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BMJ Open

A retrospective analysis of factors associated with selection of end-of-life care and actual place of death for patients with cancer

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To cite: Kondo S, Shimazu T, Morizane C, *et al*. A retrospective analysis of factors associated with selection of end-of-life care and actual place of death for patients with cancer . *BMJ Open* 2014;**4**:e004352. doi:10.1136/bmjopen-2013-004352

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-004352).

Received 29 October 2013
Revised 11 March 2014
Accepted 14 April 2014

ABSTRACT

Objectives: The factors associated with end-of-life (EOL) care that patients with cancer selected and actual place of death (POD) is less elucidated. We analysed how specific EOL care, especially anticancer therapies, selected by patients with pancreatic carcinoma affected their POD in Japan.

Setting: A retrospective cohort study using clinical records of a single institute.

Participants: This study included 433 advanced or recurrent patients with pancreatic carcinoma who had completed standard chemotherapies and were receiving hospice care in the National Cancer Center Hospital between April 2008 and April 2011.

Outcome measures: We analysed statistical association factors, demographic information, geographical differences, medical environment, EOL care selection, along with actual POD using logistic regression analysis.

Results: Of the 433 patients, 147 selected palliative care units (PCUs) as the POD; 229, hospital; and 57, home with hospice care. POD selection was associated with several factors. Notably, EOL care selection, especially the use of complementary and alternative medicine (CAM), is associated with POD selection (death in PCU; OR=0.23, p=0.02).

Conclusions: This study is, to the best of our knowledge, the first to unveil that EOL care selection is associated with POD in Japan. Certain factors such as gender, medical environment and EOL care selection might influence the POD. Patients who pursue aggressive anticancer therapies, such as CAM use, were possibly deprived of a chance of early reference to a PCU.

Strengths and limitations of this study

- This study is the first to unveil that end-of-life care selection is associated with place of death in Japan.
- Patients who pursue aggressive anticancer therapies, such as complementary and alternative medicine use, were possibly deprived of a chance of early reference to the palliative care unit.
- Limitations of this study should be considered, including its retrospective nature and the involvement of a single institution. Therefore, the findings may not be entirely representative of patients receiving cancer treatment at other Japanese cancer hospitals.

INTRODUCTION

In Japan, the Cancer Control Act was established to improve the quality of life (QOL) of all patients with cancer, and disseminating palliative care was identified as one of the most important areas to be improved. To disseminate quality palliative care, palliative care units (PCUs) and palliative care team were established. Although PCU is the most common type of specialised palliative care service in Japan,[1] patients with cancer can choose their place of death (POD) as either PCUs, home with hospice or non-PCU hospitals.

Dying at a preferred place is one of the most important determinants for terminally ill patients with cancer.[2 3] In some previous reports, POD for patients with cancer was influenced by several factors such as illness, demographic variables, personal variables, social support and relationship with the physician.[4 5] Moreover, patients who optimistically estimated their prognoses are more likely to undergo aggressive treatment, but controlling for known prognostic factors, their 6-month survival is no better.[6]

Choice of cancer therapy at the EOL is becoming increasingly complex due to more options for therapy, high expectations from therapy, less toxic treatments and better supportive care. Consequences of these choices may have an enormous impact on patients and families (caregiver) and societal healthcare costs. Although less aggressive care,

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especially palliative care, at the EOL is associated with better QOL near death,[7 8] patients with cancer are receiving increasingly aggressive care at the EOL.[9 10] The use of complementary and alternative medicine (CAM) as an aggressive anticancer therapy has been increasing worldwide over the past two decades, and an estimated 40–60% of adult patients with cancer use CAM, although it does not provide definite survival benefit and its users report clinically poor QOL.[11]

We hypothesised that aggressive anticancer therapy, especially CAM chosen by patients with cancer, limited their options of POD selection. Hence, we conducted this study to analyse the factors that influence POD and to show the evidence of influence of EOL care selection after standard chemotherapy on patients' POD. Moreover, we also analysed the factors that influence EOL care selection in this study.

METHODS

Selection criteria

Patients receiving hospice care at the National Cancer Center Hospital (NCCH) between April 2008 and April 2011 were selected. The inclusion criteria were as follows: confirmed as having carcinoma according to the results of histological tests, had advanced or recurrent pancreatic carcinoma, were receiving systemic palliative chemotherapy at the NCCH, failed to respond to standard chemotherapy and had discussed about EOL care with their attending physician. Prior to the start of chemotherapy, all patients included in the analysis were clearly informed that the chemotherapy being administered was not curative but aimed at prolonging their survival and palliating their symptoms. Their signed informed consent for the same was obtained. From the analysis, we excluded patients who had not been receiving standard chemotherapies or who did not choose POD. This study protocol was approved by the Institutional Review Board of the NCCH, Tokyo, Japan.

Data extraction and definition of terms

The following information was collected with regard to patients: (1) demographic (age, sex, relation with the attending physician, main family caregiver and state of disease), (2) geographical differences (distance from the cancer centre), (3) medical environment (involvement of a palliative care team, a case worker, a primary care doctor and regional healthcare cooperation during chemotherapy) and (4) EOL care selection (best supportive care (BSC), non-standard chemotherapy and CAM use).

In this study, we defined PCU as the institute has been covered by National Medical Insurance since 1990 and plays a central role in providing specialised palliative care services to patients with cancer. Since the NCCH does not have beds assigned for palliative care, patients were provided with information about PCUs near their homes or according to their wish at the start of chemotherapy or completion of standard chemotherapy. Dying at home was defined as dying at home with hospice. Other hospitals except PCUs and homes with hospice were defined as non-PCU hospitals in this study.

In this study, we defined standard therapy as gemcitabine-based or S-1-based chemotherapy. Aggressive anticancer therapy was defined as non-standard chemotherapies and CAM. Non-standard chemotherapy was defined as chemotherapy with other cytotoxic agents and included participation in a clinical trial. We used the definition of CAM adopted by the National Cancer Institute: 'CAM is the term for medical products and practices that are not part of standard medical care.' NCI categorises CAM as follows: CAM (any medical system, practice or product, ie, not thought of as standard care), complementary medicine (CAM therapy used along with standard medicine), alternative medicine (CAM therapy used in place of standard treatments) and integrative medicine (an approach that combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness).

Statistical analysis

We conducted statistical analyses using IBM SPSS V.18.0 (SPSS, Chicago, Illinois, USA). All patient characteristics and background factors were analysed using the logistic regression analyses. Multivariate logistic regression analyses were performed after univariate analyses to reveal strong correlation factors between POD and EOL care. p Values less than 0.05 in a two-sided test were considered significant.

RESULTS

Patient characteristics

A total of 433 patients received systemic chemotherapy for advanced and recurrent pancreatic carcinoma at the NCCH (figure 1). Of these, 147 (34%) patients chose PCU, 57 (13%) patients chose home with hospice and 229 (53%) patients chose non-PCU hospitals as their POD. In total, 357 (82%) patients chose to receive BSC and 76 (18%) patients chose aggressive anticancer treatment as EOL care. In patients with aggressive anticancer therapy, 64 (15%) patients used non-standard chemotherapies and 57 (13%) patients used CAM as EOL care (table 1).

Factors influencing POD

In multivariate logistic regression analysis using strong factors that correlated with POD in univariate analyses, patients who selected PCUs as the POD were most likely to be of female gender (OR 1.85; 95% CI 1.23 to 2.79; p=0.003) and CAM users (OR 0.23; 95% CI 0.06 to 0.81; p=0.02). Patients who selected dying at home were most likely to be supported by a case worker (OR 3.50; 95% CI 1.22 to 10.03; p=0.02) and be town dwellers (OR 2.13; 95% CI 1.18 to 3.85; p=0.01). Patients who died at non-PCU hospitals were likely to be of male gender (OR

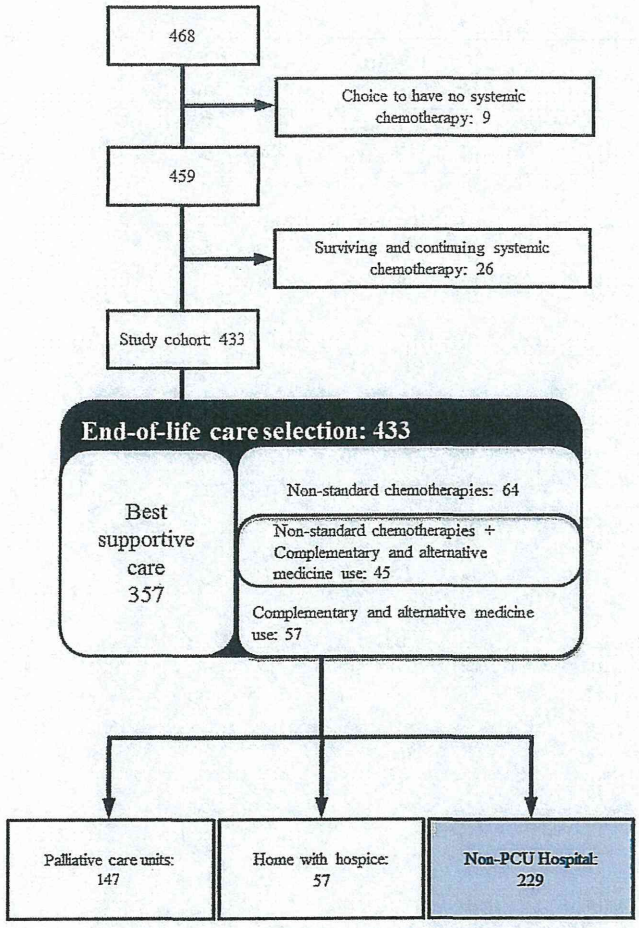

Figure 1 Patient distribution in the study. A total of 468 patients with advanced or recurrent pancreatic carcinoma were seen at the National Cancer Center Hospital. Nine patients chose best supportive care without receiving chemotherapy. Twenty-six patients are still alive and are continuing with standard chemotherapy.

1.64; 95% CI 1.10 to 2.44; p=0.02), rural dwellers (OR 1.85; 95% CI 1.24 to 2.74; p=0.002) and had involvement of a case worker (OR 2.44; 95% CI 1.43 to 4.17; p=0.001) (**table 2**). Although we conducted additional analyses including all variables (age, gender, caregiver, distance from the cancer centre, attending physician, state of disease, EOL selection and medical environment) into the model, the results were materially unchanged.

Factors influencing EOL care selection

Table 3 shows the results of multivariate analyses using significant factors after univariate analyses associated with EOL care selection were performed. Patients who selected BSC as EOL care were of older age (OR=1.67; 95% CI 1.02 to 2.78; p=0.04) and had recurrence after surgical resection (OR=1.82; 95% CI 1.02 to 3.23; p=0.04). Patients who selected non-standard chemotherapies were of younger age (OR=2.04; 95% CI 1.18 to 3.51; p=0.01). Patients who selected CAM use were of younger age (OR=2.57; 95% CI 1.43 to 4.63; p=0.01) and depended on the attending physician. Although we conducted additional analyses including all variables into the model, the results were materially unchanged.

DISCUSSION

The present study results indicate that EOL care selected by Japanese patients with pancreatic cancer after complete standard chemotherapy was correlated with the selection of POD. Notably, the factors of (1) demographic (gender), (2) geographical differences (distance from the cancer centre), (3) medical environment (involvement of a case worker) and (4) EOL care selection (CAM use) were strongly correlated with selection of POD. Moreover, patients' age, state of disease and dependence on the attending physician were strong factors that correlated with EOL care selection. We found that patients who selected aggressive anticancer therapy as EOL care, especially CAM use, tended to lose the opportunity to die in a PCU.

In Japan, a series of national surveys was conducted by the Ministry of Health, Labour and Welfare in 2008 to reveal the preferred place of care and POD. Home was the preferred place of care in general, with 29% of respondents reporting that they wanted to receive care at home and be admitted to a PCU if necessary, and 23% preferring to receive care at home and be admitted to a hospital if necessary. Another 11% chose home until death, while a considerable number of respondents reported that they want to be admitted to a hospice earlier and stay until death (18%) or be admitted to a hospital earlier and stay until death (10%). The distribution of POD in this study reflected the trend in the preference of Japanese patients with cancer with regard to place of care and POD.

In some previous reports, factors that influence selection of POD for patients with cancer were related to illness,[12] individual factors that account for the maintenance of patients' individuality, comparison of demographic variables and personal variables,[13] social support[4] and relationship with the physician.[5] The present study showed gender female associated with PCU as actual POD. On the other hand, a previous British report showed gender was not associated with POD.[4] In this study, EOL care selection, especially CAM use, influenced POD. Moreover, selection of best supportive care as EOL care associated with PCU as actual POD. Patients select aggressive anticancer therapies closer to death, with unintended consequences of late PCU referral.[14] Moreover, physicians can predict the survival time of their patients based on experience and clinical data.[15] On the other hand, patients pursue aggressive anticancer therapies, such as CAM use due to lack of awareness of their prognosis. Selecting a treatment mode without prediction of prognosis causes these patients to lose their chance of early reference to their preferred POD.

Table 1 Patient characteristics

		Total	PCU		Home with hospice		Non-PCU Hospital		
		Total	n	Per cent	n	Per cent	n	Per cent	
Total		433	147	34	57	13	229	53	p Value*
Age									
Mean (SD)		64.8 (9.3)	65.0 (9.4)		66.5 (8.8)		64.2 (9.4)		
≥65		234	82	56	31	54	121	53	0.85
<65		199	65	44	26	46	108	47	
Gender									
Male		258	72	49	36	63	150	66	0.005
Female		175	75	51	21	37	79	34	
Close relative (caregiver)									
Spouse	+	334	110	75	44	77	180	79	0.70
	–	99	37	25	13	23	49	21	
Daughter(s) or son(s)	+	326	109	74	43	75	174	76	0.92
	–	107	38	26	14	25	55	24	
Parent(s)	+	13	5	3	1	2	7	3	0.82
	–	420	142	97	56	98	222	97	
Distance from the cancer center									
Mean (SD) (km)		32 (78.1)	32 (85.6)		16 (10.4)		36.2 (82.2)		
0–19		224	83	56	38	67	103	45	0.005
≥20		209	64	44	19	33	126	55	
Attending physician									
A		127	43	29	11	19	73	32	0.45
B		62	24	16	11	19	27	12	
C		114	35	24	16	28	63	28	
D		130	45	31	19	34	66	28	
State of disease									
Advanced		350	114	78	47	82	189	83	0.46
Recurrence		83	33	22	10	18	40	17	
End-of-life care selection									
Best supportive care	+	357	129	88	48	84	180	79	0.07
	–	76	18	12	9	16	49	21	
Non-standard chemotherapies	+	64	14	10	8	14	42	18	0.06
	–	369	133	90	49	86	187	82	
CAM	+	57	10	7	7	12	40	17	0.01
	–	376	137	93	50	88	189	83	
Medical environment									
Involvement of a palliative care team	+	44	13	9	5	9	26	11	0.69
	–	389	134	91	52	91	203	89	
Involvement of a caseworker	+	354	127	86	53	92	174	76	0.002
	–	79	20	14	4	8	55	24	
Primary care doctor	+	133	46	31	12	21	75	33	0.23
	–	300	101	69	45	79	154	67	

*Using χ^2 test for categorical variables.
CAM, complementary and alternative medicine; PCU, palliative care units.

Geographical differences in established PCUs, BSC at home and regional hospitals with palliative care teams reduce the choice of POD available to patients. According to studies conducted in Europe, patients living in rural areas have increased difficulty in accessing healthcare[12] and palliative care[16]; yet, they are more likely to die at home.[4] In the present study, the choice of dying at home with hospice increased with the closer distance from the cancer centre, which is located in the centre of Tokyo. These results support the view that geographical trends affect the choice of POD in Japan and Europe.

The present study also showed that social support and involvement of a case worker affect the selection of POD. Specifically, social support influenced death at home through arrangement of medical environment by case workers. On the other hand, involvement of a palliative care team can potentially improve the timing of referral to a PCU.[17] In this study, the palliative care team had no role in influencing the selection of POD of patients with cancer. Comprehensive cancer teams including the palliative care team, psycho-oncologist and case workers can involve patients in discussions about advance planning for care or POD.

Table 2 Factors associated with place of death: multivariate analysis

Place of death	Factors	n	OR (95% CI)	p Value*
PCU	Gender			
	Male	72	1 (Ref)	0.003
	Female	76	1.85 (1.23 to 2.79)	
	Best supportive care			
	–	18	1 (Ref)	0.13
	+	129	3.85 (0.66 to 25)	
	Non-standard chemotherapies			
	–	14	1 (Ref)	0.15
	+	133	3.00 (0.68 to 13.3)	
	CAM			
	–	137	1 (Ref)	0.02
	+	10	0.23 (0.06 to 0.81)	
Home with hospice	Distance from the cancer centre			
	0–19 km	38	1 (Ref)	0.01
	≥20 km	19	0.47 (0.26 to 0.85)	
	Involvement of a caseworker			
	–	5	1 (Ref)	0.02
	+	52	3.50 (1.22 to 10.03)	
Non-PCU Hospital	Gender			
	Male	150	1 (Ref)	0.02
	Female	79	0.61 (0.41 to 0.91)	
	Distance from the cancer centre			
	0–19 km	103	1 (Ref)	0.002
	≥20 km	126	1.85 (1.24 to 2.74)	
	Best supportive care			
	–	180	1 (Ref)	0.45
	+	49	0.53 (0.10 to 2.80)	
	Non-standard chemotherapies			
	–	42	1 (Ref)	0.37
	+	187	1.87 (0.47 to 7.35)	
	CAM			
	–	40	1 (Ref)	0.13
	+	189	2.41 (0.76 to 7.63)	
	Involvement of a caseworker			
	–	55	1 (Ref)	0.001
	+	174	2.44 (1.43 to 4.17)	

*The multivariate analysis was performed using logistic regression analysis after.
CAM, complementary and alternative; PCU, palliative care units; Ref, reference.

The trend of use of aggressive chemotherapy increased even in older patients, and the use of PCU as simply a place to die in rather than to control symptoms became common.[9 15] In this study, 18% of patients with pancreatic cancer used aggressive anticancer treatment as EOL care. In the USA, the proportion of patients who choose cancer therapy at the EOL has increased from 13.8% to 18.5%.[18] Our study shows a similar proportion when compared with previous reports. On the other hand, in this study, the prevalence of CAM use in patients with pancreatic cancer was 13%. This rate was slightly lower than that found in previous studies.[19 20] The prevalence of CAM use was potentially affected by several factors, including primary cancer site. In terms of cancer site, the rate of CAM use was higher in patients with lung, breast and hepatobiliary cancers than in those with other cancers, including gastrointestinal cancer. Hence, the ratio of CAM use in pancreatic cancer may be lower than that in the previous report.[19] The multivariate analysis also revealed a close association between aggressive anticancer therapies and younger age. Previous studies showed that some factors, including younger age, were significant independent predictors of aggressive EOL care.[9 10 19 21]

Certain limitations of this study should be considered, including its retrospective nature and the involvement of a single institution. Therefore, the findings may not be entirely representative of patients receiving cancer treatment at other Japanese cancer hospitals; moreover, we could not determine some other factors that influenced the selection of POD by patients with cancer. Above all, the study focused on factors associated with choosing EOL care and how these factors affect POD choice, but it did not include analysis of some other factors such as

Table 3 Factors associated with end-of-life care selection: multivariate regression

End-of-life care	Factors	n	Multivariate analyses OR (95% CI)	p Value*
Best supportive care	Age			
	≥65	201	1 (Ref)	0.04
	<65	156	0.60 (0.36 to 0.98)	
	State of disease			
	Advanced	295	1 (Ref)	0.04
	Recurrence	62	1.82 (1.02 to 3.23)	
Non-standard chemotherapies	Age			
	≥65	25	1 (Ref)	0.01
	<65	39	2.04 (1.18 to 3.51)	
CAM	Age			
	≥65	20	1 (Ref)	0.002
	<65	37	2.57 (1.43 to 4.63)	
	Attending physician			
	A	24	1 (Ref)	0.03
	B	9	0.27 (0.11 to 0.62)	0.002
	C	16	0.37 (0.13 to 1.02)	>0.05
	D	8	0.38 (0.15 to 0.94)	0.04

*The multivariate analysis was performed using logistic regression analysis after.
†Univariate analyses.
CAM, complementary and alternative; Ref, reference.

income of patients, religion and timing of EOL discussions.

Physicians commonly avoid EOL care-related discussions with patients until they fail standard chemotherapy or are nearing death.[22] Physicians who have close, long-term relationships with patients often wish to avoid discussions around EOL care.[23] Physicians involved in longitudinal care, however, may be best equipped to have meaningful discussions about the patient's values and goals.[5] NCCH, all attending physicians informed their patients before starting chemotherapy that advanced pancreatic carcinoma had reduced chances of being cured and that chemotherapy was of limited use in palliation and prolongation of survival. Some patients who discussed EOL care or POD during treatment with standard chemotherapy collaterally underwent a checkup or received palliative care in community hospitals or PCUs. The selection of CAM use as EOL care by the attending physician points to the critical need to recognise the lack of discussion with patients about EOL care. Moreover, selecting EOL care after failing standard chemotherapy had a direct bearing on the selection of POD.

In conclusion, the present study provides new and important information on the factors influencing patients' choices at the EOL. To the best of our knowledge, this is the first report of an investigation on POD that focuses on EOL care selection, especially aggressive anticancer treatment including CAM, among Japanese patients with pancreatic cancer. Importantly, patients and physicians should share the same information related to survival benefits and places to receive EOL care and choose appropriate POD.

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Acknowledgements The authors appreciate the contributions of Keiko Kondo and Rubi Mukoyama in collecting clinical data.

Contributors SK, HH and TS designed and participated in all stages of the study. SK, TS and HH participated in statistical analyses and discussion of the results. SK and HH recruited the patients. ST, TS, HH, CM, TO and HU helped to draft the manuscript. All authors read and approved the final manuscript.

Funding This work was supported in part by the National Cancer Center Research and Development Fund (23-A-14).

Competing interests None.

Ethics approval This study protocol was approved by the Institutional Review Board of the NCCH, Tokyo.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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BMJ Open

A retrospective analysis of factors associated with selection of end-of-life care and actual place of death for patients with cancer

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BMJ Open 2014 4:
doi: 10.1136/bmjopen-2013-004352

SciMedCentral

JSM Clinical Oncology and Research

Editorial

Utility of 'Clinical' Sequence

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Submitted: 12 March 2014

Accepted: 22 April 2014

Published: 05 May 2014

EDITORIAL

Personalized cancer management provides patients with the optimum treatment according to their individual circumstances and the molecular characteristics of their tumors. While we are currently in an era of "stratified medicine," constant efforts are being made to progress to an era of personalized medicine. Innovative techniques such as next generation sequencing (NGS), a powerful tool to identify druggable mutations, are key factors for personalized medicine. The applications of NGS are multifarious. Druggable mutations and the corresponding drugs have been identified for several tumors (Table 1). For non-small cell lung cancer (NSCLC), such known mutations include *EGFR*, *ALK*, *RET*, *ROS1*, and *BRAF*. Thus, a concomitant analysiswith NGSin patient with NSCLC is time and cost effective. In addition, gene alterations common to different tumor types have been identified. For example, *ALK* mutations are common to NSCLC, inflammatory myofibroblastic tumors, neuroblastoma, colorectal cancer, and anaplastic large cell lymphoma, and crizotinib, a potential *ALK* inhibitor, has been proven to be efficacious against some of these tumors. Therefore, the clinical applications of NGS extend to the identification of druggable mutations across tumor types. To further explore the clinical utility of NGS, we conducted a prospective study entitled "ABC study" (Figure 1).The preliminary results of this study were presented at the 2013 AACR-NCI-EORTC International Conference. In this study, genomic DNA was extracted from pretreatment formalin-fixed paraffin-embedded biopsy samples, and 10 ng of double-stranded DNA was applied to the amplicon sequence using Ion AmpliSeq™ Cancer Panel ver1.0, targeting 739 COSMIC-

Table 1: Druggable mutations and the corresponding drugs.

Target	Type of Molecular Aberration	Cancer Type	Example of Drugs
BCR-ABL	Translocation	CML and ALL	Imatinib, dasatinib, nilotinib
BRAF V600E	Mutation	Melanoma	Vemurafenib, dabrafenib
C-KIT	Mutation	GIST	Imatinib, sunitinib
EGFR	Mutation	NSCLC	Erlotinib, gefitinib,afatinib
EML4-ALK	Translocation	NSCLC	Crizotinib
Hedgehog pathway (PTCH, SMO)	Mutation	Basal cell cancer	Vismodegib
HER2	Gene amplification	Breast cancer, gastric cancer	Trastuzumab, lapatinib,pertuzumab, T-DM1
JAK	Mutation	Myelofibrosis	Ruxolitinib
KRAS	Mutation	Colorectal cancer	Cetuximab, pantitumab
PML-RARα	Translocation	Acute promyelocytic leukemia	All-trans-retinoic acid, arsenic trioxide
RET	Mutation	Medullary thyroid cancer	Vandetanib, cabozantinib

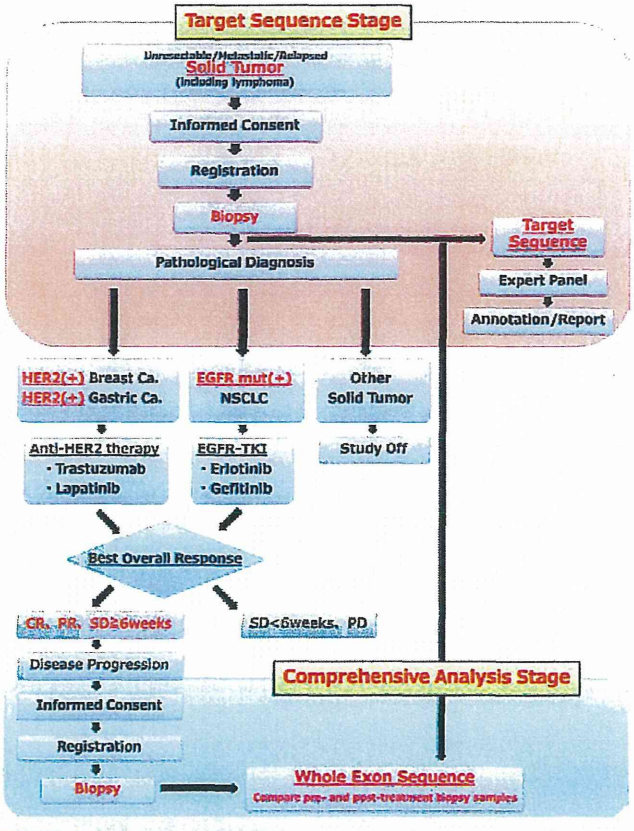

Figure 1 ABC study comprises two stages; in the "Target Sequence Stage", the profile of targeted somatic mutations in metastatic/recurrent solid tumors is investigated. "Comprehensive Analysis Stage" is the stage investigating the mechanism of drug resistance.

registered mutations of 46 oncogenes and tumor suppressor genes. Potentially targetable mutations were detected in 44% of the patients; these included *PIK3CA* (15%), *KRAS* (15%), *CTNNB1* (7.5%), *EGFR* (3.2%), *GNAS* (3.2%), *BRAF* (2.1%), *ERBB2* (2.1%), *KIT* (1.1%), and *NRAS* (1.1%).These results are consistent with those of previous studies. NGS is increasingly being adopted in clinical practice, although analytical, clinical, social, and economic issues remain to be addressed. Another application of NGS is to explore the pathogenesis of cancer. Genomic and epigenomic alterations have been reported in major cancers, and the use of NGS is expected to be expanded to sarcomas, rare cancers, and hereditary cancers. Accordingly, we are now planning a prospective, multicenter study to identify the pathogenesis of a rare, familial cancer.

CONCLUSION

NGS is now widely and increasingly being adopted in both clinical practice and research.

Cite this article

Naito Y (2014) Utility of 'Clinical' Sequence. JSM Clin Oncol Res 2(5): 1035.