for physicians, surgeons, radiologists, pathologists, dentists and other doctors working in the oncology fields with defined conditions at 2008. This is on the lines of facilitating organ-specific medicine in oncology, regardless of whether the oncologists can provide drug therapy or not. A majority of drug therapy of cancer in Japan has depended on these oncologists. The recent advancement of chemotherapy and molecular-targeted therapy, however, has urged the development of medical oncology departments specializing in drug therapy, which is inevitably accompanied by a wide variety of adverse effects. These environments prompted the national government to appoint Designated Cancer Care Hospitals and to enrich them with doctors, nurses, pharmacists and other staff members specializing in cancer care. Although the policy is worth encouraging, its actual relevance has not been validated, at least in the field of medical oncology. The present study suggested that medical oncology departments in Japan still have room for expansion and improvement with regard to their roles in providing oncology-related drug therapies. The enhanced commitment to molecular-targeted therapy, presumably because of its wide variety of adverse events, actually seems to highlight the important roles of medical oncologists. As the current situation has been achieved with a limited number of JSMO-certified medical oncologists, improvements might be naturally achievable by gradually increasing the number of trained specialists. As to radiation oncology in Japan, the radiotherapy equipment that is available at Designated Cancer Care Hospitals is reportedly comparable to that in European countries and the USA, despite a significant shortage in personnel resources and an increasing work burden, compared with Western countries (8,11). Similar to radiation oncology, medical oncology now has increasing responsibilities in the field of oncology, with the increasing use of multidrug therapies, the combined use of chemotherapeutic and molecular-targeted agents, and their involvements in clinical trials. Ample numbers of certified medical oncologists would undoubtedly contribute to a significant advancement in establishing medical oncology departments in the majority of Designated Cancer Care Hospitals. On the other hand, ~20% of the institutions that responded to the present questionnaire did not possess a medical oncology department, despite the relatively plentiful number of JSMO-certified medical oncologists ($\geq 5$ per institute), as disclosed in the present study (see Fig. 2). This finding seems to indicate that continuing social encouragement is required to further develop the field of medical oncology in Japan.

A major weakness of the present study is the absence of quality assessment of medical oncology departments. Medical oncology departments with limited numbers of the staffs and certified medical oncologists potentially have difficulty in providing excellent clinical practice for the patients and excellent education for the trainees. Other weakness is that the study covered only a small part of community practice in Japan. Much more drug therapies are given outside the institutions the present study examined.

In conclusion, medical oncology in Japan plays a somewhat important role in Designated Cancer Care Hospitals despite limited resources, and much room for expansion and further development exists. Considering the short history of this field, we envision the situation to improve significantly in the next 10 years. The present data should provide an important control for comparisons with similar investigations in the future. Further investigations elucidating the quality of medical oncology in Japan in terms of clinical practice for their patients and medical education for their trainees would be warranted.

## SUPPLEMENTARY DATA

Supplementary data are available at http://www.jjco.oxfordjournals.org.

## Acknowledgements

A part of the research was presented at the presidential symposium of the 11th Annual Meeting of Japanese Society of Medical Oncology at Sendai, Japan, on 31 August 2013. We truly appreciate the contributions from all the respondents and their institutions. The names of the institutions and, in parentheses, the respondents who provided consent are acknowledged here as follows: Fukushima Medical University Hospital (Takashi Ishida), Akita University Hospital (Hiroyuki Shibata), Yamagata Prefectural Central Hospital (Norimasa Fukushima), Tohoku University Hospital (Chikashi Ishioka), Ibaraki Prefectural Central Hospital (Hiroshi Kojima), Tochigi Cancer Center (Kiyoshi Mori), Gunma University Hospital (Norifumi Tsukamoto), Chiba Cancer Center (Hideki Tsujimura), Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Yoshiharu Maeda), The Cancer Institute Hospital of JFCR (Shunji Takahashi), Kanagawa Cancer Center (Shigeki Motomura), Niigata Cancer Center Hospital, Toyama Prefectural Central Hospital (Yousuke Hotta), Fukui Prefectural Hospital, Yamanashi Prefectural Central Hospital (Masaki Iino), Shinshu University Hospital, Shizuoka Cancer Center (Nobuyuki Yamamoto), Mie University Hospital (Kazunori Nakase), Shiga Medical Center for Adults (Takayo Suzuki), University Hospital, Kyoto Prefectural University of Medicine (Naohisa Yoshida), Kyoto University Hospital (Shigemi Matsumoto), Osaka Medical Center for Cancer and Cardiovascular Diseases, Hyogo Cancer Center, Wakayama Medical University Hospital (Hiroki Ueda), Tottori University Hospital (Kenji Oyama), Shimane University Hospital (Yukari Tsubata), Okayama University Hospital (Masahiro Tabata), Hiroshima University Hospital (Kazuhiko Sugiyama), Kagawa University Hospital (Fuminori Goda), National Hospital Organization Shikoku Cancer Center (Tomohiro Nishina), Kochi Medical School Hospital (Michiya Kobayashi), National Hospital Organization Kyushu Cancer Center (Taito Esaki), Nagasaki University Hospital, Kumamoto University Hospital (Kisato Nosaka), Kagoshima University Medical and Dental Hospital, Faculty of Medicine Hospital, University of Ryukyus (Masato Masuda), Sapporo City General Hospital (Michio Nakamura), Sunagawa City Medical Center, Nikko Memorial Hospital (Hiromi Hamada), Oji General Hospital, Japanese Red Cross Kitami Hospital (Takurou Arimoto), Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital, Kushiro City General Hospital, Hakodate Goryokaku Hospital (Akinori Takagane), KKR Sapporo Medical Center (Hiroshi Isobe), Keiyukai Sapporo Hospital (Hiroyuki Okuda), Sapporo Medical University Hospital (Rishu Takimoto), Hokkaido P.W.F.A.C Sapporo-Kosei General Hospital (Masakazu Abe), Teine Keijinkai Hospital, Hokkaido University Hospital (Hirotoshi Akita), Asahikawa Medical University Hospital (Yoshihiro Torimoto), Asahikawa City Hospital, Hirosaki University School of Medicine and Hospital (Kazufumi Terui), Hachinohe City Hospital (Shunichi Maeda), Misawa City Hospital, Iwate Prefectural Central Hospital (Satoshi Kato), Iwate Prefectural Chubu Hospital (Shukichi Miyazaki), Iwate Prefectural Iwai Hospital (Hirotaka Kato), Iwate Prefectural Miyako Hospital, Oohunato Hospital (Tatsuya Nakano), Iwate Prefectural Kuji Hospital (Osamu Shimooki), Tohoku Pharmaceutical University Hospital (Naoto Morikawa), Osaki Citizen Hospital (Makio Gamo), Japanese Red Cross Ishinomaki Hospital (Seiichi Kobayashi, Kazuya Nishi), Yamamoto Kumiai General Hospital, Yuri Kumiai General Hospital, Odate Municipal General Hospital (Hitoshi Ogasawara), Akita Kumiai General Hospital (Kazuhiko Endo), Yamagata Prefectural Central Hospital (Tomoharu Ishiyama), Tsuboi Cancer Center Hospital (Masahiro Ando), Southern Tohoku General Hospital (Yoshinao Takano), Takeda General Hospital (Shinji Kimoto), Fukushima Accident Hospital (Atsushi Muto), Shirakawa Kosei General Hospital, Hitachi General Hospital, Tsuchiura Kyodo General Hospital, Tsukuba Medical Center Hospital (Shingo Ishiguro), University of Tsukuba Hospital (Ichinosuke Hyodo), Tokyo Medical University Ibaraki Medical Center (Kinya Furukawa), National Hospital Organization Mito Medical Center (Hamaichi Ueki), Jichi Medical University Hospital, Dokkyo Medical University Hospital (Kimio Morita), Maebashi Red Cross Hospital (Atsushi Takise), National Hospital Organization Takasaki General Medical Center (Yuji Shimizu), Fujioka General Hospital, Public Tomioka General Hospital, Gunma Prefectural Cancer Center, Numata Hospital (Roppongi Takashi), Saitama Red Cross Hospital (Kouji Nakagawa), Saitama Medical Center, National Hospital Organization Saitama National Hospital (Tetsuo Monma), Saitama Medical University International Medical Center (Toshiaki Saeki), Fukaya Red Cross Hospital (Hiroshi Ito), Saiseikai Kawaguchi General Hospital, Chiba University Hospital (Yuichi Takiguchi), National Organization Chiba Medical Center, Funabashi Municipal Medical Center (Takashi Maruyama), Juntendo University Urayasu Hospital (Akio Kidokoro), The Jikei University Kashiwa Hospital (Kaichi Nishiwaki), Matsudo City Hospital (Takashi Saotome), Narita Red Cross Hospital (Takayuki Ishii), Kameda Medical Center (Yu Oyama), Kimitsu Chuo Hospital (Mitsutoshi Shiba), The University of Tokyo Hospital (Kiyoshi Miyakawa), Nippon Medical School Hospital (Akihiko Genma), St. Luke's International Hospital, NTT Medical Center Tokyo, Japanese Red Cross Medical Center (Yasuaki Nakagawa), Tokyo Women's Medical University Hospital (Kazuhiko Hayashi), Teikyo University Hospital (Nobuhiko Seki), Ome Municipal General Hospital (Osamu Noguchi), Tokyo Medical University Hachioji Medical Center (Shinichiro Taira), Japanese Red Cross Musashino Hospital (Minoru Nakane), Kyorin University Hospital (Junji Furuse), Showa University Hospital (Yasutsuna Sasaki), Keio University Hospital (Hiromasa Tamaishi), Toho University Omori Medical Center (Hideaki Shimada), National Hospital Organization Tokyo Medical Center (Yoshitaka Oyamada), Yokohama Rosai Hospital (Takamitsu Ariga), Yokohama Municipal Citizen's Hospital (Hiroaki Okamoto), Yokohama

City University Hospital (Yasushi Ichikawa), St. Marianna University School of Medicine Hospital, Yokosuka Kyosai Hospital (Eiko Kojima), Fujisawa City Hospital (Masanori Nishikawa), Kitasato University Hospital, Odawara Municipal Hospital, Yokohama City Minato Red Cross Hospital (Tetsuo Abe), Shibata Hospital—Niigata Prefectural Hospital (Nobuyoshi Seki), Niigata City General Hospital, Niigata University Medical and Dental Hospital (Yasuo Saijyo), Nagaoka Chuo General Hospital (Takashi Tomidokoro), Nagaoka Red Cross Hospital, Saiseikai Niigata Daini Hospital (Yasuo Sakai), Kurobe City Hospital, Toyama City Hospital (Yoshihisa Ishiura), Kouseiren Takaoka Hospital (Kazuhiko Shibata), Takaoka City Hospital (Takashi Kobayashi), National Hospital Organization Kanazawa Medical Center (Makoto Hayashi), Ishikawa Prefectural Central Hospital, Kanazawa Medical University Hospital (Yoshiharu Motoo), University of Fukui Hospital, Fukui Red Cross Hospital (Yuki Hirose), Fukui-Ken Saiseikai Hospital (Shun Nakayama), Kofu Municipal Hospital (Zennosuke Ooki), Fujiyoshida Municipal Medical Center (Yuji Honda), Suwa Red Cross Hospital, Iida Municipal Hospital, Aizawa Hospital (Masato Nakamura), Nagano Red Cross Hospital, Ina Central Hospital (Norio Ito), Gifu Prefectural General Medical Center (Katsuyuki Kunieda), Gifu Municipal Hospital (Toshiyuki Sawa), Ogaki Municipal Hospital, Kizawa Memorial Hospital, Juntendo University Shizuoka Hospital, Numazu City Hospital (Akira Nagayama), Shizuoka General Hospital (Keisei Taku), Shizuoka Hospital, Fujieda Municipal General Hospital (Hidetaro Yokoyama), Seirei Mikatahara General Hospital (Yukihiro Kunimoto), Hamamatsu Medical Center (Kazuyuki Shigeno), Hamamatsu University Hospital, Iwata City Hospital, National Hospital Organization Nagoya Medical Center (Hideo Saka), Nagoya University Hospital (Yuichi Ando), Social Insurance Chukyo Hospital (Keiko Nakamura), Nagoya City University Hospital (Hirokazu Komatsu), Japanese Red Cross Nagoya Daiichi Hospital (Shirou Nomura), Tosei General Hospital (Toshihito Ohno), Komaki City Hospital (Kazuyuki Naito), Anjo Kosei Hospital (Masashi Sawa), Mie Prefectural General Medical Center, Mie Chuo Medical Center, Suzuka General Hospital (Keiki Kawakami), Kohga Public Hospital, Nagahama City Hospital (Yuji Kanda), Fukuchiyama City Hospital, Japanese Red Cross Kyoto Daiichi Hospital (Norimasa Yoshida), Japanese Red Cross Kyoto Daini Hospital (Yutaka Kobayashi), National Hospital Organization Kyoto Medical Center (Hisateru Yasui), Toyonaka Municipal Hospital, Higashiosaka City General Hospital (Shusei Tominaga), National Hospital Organization Osaka Minami Medical Center (Yasuhiro Maeda), Osaka Rosai Hospital (Riichiro Nezu), Kishiwada City Hospital, Osaka City General Hospital (Koji Takeda), Osaka Red Cross Hospital, Osaka Medical College Hospital (Masahiro Goto), National Hospital Organization Osaka National Hospital, Kobe University Hospital (Hironobu Minami), Kobe City Medical Center General Hospital (Akihito Tsuji), Kansai Rosai Hospital (Shigeyuki Tamura), The Hospital of Hyogo College of Medicine (Kazuya Fukuoka), Kinki Central Hospital (Kenji Kobayashi), Nishiwaki Municipal Hospital, National Hospital Organization Himeji Medical Center (Yasuharu Nakahara), Ako City Hospital, Hyogo Prefectural Awaji Medical Center, Nara Prefectural Nara Hospital, Tenri Hospital (Teruhisa Azuma), Naga Hospital (Takeshi Tamaki), Social Insurance Kinan Hospital, National Hospital Organization Minami Wakayama Medical Center (Takahiro Kinoshita), Tottori Prefecture Chuo Hospital, Tottori Prefectural Kousei Hospital (Shunsuke Fukino), Matsue City Hospital, Okayama Saiseikai General Hospital (Haruyuki Kawai), Japanese Red Cross Okayama Hospital (Akihiro Bessho), National Hospital Organization Okayama Medical Center, Hiroshima Prefectural Hospital (Katsunori Shinozaki), Hiroshima City Hospital, Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital, Hiroshima General Hospital (Yuji Imamura), Onomichi General Hospital (Toshio Noriyuki), Hiroshima City Asa Hospital (Souichi Kitaguchi), Shuto General Hospital, Tokuyama Central Hospital, Yamaguchi Grand Medical Center, Yamaguchi Red Cross Hospital (Hirotaka Ueda), Kagawa Prefectural Central Hospital (Kimihiro Kawakami), Kagawa Rousai Hospital (Atsushi Muraoka), Ehime University Hospital (Yoshihiro Yakushijin), Ehime Prefectural Central Hospital (Masamichi Hara), Matsuyama Red Cross Hospital (Takeshi Shiraishi), Kochi Health Sciences Center, Hata Kenmin Hospital, Kyushu Medical Center (Koji Ikejiri), Saiseikai Fukuoka General Hospital (Yasunori Emi), Fukuoka University Hospital (Toshihiro Tanaka), Kurume University Hospital (Takashi Okamura), Omuta City Hospital, Iizuka Hospital, Tagawa Hospital, University of Occupational and Environmental Health, Saga-Ken Medical Center Koseikan, Karatsu Red Cross Hospital (Seiji Yunotani), Ureshino Medical Center, Nagasaki Municipal Hospital, National Hospital Organization Nagasaki Medical Center (Shinichiro Yoshida), Nagasaki Prefectural Shimabara Hospital (Akitoshi Kinoshita), Kumamoto City Hospital (Hiroto Kishi), Japanese Red Cross Kumamoto Hospital, Saiseikai Kumamoto Hospital (Kenji Sakai), Arao Municipal Hospital (Koichi Nomura), Health Insurance Hitoyoshi General Hospital, Beppu Medical Center (Atsujiro Yano), Oita Red Cross Hospital (Kengo Fukuzawa), Oita Prefectural Hospital (Yuji Kato), Saiseikai Hita Hospital, Almeida Memorial Hospital (Eiji Ohno), Nakatsu Municipal Hospital (Yasuo Fukuyama), Miyazaki Prefectural Miyazaki Hospital (Yoshihiro Shibata), National Hospital Organization Kagoshima Medical Center, Minami Kyushu National Hospital (Seiji Kawabata), Imakiire General Hospital, Naha City Hospital, National Cancer Center Hospital (Kenji Tamura).

## Funding

This work was financially supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan.

## Conflict of interest statement

None declared.

## References


1. Numico G, Fasola G. Medical oncology: in search of a definition. *Ann Oncol* 2014;25:1075–6.
2. Popescu RA, Schäfer R, Califano R, et al. The current and future role of the medical oncologist in the professional care for cancer patients: a position paper by the European Society for Medical Oncology (ESMO). *Ann Oncol* 2014;25:9–15.
3. de Azambuja E, Ameye L, Paesmans M, Zielinski CC, Piccart-Gebhart M, Preusser M. The landscape of medical oncology in Europe by 2020. *Ann Oncol* 2014;25:525–8.
4. Training resource document for curriculum development in medical oncology. Adopted on February 20, 1997 by the American Society of Clinical Oncology. *J Clin Oncol* 1998;16:372–9.
5. Wagener DJT, Vermorken JB, Hansen HH, Hossfeld DK. The ESMO programme of certification and training for medical oncology. *Ann Oncol* 1998;9:585–7.
6. Hansen HH, Bajorin DF, Muss HB, Purkalne G, Schrijvers D, Stahel R. Recommendations for a global core curriculum in medical oncology. *J Clin Oncol* 2004;22:4616–25.
7. Maeda M. A review of cancer control strategy in Japan (in Japanese). *J Natl Inst Public Health* 2008;57:304–7.
8. Numasaki H, Nishio M, Ikeda H, et al. Japanese structure survey of radiation oncology in 2009 with special reference to designated cancer care hospitals. *Int J Clin Oncol* 2013;18:775–83.
9. Izumi Y, Isozumi K. Modern Japanese medical history and the European influence. *Keio J Med* 2001;50:91–9.
10. Kim O, Takuya M. Development of modern medical doctors in Japan from late Edo to early Meiji. *Korean J Med Hist* 2011;20: 493–554.
11. Numasaki H, Shibuya H, Nishio M, et al. Japanese structure survey of radiation oncology in 2007 with special reference to designated cancer care hospitals. *Strahlenther Onkol* 2011;187:167–74.

総　説

日耳鼻 117：161-167，2014

「他領域からのトピックス」

# 他科における最新の診断方法
## —乳がん治療におけるコンパニオン診断薬と分子標的薬を用いる個別化医療の現状と展望—

橋本　淳
田村　研治
藤原　康弘

独立行政法人
国立がん研究センター中央病院
乳腺・腫瘍内科

がん治療領域において，分子標的治療が臨床現場に導入され10年以上が経過した．その間にヒトの遺伝子配列の解読や新たな治療標的分子の発見など，個々人に最適な医療を提供する個別化医療の研究も進み，その成果が発揮され始めている．個別化医療においてカギを握るのがコンパニオン診断薬という体外診断薬である．1990年代にその概念が提唱され，欧米では2011年にコンパニオン診断薬についてのガイダンスが発表され，本邦では現在作成中である．乳がん領域においては，HER2を標的としたトラスツズマブが国内の個別化医療として最初に登場し，コンパニオン診断は脚光を浴びた．トラスツズマブは投与前にHER2蛋白の過剰発現やHER2遺伝子の増幅を調べることにより，トラスツズマブの効果が期待できる患者層を選定することが可能である．蛋白発現判定のための免疫染色，遺伝子増幅判定のためのFISH法がコンパニオン診断薬として承認されている．最近では，複数の遺伝子をチェックし，そのパターンから再発可能性や治療効果を予測する診断法も開発されている．乳がん領域においても，21種類の遺伝子の発現を調べてスコア化し，早期乳がん患者に対する化学療法の効果および再発可能性を予測する診断検査であるOncotype Dx®の開発が進んでいる．これからの展望としては，感度や精度の高い診断法が，対象となる新薬とともに整合性よく市場に提供されることが望まれ，今後もさらにコンパニオン診断薬の研究開発が進んでいく一方で，新薬が次々と開発される状況，診断検査の精度管理，コストといった取り組むべき課題も多く存在する．コンパニオン診断薬の開発は個別化医療の推進において非常に重要であり，産官学を挙げて研究開発を進めていくことが必要である．

**キーワード：** Companion diagnostics, personalized medicine, breast cancer, HER2, Oncotype Dx®

### はじめに

個別化医療の中心をなす分子標的治療が臨床現場に導入され10年以上が経過した．その先駆けとなったのはヒト上皮細胞増殖因子受容体2（human epidermal growth factor receptor type 2；HER2）分子を標的とした治療と診断・検査の組み合わせであり，大きな成果を挙げ個別化医療におけるその後の研究開発に大きな影響を与えた．コンパニオン診断薬とは，「体外診断薬のうち，特定の薬剤の有効性や安全性に関する患者集団を特定するための患者層別マーカー（バイオマーカー）を測定するもの」とされている[1]．本稿ではコンパニオン診断薬とそれを活用する個別化医療の現状と展望について乳がん領域を中心に概説する．

### コンパニオン診断薬と個別化医療

“Companion diagnostics”という用語は1990年代後半ごろより用いられ始めたが，2006年のNature Biotechnology誌において初めて学術雑誌上で使用された[2]．その背景には乳がんにおけるHER2を標的としたトラスツズマブ，慢性骨髄性白血病に対するイマチニブが承

表1　がん治療領域におけるコンパニオン診断薬

| がん種 | 薬剤（商品名） | 薬理作用 | コンパニオン診断検査項目 | 検査結果の解釈 |
|---|---|---|---|---|
| 乳がん | トラスツズマブ（ハーセプチン®）<br>ペルツズマブ（パージェタ®）<br>ラパチニブ（タイケルブ®） | 抗HER2モノクローナル抗体<br>HER2チロシンキナーゼ阻害 | 乳がんHER2/neu蛋白（IHC法） | IHC法3＋もしくはIHC法2＋かつFISH法陽性の場合投与対象 |
| | | | 乳がんHER2遺伝子（FISH法） | FISH法陽性が投与対象 |
| 胃がん | トラスツズマブ（ハーセプチン®） | 抗HER2モノクローナル抗体 | 胃がんHER2蛋白（IHC法） | IHC法3＋もしくはIHC法2＋かつFISH法陽性の場合投与対象 |
| | | | 胃がんHER2遺伝子（FISH） | FISH法陽性が投与対象 |
| 大腸がん | セツキシマブ（アービタックス®）<br>パニツムマブ（ベクティビックス®） | 抗EGFR抗体 | EGFR蛋白（酵素抗体法） | EGFR陽性が投与対象（セツキシマブ） |
| | | | KRAS遺伝子codon12, 13遺伝子変異解析（Scorpion-ARMS法） | 「変異検出せず」が投与対象<br>「変異あり」の場合，治療効果が期待できない |
| 肺がん | ゲフィチニブ（イレッサ®）<br>エルロチニブ（タルセバ®） | EGFRチロシンキナーゼ阻害 | EGFR遺伝子変異解析（Scorpion-ARMS法，PCR-invader法など） | Exon18，19，21に変異ありの場合奏効率が高い，Exon20の変異は治療抵抗性 |
| | クリゾチニブ（ザーコリ®） | ALKチロシンキナーゼ阻害 | ALK遺伝子（FISH法，PCR-invader法など） | ALK融合遺伝子陽性の場合投与対象 |
| 慢性骨髄性白血病 | イマチニブ（グリベック®） | BCR-ABLチロシンキナーゼ阻害 | BCR-ABL遺伝子（TMA-HPA法） | BCR-ABLキメラ遺伝子陽性の場合投与 |
| 成人T細胞白血病 | モガムリズマブ（ポテリジオ®） | 抗CCR4抗体 | CCR4蛋白（IHC法，FCM法） | CCR4蛋白陽性の場合投与 |

認され，臨床診療へ導入されたことも関係している．その後，2011年7月に米国食品医薬品局（Food and Drug Administration；FDA）からコンパニオン診断薬（“in vitro companion diagnostic devices”）という項目でドラフト・ガイダンスが公表された．このガイダンスの中で，コンパニオン診断薬とは，医薬品の臨床使用に際して用いられる体外診断薬で，医薬品のベネフィットが最も期待される患者を特定するもの，医薬品の重篤な有害事象のリスクが大きい患者を特定するもの，あるいは治療法最適化（治療スケジュール，用量，投与中止等）のために反応性をモニターするもの，などと定義されている．また，新規に開発される医薬品は，薬効や副作用を投薬前に予測するためのコンパニオン診断法も同時に開発し，承認を受けることが推奨されている．以上のように，コンパニオン診断とは，薬剤に対する患者個人の反応性を治療前に検査することで，個別化医療（もしくはオーダーメイド医療）を推進するために用いられ，通常の臨床検査とは区別される．

## コンパニオン診断薬の現状

FDAは，前項で述べたようにコンパニオン診断薬という品目分類を診断機器審査の中で明確に位置づけている[3]．2011年8月に，BRAF遺伝子変異（V600E）陽性の切除不能あるいは転移性悪性黒色腫に対するBRAF阻害剤であるVemurafenibおよびALK融合遺伝陽性の局所進行あるいは転移性非小細胞肺がんに対するALK阻害剤であるクリゾチニブがFDAに承認された．これらの薬剤については，indication and usage（日本の添付

**表2**　HER2検査に用いる体外診断用医薬品として承認されている免疫染色用キット

| 製品名 | 販売元／販売会社 | 抗原認識部位 | 抗体タイプ | クローン名 |
|---|---|---|---|---|
| ダコ Hercep Test II | ダコ・ジャパン | ICD | ポリクローナル | |
| ヒストファイン HER2 キット (POLY) | ニチレイバイオサイエンス | ICD | ポリクローナル | |
| ヒストファイン HER2 キット (MONO) | ニチレイバイオサイエンス | ECD | モノクローナル | SV2-61γ |
| Bond ポリマーシステム HER2 | ライカマイクロシステムズ | ICD | モノクローナル | CB11 |
| ベンタナ I-VIEW パスウェー HER2 (4B5) | ロシュ・ダイアグノスティックス | ICD | モノクローナル | 4B5 |

ICD：細胞内領域，ECD：細胞外領域

文書の効能・効果欄に相当）において，「FDAが承認した診断キットを用いること」と明確に示されている．この2つのキットは，FDAが初めてコンパニオン診断薬として世の中に出したものである．

欧州では欧州医薬品庁（European Medicines Agency；EMA）が2010年6月24日および2011年6月9日の2回にわたり，コンパニオン診断に関するドラフト・ガイダンスを発表した．ガイダンスは，ゲノム薬理学によるバイオマーカーおよび診断法の医薬開発への導入についての内容となっている．

本邦では，明確にコンパニオン診断薬という体外診断薬のカテゴリーが存在しているわけではないが，がん治療領域において，抗がん剤の投与に当たり，その有効性や安全性に関する患者集団を特定するためにいくつかのバイオマーカーが日常診療に導入されている（表1）．現在，厚生労働省および医薬品医療機器総合機構（Pharmaceutical and Medical Devices Agency；PMDA）が，コンパニオン診断薬に関するガイダンスを作成中である．

## 乳がん領域におけるコンパニオン診断

本邦において，現在の乳がん診療におけるコンパニオン診断にはホルモン受容体（エストロゲン受容体：ER，プロゲステロン受容体：PR）の免疫染色，およびHER2過剰発現の組織学的検索がある．ホルモン受容体はホルモン療法の治療感受性因子に，HER2過剰発現は抗HER2療法の治療感受性因子となる．また，日本では未承認だが，術後化学療法の要否判断におけるOncotype Dx®がある．本項ではこれらのうちHER2検査，Oncotype Dx®についての現状およびコンパニオン診断薬の展望と課題について述べる．

### 1.　HER2陽性乳がん

HER2陽性乳がんとは，HER2遺伝子の発現によりHER2蛋白も過剰発現している乳がんであり，全乳がんの20～30％を占める[4)5)]．HER2は乳がん，卵巣がん，胃がんなどにおいてがん化の過程に深く関与しており[6)]，HER2遺伝子の増幅もしくはHER2蛋白の過剰発現を伴う乳がんは予後不良である[4)7)]．このHER2を標的とした治療開発として，1992年に海外において抗HER2モノクローナル抗体であるトラスツズマブの臨床試験が開始された．トラスツズマブはHER2陽性乳がんに対して12～40％程度の奏効率が報告されている[8)9)]．一方で，再発後の一次治療としてのトラスツズマブ単独療法において，HER2蛋白過剰発現例（免疫組織染色（Immunohistochemistry；IHC）2＋/3＋）では奏効率は35％であったが，低発現例（IHC 0/1＋）では奏効例を認めなかった[10)]．その後，転移性HER2陽性乳がん患者に対して，化学療法との併用による生存期間の延長が無作為化比較試験により示された[11)]（化学療法単独 対 化学療法＋トラスツズマブ無再発生存期間中央値；4.6カ月 対 7.4カ月，$p<0.001$，全生存期間中央値；20.3カ月 対 25.6カ月，$p=0.046$）．米国では1998年，欧州では2000年，日本では2001年に転移性乳がんに対する治療薬として承認された．

標的であるHER2陽性の診断は，臨床試験においては抗HER2モノクローナル抗体であるクローンCB11もしくは4D5を用いてIHC法により評価が行われた．しかし，これらは研究的なものであり日常診療における診断法としては適さず，改良の後にHER2過剰発現に対する最初のコンパニオン診断薬が開発された．体外診断用医薬品として市販されている免疫組織染色用抗体を表2に示す．

また，HER2遺伝子過剰発現の検出法の一つとして蛍

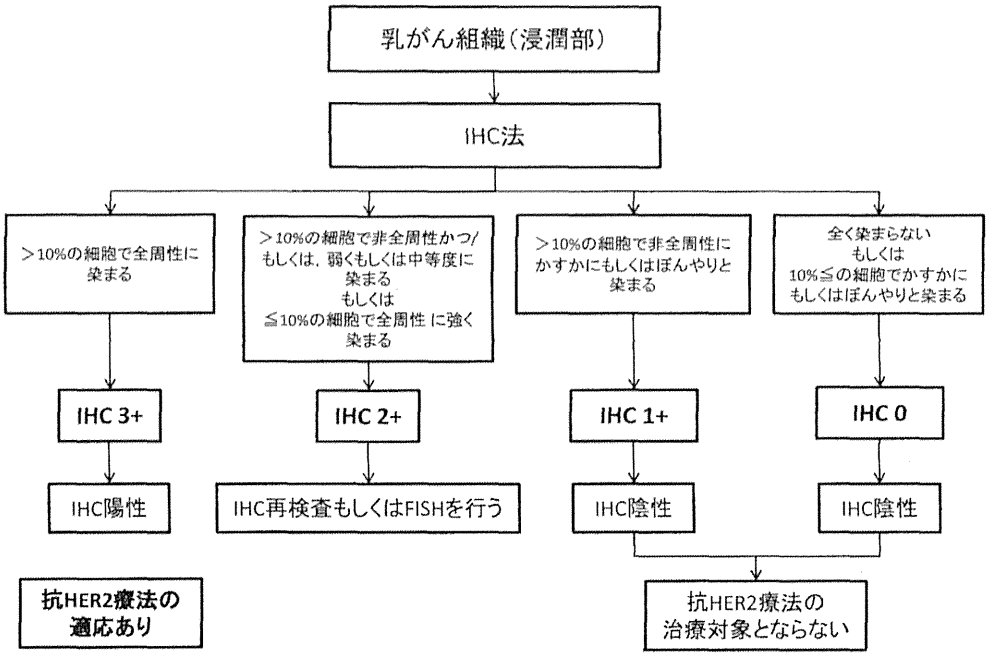



**図1**　IHC法によるHER2蛋白発現評価のアルゴリズム（文献12)より改変）

光 *in situ* ハイブリダイゼーション（fluorescence *in situ* hybridization；FISH）法がある．ホルマリン固定パラフィン包埋組織切片上で，蛍光標識したHER2 DNAプローブを用いてHER2遺伝子のコピー数を検出する方法である．日本では，パスビジョン®HER-2 DNAプローブキット（アボットジャパン），HER2 FISH pharmDx「ダコ」（ダコ・ジャパン），ヒストラHER2 FISHキット（常光）が体外診断用医薬品として承認されている．また，FISH法と同じHER2遺伝子増幅の検出法の一つである色素 *in situ* ハイブリダイゼーション（Chromogenic *in situ* hybridization；CISH）法の開発も進んでいる．FISH法がHER2遺伝子増幅を蛍光シグナルとして抽出させるのに対し，CISH法は色素産生物質によって染色体シグナルを可視化するもので，光学顕微鏡下で判定でき，標本の永久保存が可能である．日本ではベンタナインフォームDual ISH HER2キット（ロシュ・ダイアグノスティックス）が体外診断用医薬品として承認されている．

現在，IHC法およびFISH法をもとにHER2検査・判定が行われているが，抗HER2療法は転移性乳がんだけでなく術後療法として早期乳がんにおいても使用が可能となりHER2判定の頻度が著しく増加し，その重要性がますます高まってきた．そのため，米国臨床腫瘍学会（American Society of Clinical Oncology；ASCO)/米国臨床病理医協会（College of American Pathologists；CAP）では，HER2検査・判定のさらなる精度向上，精度管理を目的として，臨床腫瘍の専門医，病理学者をはじめ米国立機関の担当者から構成されるエキスパートパネルを組織し，ガイドラインが定められている．最も新しいものとしては，2013年10月10日に改定したガイドラインが公表されている[12]（図1，2）．

2．Oncotype Dx®

Oncotype Dx®乳がん検査は，乳がん組織における21種類の遺伝子の発現を調べるもので，早期乳がん患者に対する化学療法の効果予測および再発可能性を予測することを目的とした診断検査である．Oncotype Dx®はホルモン受容体陽性の早期乳がんにおける再発リスクを0から100の数値で表し（図3），低リスク（18未満），中間リスク（18～30），高リスク（31以上）に分類する．このリスク分類により，高リスク群についてはホルモン療法に化学療法を加えると上乗せ効果を認めるが（タモキシフェン単独 対 タモキシフェン＋化学療法；10年無遠隔転移生存割合60% 対 88%，$p<0.01$），低リスク群では上乗せ効果がほとんどない（タモキシフェン単独 対 タモキシフェン＋化学療法；10年無遠隔転移生存割97% 対 96%，$p=0.61$）ことが報告されている[13]．中間リスクに関しては，化学療法の上乗せ効果を検証するTAILORx試験[14]が実施されており，その結果が待たれる．現在，米国ではFDAの承認はないものの公的保険のMedicareおよび多くの民間医療保険を合わせて，約90%の被保険者が保険によるOncotype Dx®検査を受けることができるまでに至っている．また，ASCOおよび全米総合がん情報ネットワーク（National Comprehensive Cancer Network；NCCN）が，それぞれの乳がん

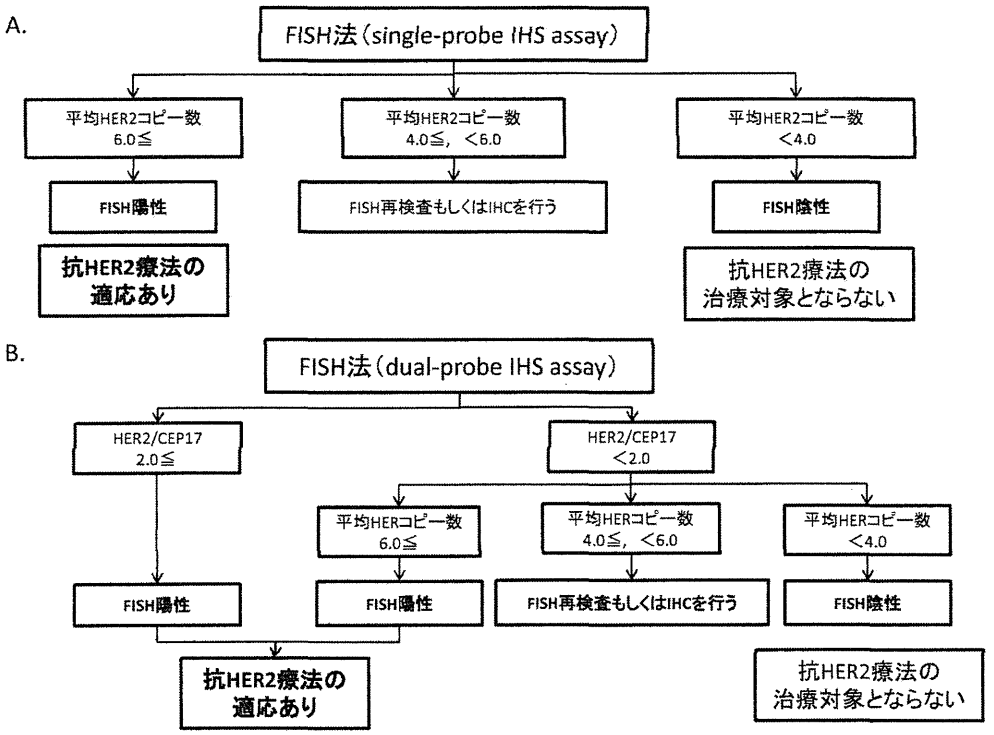



**図2**　FISH法によるHER2遺伝子増幅評価のアルゴリズム（文献12)より改変）

**21遺伝子**

| PROLIFERATION | INVATION | HER2 |
|---|---|---|
| Ki67<br>STK15<br>Survivin<br>Cyclin B1<br>MYBL2 | Stromelysin 3<br>Cathepsin L2 | GRB7<br>HER2 |
| **ESTROGEN** | **OTHER** | **REFERENCE** |
| ER<br>PR<br>Bcl-2<br>SCUBE2 | GSTM1<br>CD68<br>BAG1 | B-actin<br>GAPDH<br>RPLPO<br>GUS<br>TFRC |

**リスクスコア**

+0.47 × HER2 group score
-0.34 × ESTROGEN group score
+1.04 × PROLIFERATION group score
+0.10 × INVATION group score
+0.05 × CD68
-0.08 × GSTM1
-0.07 × BAG1

**図3**　Oncotype DX® における測定・解析遺伝子および再発リスクの算出

治療ガイドラインの中で，リンパ節転移がなく，ER陽性，および/またはPR陽性の乳がん患者に対して，Oncotype Dx® 検査を行うことを推奨している．

3.　乳がんにおけるコンパニオン診断薬の展望と課題

1)　新たな抗HER2療法の出現

抗HER2抗体であるトラスツズマブ，小分子化合物であるラパチニブに続き，ペルツズマブ，T-DM1といったHER2を標的とする新たな薬剤の開発が進んできている．トラスツズマブ，ラパチニブ，ペルツズマブはいずれもHER2を分子標的とする薬剤であるが，作用機序に差があり，これらの薬剤をどのような順番で使用するか，またどのように組み合わせて使用するかが現在の課題である．トラスツズマブはHER2-HER2 homodimerを最も効果的に阻害し，ペルツズマブはHER2-HER3 homodimerに阻害効果が強い[15][16]．ラパチニブは細胞内のリン酸化部位を阻害するのでEpidermal Growth Factor Receptor（EGFR）-HER2，HER2-HER2，HER2-HER3のすべてに阻害効果がみられている．現在

HER2を標的としたすべての薬剤においてHER2過剰発現がコンパニオン診断薬とされているが，上述したようにその作用機序はさまざまであり，これまでのHER2蛋白の過剰発現の有無を調べるだけではなく，新たな診断対象分子の検索や組み合わせについての検討が必要かもしれない．

2)　新規標的治療の開発

近年，さまざまな新規標的分子に対する標的治療薬の開発が進んでいる．乳がん領域においてもcell cycle dependent kinase 4/6(CDK4/6)やphosphoinositide 3-kinase(PI3K)/AKT/mammalian target of rapamycin(mTOR)経路を標的とした薬剤が早期試験において良好な結果を示している．治療開発が進む中で，PI3K/AKT/mTOR経路の標的治療における治療効果を予測するバイオマーカーとしてPI3K/AKT/mTOR経路の活性化などが前臨床試験や早期臨床試験の結果から報告されており[17][18]，コンパニオン診断の候補として有望視されている．今後，より感度や精度の高いアッセイ系の確立および前向き臨床試験での再現性の確認が必要である．

3)　コスト

日常診療の中にコンパニオン診断薬を導入する際には，その価格に注意が必要である．どの方法も操作性や技術特性から従来の臨床検査とは異なったプロセスおよび精度の管理や結果判定の厳密性が求められ，検査法の開発費用だけでなく実施費用を含め検査全体のコストは高額となる傾向にある．前述したOncotype Dx®は，薬事承認も診療報酬表への収載もなく，自由診療で使用せざるを得ない状況であるため，検査の実施に40万円前後の費用が必要となる．コンパニオン診断薬の日常診療への導入において，その薬価が低く設定されていることは個別化医療の普及を阻害する要因の一つであった．しかし，2012年に本邦において新薬と同時に薬事承認申請されたALK FISH Probe検査とC-C chemokine receptor type 4(CCR4)蛋白検査の保険点数はそれぞれ6,520点と10,000点であり，これまで遺伝子検査の上限と考えられていた2,000点（いわゆる「2,000点問題」）から大幅に引き上げられ，技術コストだけでなく検査の価値が評価された．一方で，非小細胞肺がん患者のうちALK融合遺伝子が陽性の患者は5％程度のみであり，約2万円の検査料金を支払い検査結果が陰性となり，標的治療を受けられない結果となる患者が95％であるということになる．これは患者にとっては精神的に辛いことと考えられる．コンパニオン診断薬の値段設定は，日常診療への個別化医療の普及に大きな課題になると思われる．

4)　精度管理

HER2病理診断の再現性と信頼性を保証するために，免疫染色やFISH法の精度管理が重要であるが，いまだ課題が多い．日本では，ほとんどの病理診断現場において，体外診断用医薬品（In-Vitro Diagnostics；IVD）承認が得られた診断薬を用いてIHC検査やFISH検査が行われているが，国内において検査実施施設数が多く，施設当たりの検査件数が少ないために精度の維持が困難であり，施設間格差もみられている．診断検査の精度管理において，新たな検査導入時の妥当性評価，継続的な精度管理と設備保全，検査導入時および継続的なトレーニングと習熟度評価などの内部精度管理（Internal Quality Control；IQC）や，外部監査，外部習熟度テストプログラムなどの外部精度評価（External Quality Assessment；EQA）システムの構築が必要である．

## おわりに

個別化治療の発展に伴い，コンパニオン診断薬は今後，より一層必要性を増していくことは明確である．治療薬と治療効果予測因子となるコンパニオン診断法が，整合性よく市場に提供されることが望ましいが，現実には必ずしも理路整然とは進行しない．治療薬の標的分子が必ずしも治療効果予測因子とならないことも多く，またアッセイ系の確立までに多くの前臨床および臨床研究を重ねることが必要とされることも多い．コンパニオン診断が実施され10年以上が経過したが，いまだ校正すべき多くの問題を抱えており，上記以外にも課題は山積みしているといってもよい．適切なコンパニオン診断はより正確な患者の層別化や治療の個別化を可能にし，これにより医療の質や効率化の向上，ひいては医療費削減などの医療経済的効果をもたらす．こうしたことを踏まえ，本邦でも産官学を挙げてコンパニオン診断薬の研究開発を進めていくことが必要である．

## 参考文献

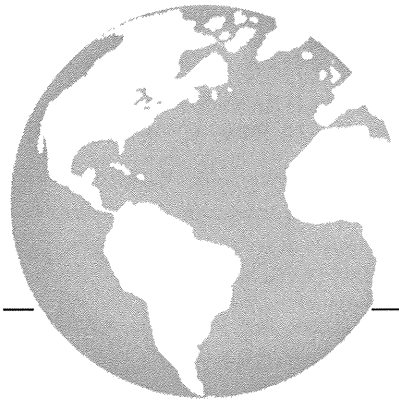
1) 藤原康弘：コンパニオン診断薬の現状と課題．腫瘍内科 2013；11：263-268.
2) Papadopoulos N, Kinzler KW, Vogelstein B：The role of companion diagnostics in the development and use of mutation-targeted cancer therapies. Nat Biotechnol 2006；24：985-995.
3) コンパニオン診断薬．FDAのサイト．入手先<http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm.>，(参照2013-11-10).
4) Slamon DJ, Clark GM, Wong SG, et al：Human breast cancer：correlation of relapse and survival with amplification of the HER2-2/neu oncogene. Science 1987；

235：177-182.
5) Slamon DJ, Godolphin W, Jones LA, et al：Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989；244：707-712.
6) Menard S, Casalini P, Campiglio M, et al：HER2 over expression in various tumor types, focusing on its relationship to the development of invasive breast cancer. Ann Oncol 2001；12 (suppl1)：S15-19.
7) Tsuda H, Hirohashi S, Shimosato Y, et al：Immunohistochemical study on overexpression of c-erbB-2 protein in human breast cancer：its correlation with gene amplification and long-term survival of patients. Jpn J Cancer Res 1990；81：327-332.
8) Baselga J, Tripathy D, Mendelsohn J, et al：Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 1996；14：737-744.
9) Cobleigh MA, Vogel CL, Tripathy D, et al：Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999；17：2639-2648.
10) Vogel CL, Cobleigh MA, Tripathy D, et al：Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002；20：719-726.
11) Slamon DJ, Leyland-Jones B, Shak S, et al：Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001；344：783-792.
12) Wolff AC, Hammond ME, Hicks DG, et al：Recommendations for human epidermal growth factor receptor 2 testing in breast cancer：american society of clinical oncology/college of american pathologists clinical practice guideline update. J Clin Oncol 2013；31：3997-4013.
13) Paik S, Tang G, Shak S, et al：Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006；24：3726-3734.
14) National Cancer Institute ホームページ. The TAILORx Breast Cancer Trial. 入手先<http://www.cancer.gov/clinicaltrials/noteworthy-trials/tailorx>, (参照2013-11-10).
15) Ghosh R, Narasanna A, Wang SE, et al：Trastuzumab has preferential activity against breast cancers driven by HER2 homodimers. Cancer Res 2011；71：1871-1882.
16) Olson EM：Maximizing human epidermal growth factor receptor 2 inhibition：a new oncologic paradigm in the era of targeted therapy. J Clin Oncol 2012；30：1712-1714.
17) Kwei KA, Baker JB, Pelham RJ：Modulators of sensitivity and resistance to inhibition of PI3K identified in a pharmacogenomic screen of the NCI-60 human tumor cell line collection. PLoS One 2012；7：e46518.
18) Janku F, Wheler JJ, Westin SN, et al：PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol 2012；30：777-782.

連絡先　〒104-0045 東京都中央区築地5-1-1
独立行政法人国立がん研究センター中央病院
乳腺・腫瘍内科　橋本　淳

*Curr Oncol*, Vol. 21, pp. 84-90; doi: http://dx.doi.org/10.3747/co.21.1743

ORIGINAL ARTICLE



# Can oncologists predict survival for patients with progressive disease after standard chemotherapies?

*T.K. Taniyama* MD,* *K. Hashimoto* MD,*
*N. Katsumata* MD PhD,† *A. Hirakawa* PhD,‡
*K. Yonemori* MD PhD,* *M. Yunokawa* MD,* *C. Shimizu* MD,*
*K. Tamura* MD PhD,* *M. Ando* MD,§ *and Y. Fujiwara* MD PhD*

## ABSTRACT

### Background

Prediction of prognosis is important for patients so that they can make the most of the rest of their lives. Oncologists could predict survival, but the accuracy of such predictions is unclear.

### Methods

In this observational prospective cohort study, 14 oncologists treating 9 major adult solid malignancies were asked to complete questionnaires predicting survival based on performance status, oral intake, and other clinical factors when patients experienced progressive disease after standard chemotherapies. Clinically predicted survival (CPS) was calculated by the oncologists from the date of progressive disease to the predicted date of death. Actual survival (AS) was compared with CPS using Kaplan–Meier survival curves, and factors affecting inaccurate prediction were determined by logistic regression analysis. The prediction of survival time was considered accurate when the CPS/AS ratio was between 0.67 and 1.33.

### Results

The study cohort consisted of 75 patients. Median CPS was 120 days (interquartile range: 60–180 days), and median AS was 121 days (interquartile range: 40–234 days). The participating oncologists accurately predicted AS within a 33% range 36% of the time; the survival time was overestimated 36% of time and underestimated 28% of the time. The factors affecting the accuracy of the survival estimate were the experience of the oncologist, patient age, and information given about the palliative care unit.

### Conclusions

Prediction of CPS was accurate for just slightly more than one third of all patients in this study. Additional investigation of putative prognostic factors with a larger sample size is warranted.

## KEY WORDS

Survival prediction, cancer patient survival, chemotherapy

## 1. INTRODUCTION

Prediction of survival is important for patients with advanced cancer so that they can make the most of the rest of their lives. Many cancer patients want to obtain information about their prognosis in a direct and honest manner[1–3]. Nevertheless, clinicians are often averse to predicting survival[4] and divulging prognostic information[5], possibly because breaking bad news to a patient can be stressful for the physician.

A physician's level of experience in estimating survival might affect how prognosis is formulated. For example, an inexperienced physician might guess or use "intuition," ask an "expert," consult a textbook, search the electronic literature for prognostic studies, rely on their own judgment, or use a prognostic index[6]. However, even experienced oncologists find it difficult to predict survival time. Indeed, previous studies reported that clinically predicted survival (CPS) by oncologists was uncertain[7] and optimistic in terminally ill patients with cancer[8–11]. A systematic review of eight studies reported that CPS for terminal ill cancer patients was accurate for only 25%, 43%, and 61% within, respectively, 1, 2, and 4 weeks of actual survival (AS)[11]. Some studies reported that only 20%–25% of predictions were accurate (within ±33% of AS); others reported that survival was overestimated in 63%–83% of terminally ill patients[8–10,12].

Prediction of survival for patients before terminal illness is more important than that for the terminal stage, because a prediction 1–4 weeks ahead of death might be too late for patients to make the most of their remaining life.

In previous studies, predictions of survival were limited to terminally ill patients with cancer, except in work by Stockler and colleagues[7]. No reports have addressed CPS in patients who finished standard chemotherapies and experienced progressive disease. Predictors of prognosis have to be determined to improve the accuracy of CPS estimates for such patients. In this prospective study, we examined the accuracy of CPS estimates for patients who experienced progressive disease after standard chemotherapies.

## 2. METHODS

This single-centre prospective study was based on a questionnaire (Table I). The study was approved by the institutional review board.

### 2.1 Patients

At the National Cancer Center Hospital in Japan, between October 2010 and October 2011, our study recruited patients with advanced unresectable cancer and patients with progressive disease after standard chemotherapies (Table II). This observational cohort consisted of adult patients with various solid malignancies, including those of breast, lung, pancreas, colon and rectum, stomach, cervix, endometrium, and ovary, and sarcoma. The attending oncologists ($n = 14$) were asked to complete the CPS questionnaire for patients who had acquired resistance to standard chemotherapies. The CPS was estimated by the attending doctor within 7 days (at most) after the diagnosis of progressive disease after standard chemotherapy. Doctors were asked to write the predicted survival as a number of months, weeks, or days at the time of prediction. All completed questionnaires were sent to the clinical trials office. The patients were all followed until death.

### 2.2 Definition of Terms

All primary cancers were diagnosed by pathology examination. The AS was defined as the time from the date of diagnosis of progressive disease after standard chemotherapy to the date of death. The CPS was defined as the time from the date the questionnaire was completed to the predicted date of death.

Oral intake was judged mainly by the attending doctor using a simple open-ended question: How do you feel about your appetite? The answer was then scored: 1, normal or good; 2, more than 50% of normal oral intake; or 3, less than 50% of normal oral intake. A palliative care unit (PCU) was defined as a place for palliation and residency without chemotherapy and included inpatient or outpatient PCUs and home-based hospices. Best supportive care referred to hospice care based in a hospital or at home without any intensive chemotherapy[13].

### 2.3 Statistical Analysis

We calculated the Spearman correlation coefficient between the AS and the CPS. The ratio of the CPS to the AS was calculated for each patient to examine the concordance between the variables. The prediction of survival time was considered accurate when the ratio was in the range 0.67–1.33 (that is, a concordance of ±33%)[8]. Survival analysis was performed using the Kaplan–Meier method. Using multivariate regression analysis, we assessed factors affecting the difference between AS and CPS. Putative factors affecting successful prediction of survival were examined using multivariate logistic regression analysis. In all statistical analyses, values of $p < 0.05$ were considered significant. The statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, U.S.A.).

## 3. RESULTS

### 3.1 Patient and Physician Characteristics

The study enrolled 75 patients who met the eligibility criteria. Oncologists were stratified according to professional experience: less than 10 years' experience ($n = 7$) and 10 or more years' experience ($n = 7$). Table III shows patient and oncologist characteristics, and Table IV shows the decisions of the oncologists based on patient factors. Nearly 70% of the study patients had a performance status of 0–1 at the time of progressive disease. At that time, approximately 60% were considered preferable for best supportive care by their oncologist, but 70% of all patients did not receive any information about their prognosis. The main reason for that information not being conveyed was uncertainty about the survival prediction or lack of a request for the information. Although the patients had experienced progressive disease after standard chemotherapy, 35% were supposed to receive further chemotherapy. In cases of progressive disease after standard chemotherapies, 80% of patients were referred to hospice before death, and 80% of referred patients died at hospice.

### 3.2 Survival Estimates

In the 75 patients, median CPS was 120 days (interquartile range: 60–180 days), and the median AS was 121 days (interquartile range: 40–234 days). Figure 1 shows the Kaplan–Meier curves for CPS and AS. The median difference between CPS and AS (CPS − AS) was −5 days (interquartile range: −74 to 43 days). The Spearman correlation coefficient indicated a highly

TABLE I The questionnaire

1 Oncologist's name: _____

2 Malignancies

☐ Lung cancer ☐ Breast cancer ☐ Gastric cancer ☐ Colorectal cancer

☐ Sarcoma ☐ Ovarian cancer ☐ Pancreatic cancer ☐ Endometrial cancer

3 Performance status (PS)

☐ 1 ☐ 2 ☐ 3 ☐ 4

4 Patient's oral intake

☐ Normal ☐ Moderately reduced ☐ Severely reduced

5 Clinical prediction survival (CPS), defined as the period between the date of questionnaire completion and the predicted date of death

_____ month(s) _____ week(s)/day(s)

6 Main factor for CPS

☐ PS ☐ Metastatic lesion ☐ Other _____

☐ Clinical symptoms

(☐ dyspnea ☐ oral intake ☐ edema ☐ delirium)

7 Disclosure

Did you communicate the CPS?

☐ To the patient ☐ To the family ☐ To neither

If you did NOT communicate the CPS ("to neither"), why?

☐ Uncertainty ☐ They did not ask ☐ You dared not tell

☐ Other _____

8 Ways in which you treated the patient

☐ Best supportive care ☐ Chemotherapy ☐ Alternative medicine ☐ Second opinion

☐ Other ☐ Surgery ☐ Clinical trial ☐ Palliative radiation

_____

9 If you did NOT refer to palliative care unit (PCU), why?

☐ Inappropriate time ☐ You dared not suggest the PCU ☐ Other

_____

10 Final decision

☐ Best supportive care ☐ Chemotherapy ☐ Alternative medicine ☐ Second opinion

☐ Other ☐ Surgery ☐ Clinical trial ☐ Palliative radiation

_____

_____