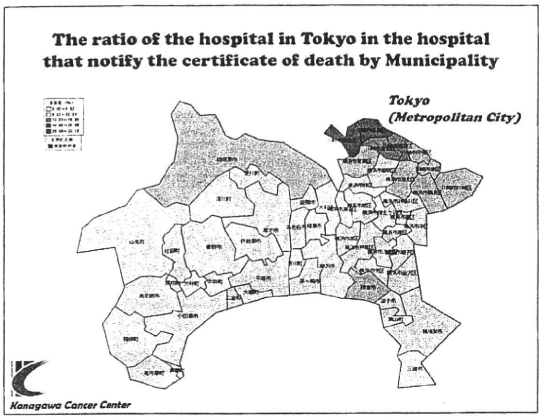
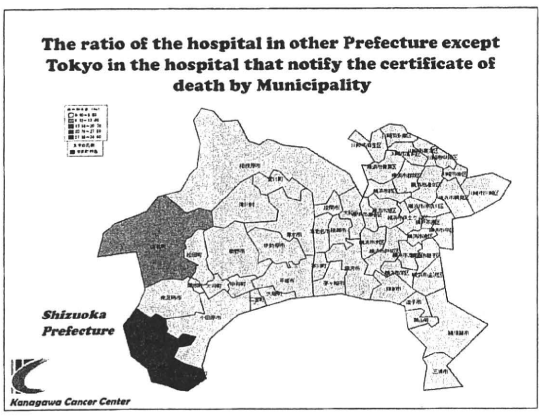
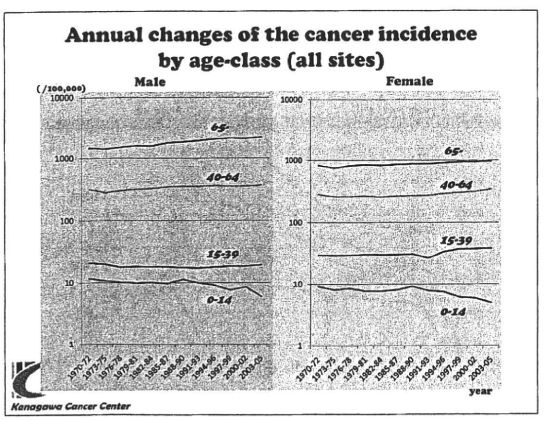
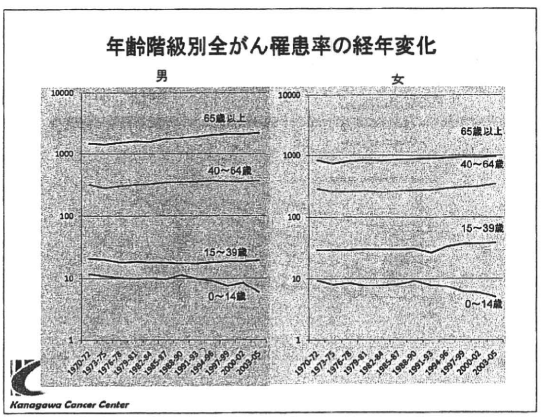

The ratio of the hospital in Tokyo in the hospital that notify the certificate of death by Municipality
Tokyo (Metropolitan City)
Kanagawa Cancer Center

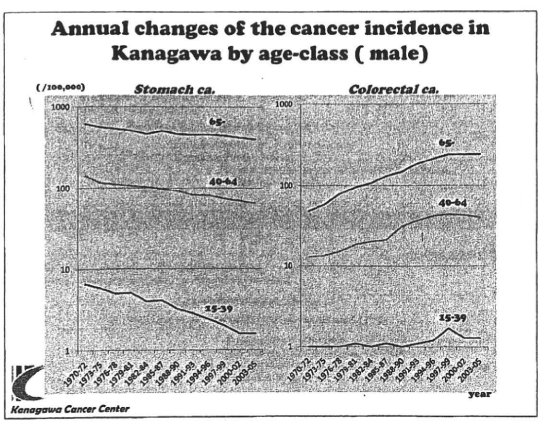

市区町村別「がん死亡者の届出」が東京である割合
東京都
Kanagawa Cancer Center

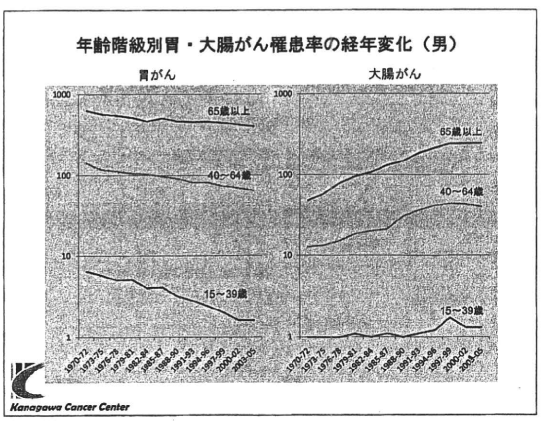

The ratio of the hospital in other Prefecture except Tokyo in the hospital that notify the certificate of death by Municipality
Shizuoka Prefecture
Kanagawa Cancer Center

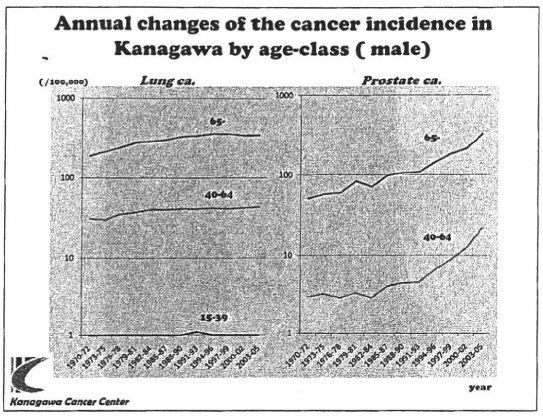

市区町村別「がん死亡者の届出」が他県(東京以外)である割合
静岡県
Kanagawa Cancer Center

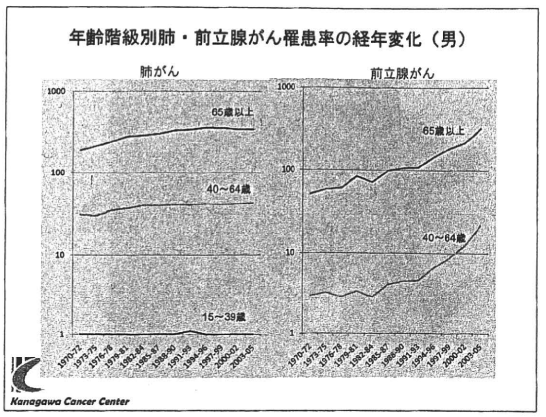

Annual changes of the cancer incidence by age-class (all sites)
Male
Female
(/100,000)
65-
40-64
15-39
0-14
year
Kanagawa Cancer Center

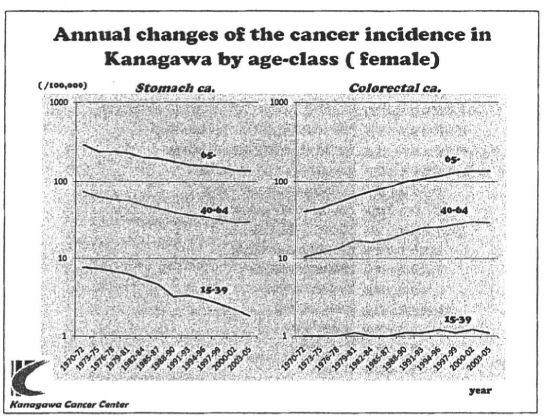

年齢階級別全がん罹患率の経年変化
男
女
65歳以上
40～64歳
15～39歳
0～14歳
Kanagawa Cancer Center

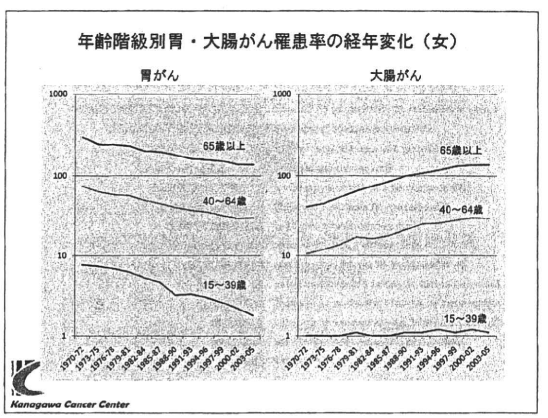

Annual changes of the cancer incidence in Kanagawa by age-class (male)
(/100,000)
Stomach ca.
Colorectal ca.
65-
40-64
15-39
year
Kanagawa Cancer Center

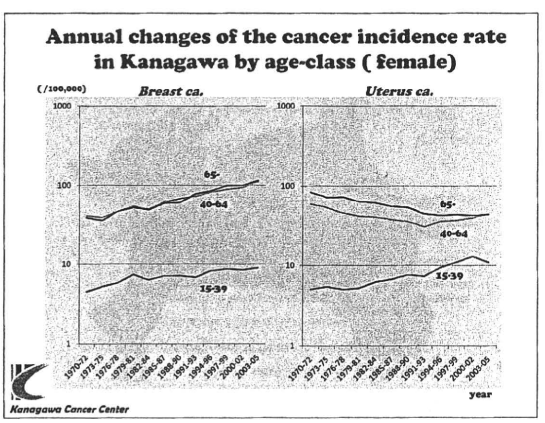

年齢階級別胃・大腸がん罹患率の経年変化（男）
胃がん
大腸がん
65歳以上
40～64歳
15～39歳
Kanagawa Cancer Center

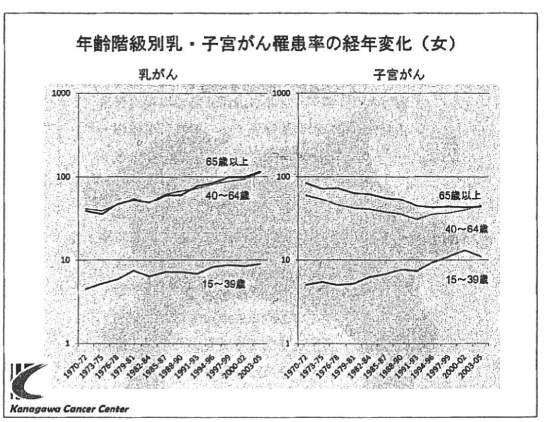

Annual changes of the cancer incidence in Kanagawa by age-class (male)
(/100,000)
Lung ca.
Prostate ca.
65-
40-64
15-39
year
Kanagawa Cancer Center

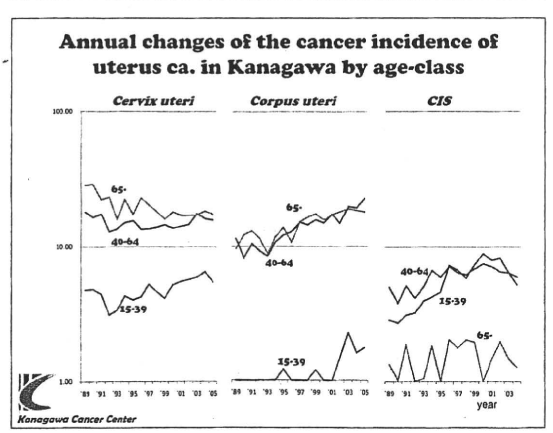

年齢階級別肺・前立腺がん罹患率の経年変化（男）
肺がん
前立腺がん
65歳以上
40～64歳
15～39歳
Kanagawa Cancer Center

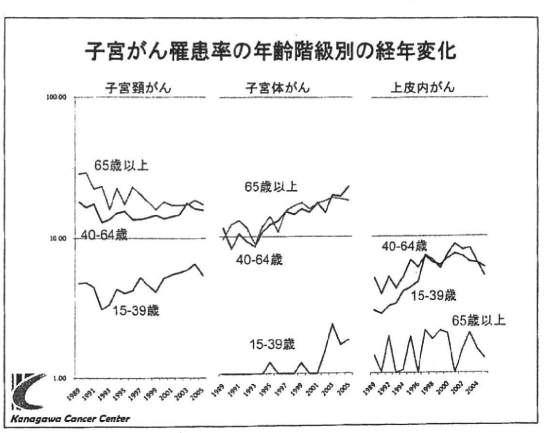

Annual changes of the cancer incidence in Kanagawa by age-class (female)
(/100,000)
Stomach ca.
Colorectal ca.
65-
40-64
15-39
year
Kanagawa Cancer Center


年齢階級別胃・大腸がん罹患率の経年変化（女）
胃がん
大腸がん
65歳以上
40～64歳
15～39歳
Kanagawa Cancer Center


Annual changes of the cancer incidence rate in Kanagawa by age-class (female)
(/100,000)
Breast ca.
Uterus ca.
65-
40-64
15-39
year
Kanagawa Cancer Center

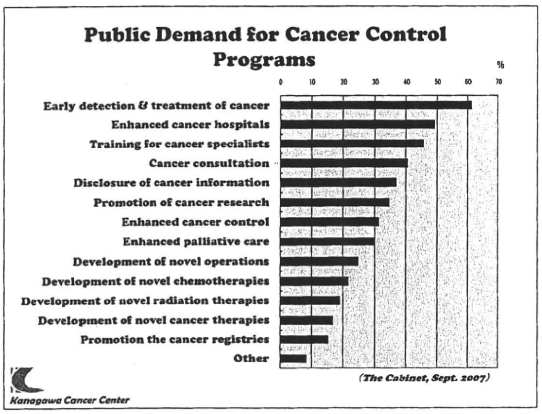

年齢階級別乳・子宮がん罹患率の経年変化（女）
乳がん
子宮がん
65歳以上
40～64歳
15～39歳
Kanagawa Cancer Center


Annual changes of the cancer incidence of uterus ca. in Kanagawa by age-class
Cervix uteri
Corpus uteri
CIS
65-
40-64
15-39
year
Kanagawa Cancer Center

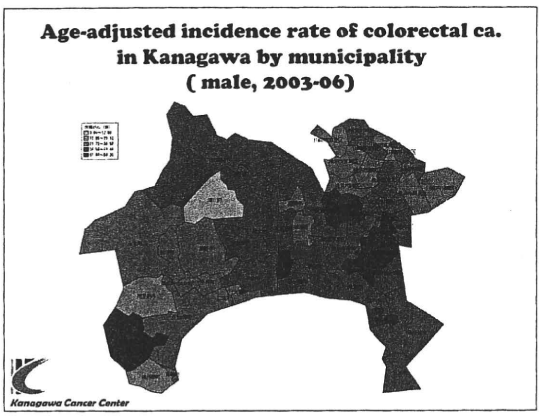

子宮がん罹患率の年齢階級別の経年変化
子宮頸がん
子宮体がん
上皮内がん
65歳以上
40-64歳
15-39歳
Kanagawa Cancer Center

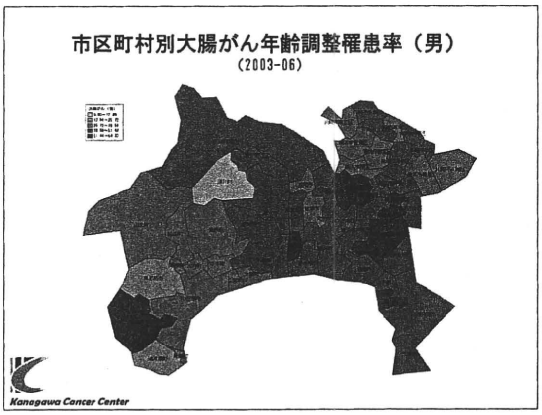

Challenge against Cancer: 10-year Strategy
がんへの挑戦：10か年戦略
～がんにならない 負けない 神奈川づくり～
平成17年3月 March, 2005
神奈川県 Kanagawa Prefecture
Kanagawa Cancer Center

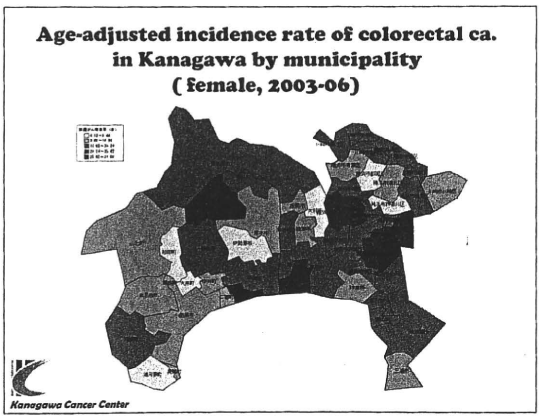

2005年3月
がんへの挑戦：10か年戦略
～がんにならない 負けない 神奈川づくり～
平成17年3月
神奈川県
Kanagawa Cancer Center

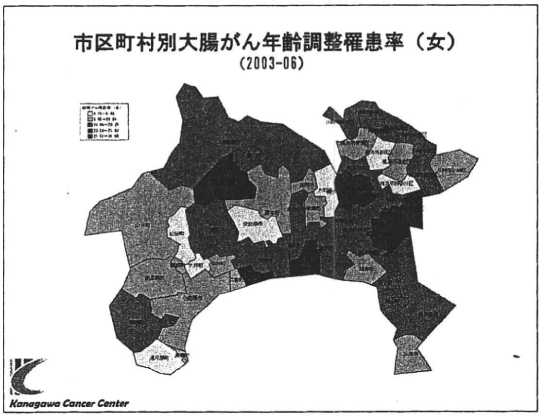

Public Demand for Cancer Control Programs
%
0 10 20 30 40 50 60 70
Early detection & treatment of cancer
Enhanced cancer hospitals
Training for cancer specialists
Cancer consultation
Disclosure of cancer information
Promotion of cancer research
Enhanced cancer control
Enhanced palliative care
Development of novel operations
Development of novel chemotherapies
Development of novel radiation therapies
Development of novel cancer therapies
Promotion the cancer registries
Other
(The Cabinet, Sept. 2007)
Kanagawa Cancer Center


がん対策に対する政府への要望
（内閣府平成19年9月調査）
%
0 10 20 30 40 50 60 70
がんの早期発見（がん検診）
がん医療機関の充実
がん専門医療従事者の養成
がんに関する相談やその支援
がん情報の提供
がん研究の推進
がん予防対策の充実
緩和ケアの充実
手術療法の開発
化学療法の開発
放射線治療の開発
新たながん治療の開発
がん登録の推進
その他、無回答
Kanagawa Cancer Center

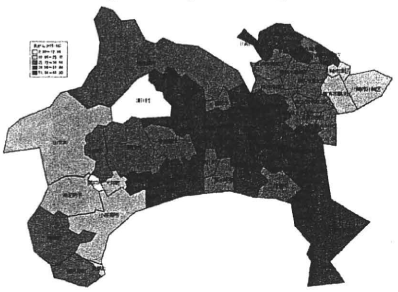

Age-adjusted incidence rate of colorectal ca. in Kanagawa by municipality
(male, 2003-06)
Kanagawa Cancer Center


市区町村別大腸がん年齢調整罹患率（男）
(2003-06)
Kanagawa Cancer Center


Age-adjusted incidence rate of colorectal ca. in Kanagawa by municipality
(female, 2003-06)
Kanagawa Cancer Center

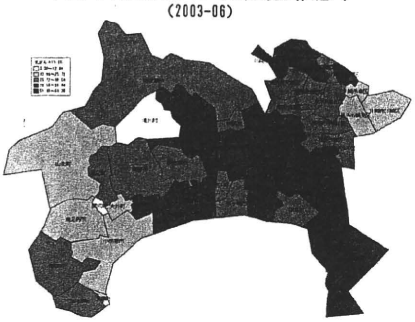

市区町村別大腸がん年齢調整罹患率（女）
(2003-06)
Kanagawa Cancer Center

Age-adjusted incidence rate of breast ca. in Kanagawa by municipality (female, 2003-06)



Kanagawa Cancer Center

市区町村別乳がん年齢調整罹患率 (2003-06)



Kanagawa Cancer Center

An Image of Kanagawa in the Future

To execute the overall cancer control program and promote cancer prevention, early detection, novel cancer therapies, palliative care, etc. by 2014

- **Promote lifestyles with a reduced cancer risk**
  - ***Stop smoking, prevent passive smoking***
  - ***Improve lifestyle overall***
  - ***Enhance cancer screening***
  - ***Offer accurate cancer information***
- **Promote control programs to overcome cancer**
  - ***Specify base hospitals for cancer treatment***
  - ***Promote advanced cancer therapy and research***
  - ***Enhance palliative care***

Kanagawa Cancer Center

目指す神奈川のすがた

予防、早期発見、治療、ターミナルケアまでを見通した総合的ながん対策の展開、平成26年までに目指す

- **●がんにならない神奈川づくり**
  - **・禁煙、分煙の徹底　・食生活、運動などの生活改善**
  - **・がん検診の充実　・がんの情報提供**
- **●がんに負けない神奈川づくり**
  - **・がん診療連携拠点病院　・高度ながん医療や研究**
  - **・緩和ケアの充実**

Kanagawa Cancer Center

Emphatic Measures to Achieve an Effective Cancer Control Program

1. **Promote cancer prevention measures citizens can do themselves**
   - ***Stop smoking and improve lifestyle***
2. **Detect cancer early**
   - ***Strengthen the breast cancer screening program***
3. **Offer advanced cancer therapy and construct a regional cancer treatment network**
   - ***Introduce state-of-the-art medical equipment***
   - ***Promote clinical cancer research cooperatively within the public-industrial-academic complex***
   - ***Construct a hospital network***
4. **Enhance the regional system for terminal care**
   - ***Offer terminal care to esteem of individuals***

Kanagawa Cancer Center

神奈川のすがたの実現へ向けた重点施策

1．県民に身近な自ら取組みやすい予防対策の推進
- ・喫煙率の低下　→　受動喫煙防止条例の制定へ
- ・食生活改善、生活習慣改善

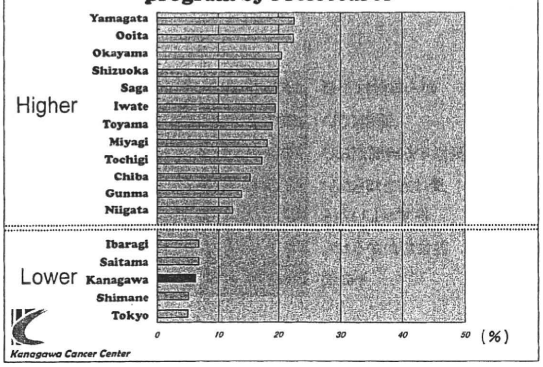
2．がんを早期に発見する体制の整備
- ・乳がん検診の充実強化

3．高度ながん医療の提供と地域がん医療のネットワークづくり
- ・最先端医療機器の導入
- ・産学公共同による臨床研究、情報提供
- ・地域がん診療連携拠点病院のネットワークづくり

4．地域でのターミナルケア体制の充実
- ・一人ひとりを尊重したターミナルケアの提供

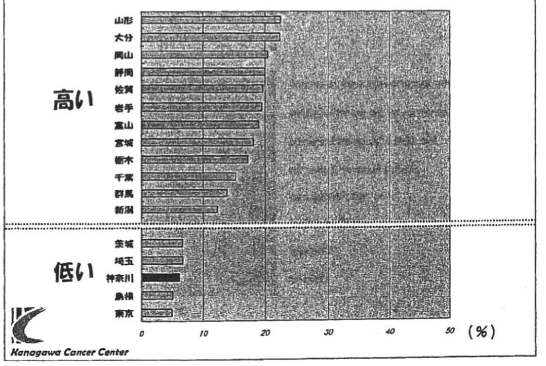
Kanagawa Cancer Center

Participation rate of breast cancer screening program by Prefectures

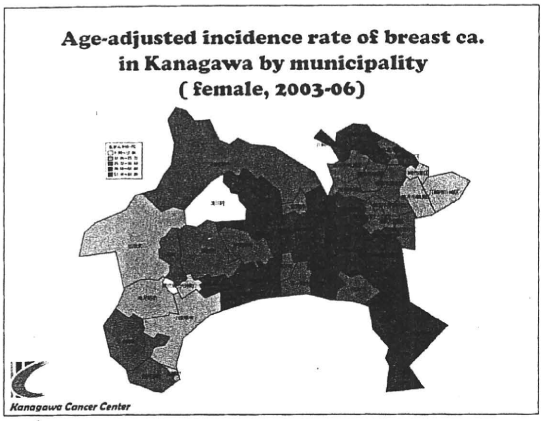


Kanagawa Cancer Center

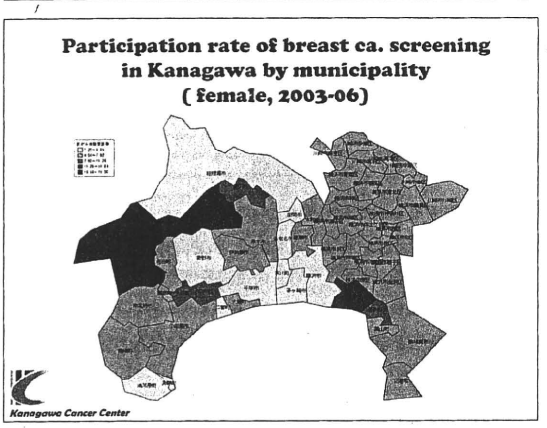
都道府県別乳がん検診受診率の比較

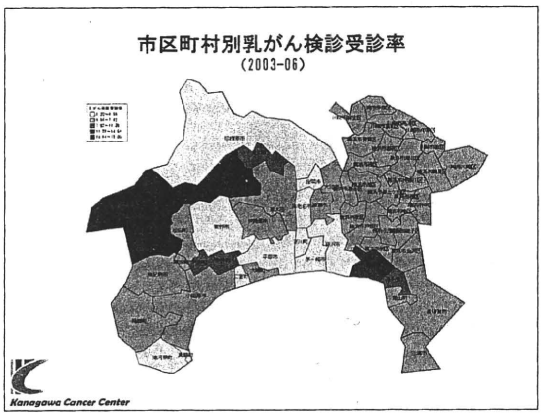


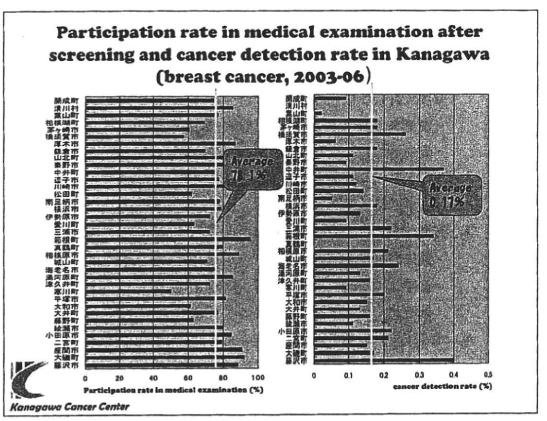
Kanagawa Cancer Center

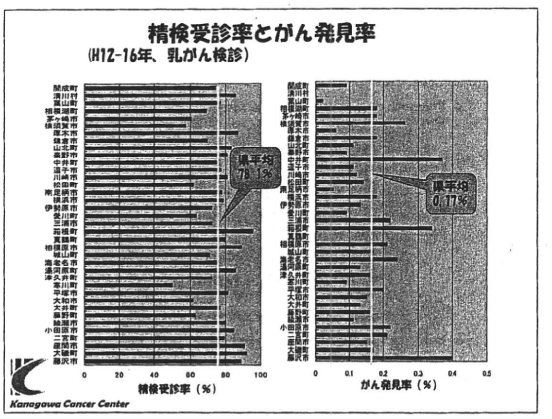

Age-adjusted incidence rate of breast ca.
in Kanagawa by municipality
(female, 2003-06)
Kanagawa Cancer Center

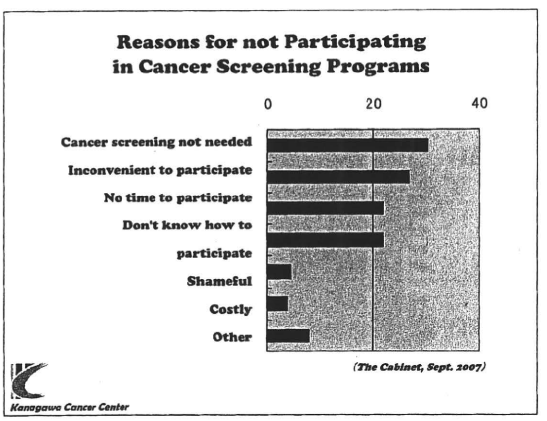

市区町村別乳がん年齢調整罹患率
(2003-06)
Kanagawa Cancer Center

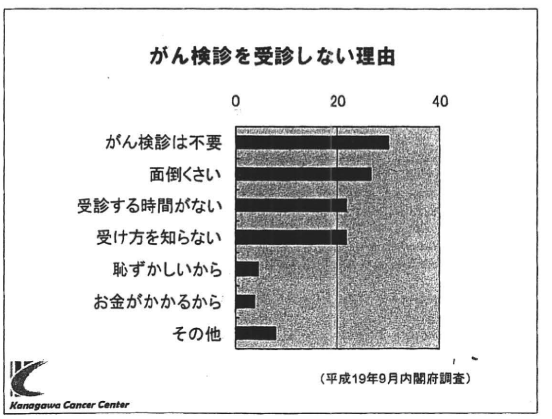

Participation rate of breast ca. screening
in Kanagawa by municipality
(female, 2003-06)
Kanagawa Cancer Center


市区町村別乳がん検診受診率
(2003-06)
Kanagawa Cancer Center


Participation rate in medical examination after
screening and cancer detection rate in Kanagawa
(breast cancer, 2003-06)
Average
71.1%
Average
0.11%
0 20 40 60 80 100
Participation rate in medical examination (%)
0 0.1 0.2 0.3 0.4 0.5
cancer detection rate (%)
Kanagawa Cancer Center


精検受診率とがん発見率
(H12-16年、乳がん検診)
県平均
71.1%
県平均
0.11%
0 20 40 60 80 100
精検受診率（%）
0 0.1 0.2 0.3 0.4 0.5
がん発見率（%）
Kanagawa Cancer Center


Reasons for not Participating
in Cancer Screening Programs
0
20
40
Cancer screening not needed
Inconvenient to participate
No time to participate
Don't know how to
participate
Shameful
Costly
Other
(The Cabinet, Sept. 2007)
Kanagawa Cancer Center


がん検診を受診しない理由
0
20
40
がん検診は不要
面倒くさい
受診する時間がない
受け方を知らない
恥ずかしいから
お金がかかるから
その他
（平成19年9月内閣府調査）
Kanagawa Cancer Center

Numerical Targets for the Control of Breast Cancer Mortality

From the second to last (worst) position to within the top ten (best)

- Promote participation in breast cancer screening
  - *Spread enlightenment activities*
  - *Cooperate in regions and occupational organizations*
- Maintain the cancer screening system
  - *Introduce mammographies*
  - *Deploy a mass screening car*
- Improve the accuracy of cancer screening
  - *Promote specialization*
  - *Enhance training at cancer base hospitals*
  - *Control accuracy thoroughly*
- Promote of self management
  - *Manage the historical data for each participant in the cancer screening program*
  - *Promote thorough examination consultation*

Kanagawa Cancer Center

数値目標(乳がんに関して)

乳がん死亡、ワースト2位からベスト10以内へ

1．がん検診の受診促進
- ・普及啓発　・地域、職域の連携

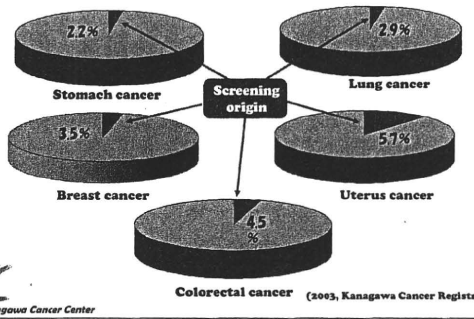
2．がん検診体制の整備
- ・マンモグラフィーの導入　・集団検診車の整備

3．がん検診の精度向上
- ・人材育成　・拠点病院での研修　・精度管理の徹底

4．一人ひとりの生涯自己管理のしくみ
- ・がん検診受診歴の管理　・精密検査受診の促進

Kanagawa Cancer Center

Ratio of cancer patient of cancer screening origin

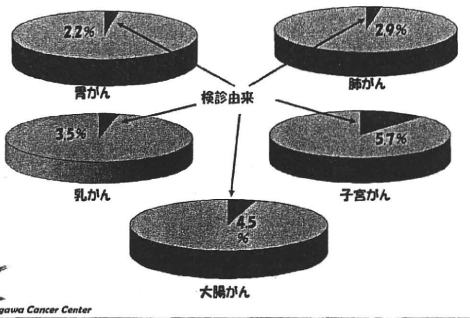


(2003, Kanagawa Cancer Registry)

Kanagawa Cancer Center

がん検診由来の患者割合

(H15年、神奈川県地域がん登録データより)



Kanagawa Cancer Center

Summary

- In 1970, Kanagawa Prefecture established its population- based cancer registry for the "Surveillance of actual cancer contraction in Kanagawa Prefecture." The number of notified data now exceeds 770,000.
- With regard to the accuracy of registration, the DCO% and ID ratio have been sharply improved, but the introduction of the personal computer system for Chinese character input has been insufficient.
- Regarding cancer reduction and cancer deaths in Kanagawa Prefecture, the incidences and mortalities of colorectal cancer, breast cancer, and corpus uteri cancer are all high.
- Kanagawa is taking measures focused on breast cancer as a ten-year strategy for the cancer control program.
- If more cancers are registered directly via medical examinations, we can expect improvements in cancer control.
- Population-based cancer registration is an indispensable material for the search for cancer trends.
- Kanagawa Prefecture wants its inhabitants and medical personnel to further understand and enhance the cancer registration system as a means of contributing to the cancer control program.

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まとめ

- 神奈川県地域がん登録は1975年から「県内のがん罹患のサーベーランス」を目的として開始され、登録データも77万件を越す量となっている。
- 登録の精度(DCO%やID比)はパソコンシステム(漢字入力対応)の導入までは不十分であったが、近年、大きな改善がなされている。
- 神奈川県のがん罹患・死亡の特徴は、大腸がん、乳がん、子宮体がんの罹患率・死亡率が高い。
- 神奈川県では、がん対策10カ年戦略として「乳がん」に焦点を当てた対策が取られている。
- 登録されたデータのなかで、がん検診由来の登録が増加することで、がん対策の評価ができる。
- がんの動向を探るうえで、地域がん登録は必要不可欠な資料となっている。
- 県民の皆さまや医療関係者の皆さまの更なるご理解をいただき、がん対策に貢献できる地域がん登録を充実させたい。

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Original Article

Diffuse large B-cell lymphoma in the spinal epidural space: A study of the Osaka Lymphoma Study Group ☆

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) involving spinal epidural space (SEDLBCL) is relatively rare, constituting 1.8% of DLBCLs in Osaka, Japan. The aim of this study was to analyze SEDLBCL cases for their clinical and histopathologic findings, including an association with Epstein-Barr virus (EBV) and immunohistochemical characteristics.

We analyzed the clinicopathologic findings of 27 SEDLBCL cases. They consisted of 16 males and 11 females, their age ranging from 37–86 years (median 64 years). Eight patients had stage I disease, 3 had stage II, 5 had stage III, and 11 had stage IV. Based on the staining pattern for anti-CD10, bcl-6, and MUM-1, the cases were categorized into 17 cases of the germinal center B-cell (GCB) type and nine of the non-GCB type. There was a 4%-positive rate for EBV in the tumor cells. When compared to nodal DLBCL, the frequency of patients with a high performance status (PS) is higher in SEDLBCL. Compared to the DLBCL of the central nervous system (CNS), the frequency of cases with high stage, 2 or more extranodal lesions, high international prognostic index (IPI), and GCB-type is higher in SEDLBCL. There were no significant differences in the histologic features between SEDLBCL and nodal/CNS DLBCL. Univariate analysis revealed that advanced stage was an unfavorable factor for overall survival (P=0.060).

SEDLBCL is different from nodal and CNS DLBCL, but an association with EBV is unlikely in every group.

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1. Introduction

In the World Health Organization (WHO) classification for lymphoid neoplasias, malignant lymphomas are largely divided into B-cell neoplasias, T/NK-cell neoplasias, and Hodgkin's lymphomas (HL). Diffuse large B-cell lymphoma (DLBCL), the most common category, representing approximately 30% of all non-Hodgkin's lymphomas (NHL) worldwide, is defined as diffuse proliferation of large neoplastic lymphoid B-cells [19,21]. Patients with DLBCL present with a predominantly nodal disease, but approximately 40% of the cases initially present with extranodal lesions. The gastrointestinal tract, especially the stomach, is most commonly involved [19]. Several subtypes of DLBCL are listed in the classification according to the specific sites of involvement, for example primary DLBCL of the central nervous system, primary cutaneous DLBCL, leg type, primary mediastinal (thymic) large B-cell lymphoma, and primary effusion lymphoma [19].

Spinal epidural NHL is a rare disease accounting for 10% to 30% of all epidural malignancies [3], and for 0.1% to 3.3% of all lymphomas [11]. Since the introduction of lymphoid neoplasm as a new modality for lymphoma classification (1994) into the Revised European–American Classification of Lymphoid Neoplasms (REAL), clinicopathologic findings of approximately 200 cases of spinal epidural malignant lymphomas have been reported to date. Information for immunophenotypes is available in 94 cases, in which B-cell lymphomas account for 84 cases and T-cell

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lymphomas for 10. A diagnosis of DLBCL was rendered in 30 cases: the items evaluated in these cases varied from report to report [2,5,7–9,12,13,17]. There is no information or only limited information available regarding the frequency of the germinal center B-cell (GCB) type and the non-GCB type of DLBCL, the accurate frequency of Epstein-Barr virus (EBV)-positive cases, and factors affecting prognosis.

Reviewing the cases registered by the Osaka Lymphoma Study Group (OLSG) between 1999 and 2009, we found that 33 cases had undergone histologic examination for spinal epidural malignant lymphoma (SEML). They consisted of 27 DLBCL cases, 2 HLs, 2 plasmacytomas, 1 marginal zone B-cell lymphoma, and 1 hematopoietic neoplasia not further specified. In this study, twenty-seven cases of spinal epidural DLBCL (SEDLBCL) were analyzed for their clinical and histopathologic findings, including the association with EBV and immunohistochemical characteristics.

2. Material and methods

2.1. Patients

Between November 1999 and February 2009, a total of 4162 cases were registered by OLSG, Japan. The histologic specimens obtained by biopsy were fixed in 10% formalin and routinely processed for paraffin-embedding. Histologic sections (4 μm) were stained with hematoxylin/eosin and immunoperoxidase (ABC method). All of the histologic sections were reviewed by one of the authors (KA) and classified according to the WHO classification. The diagnosis of malignant lymphoma was confirmed in 3307 (79.5%) of 4162 cases. Of these 3307 cases, 3031 (91.7%) were NHL and 276 (8.3%) HL. There were 1471 DLBCL cases, constituting 48.5% of all NHLs. In 33 cases, spinal epidural space was the site mainly involved, and was subject to surgery: DLBCL was diagnosed in 27 cases, HL in 2, plasmacytoma in 2, marginal zone B-cell lymphoma in 1, and hematopoietic neoplasia, not further specified in 1. Twenty-seven cases of DLBCL involving the spinal epidural space (SEDLBCL) were selected for the present study. Thirty-nine cases of nodal DLBCL and 31 cases of central nervous system (CNS) DLBCL with adequate clinical data and unstained sections for additional immunohistochemical analyses and in situ hybridization were included as controls: the nodal DLBCLs were registered by OLSG between April 2000 and February 2005, and the CNS cases at the Department of Neurosurgery, Osaka University, between December 1999 and July 2009.

Table 1 summarizes the clinicopathologic findings of SEDLBCL and the control groups. The SEDLBCL group consisted of 16 males and 11 females, their age ranging from 37–86 (median 64) years. Every patient had its main lesion in the spinal epidural space. Based on the records of physical examinations, surgical notes, and pathologic examinations of the specimens, the Ann Arbor staging system was applied. Eight cases had stage I of disease, 3 had stage II, 5 had stage III, and 11 had stage IV. The IPI score was calculated using five adverse factors (age > 60 years; Ann Arbor stages III and IV; Eastern Cooperative Oncology Group performance score 2–4; elevation of serum lactate dehydrogenase (LDH); and 2 or more extranodal lesions) present at the time of diagnosis [20]. For cases under 60 years, an age-adjusted IPI score was applied, in which advanced stage, high performance score (PS), and elevation of LDH were considered as adverse factors [20]. The IPI score 0/1 or age-adjusted IPI score 0 was categorized as low risk group, IPI score 2 or age-adjusted IPI score 1 as low-intermediate, IPI score 3 or age-adjusted IPI score 2 as high-intermediate, IPI score 4/5 or age-adjusted IPI score 3 as high. Twelve patients with SEDLBCL received a combination of radiotherapy and chemotherapy, and 15 patients received chemotherapy only. The clinical outcome was evaluated according to the guidelines of the International Workshop to standardize response criteria for NHL [4].

2.2. Immunohistochemistry

For immunophenotyping the following monoclonal antibodies were used: CD20, CD3, Bcl-6, MUM1, MIB-1 (Dakocytomation, Glostrup, Denmark, dilution at 1:400, 1:50, 1:50, 1:100, 1:1, respectively), and CD10 (NICHIREI BIOSCIENCES, Tokyo, Japan, used as prediluted antibody). Tonsils with reactive lymphoid hyperplasia served as external control tissues. In MIB-1 staining, the number of positive cells among 300–1000 large lymphoid cells was counted: MIB-1 index was calculated as positive cells/100 cells.

2.3. In situ hybridization

RNA in situ hybridization using the EBER-1 (Epstein-Barr encoded RNAs) probe was performed to examine the presence of EBV genome on the formalin-fixed, paraffin-embedded sections

Table 1
Brief clinicopathologic findings of diffuse large B-cell lymphoma in spinal epidural space and others.

Characteristic	Site			P
		Control		vs. Lymph node / CNS
	Spinal epidural space	Lymph node (n=39)	CNS (n=31)	
Age (years): range (mean/median)	37–86 (64.9/64)	38–79 (61.3/61)	31–82 (64.3/67)	NS/NS
Age > 60 years, n (%)	19/27 (70.4%)	20/39 (51.3%)	22/31 (71.0%)	NS/NS
Sex, male:female	16:11	25:14	15:16	NS/NS
Serum LDH level > normal, n (%)	16/26 (61.5%)	24/39 (61.5%)	14/27 (51.9%)	NS/NS
Performance status 2–4, n (%)	21/27 (77.8%)	8/39 (20.5%)	19/31 (61.3%)	< 0.01/NS
Stage 3/4, n (%)	16/27 (59.3%)	22/39 (56.4%)	1/31 (3.2%)	NS/ < 0.01
Involved extranodal organ > 1, n (%)	13/27 (48.1%)	10/39 (25.6%)	0/31 (0%)	0.059/ < 0.01
IPI, HI/H, n (%)	19/26 (73.1%)	20/39 (51.3%)	10/27 (37.0%)	0.079/ < 0.01
Fibrosis, present:absent	16:11	16:23	0:28	NS/ < 0.01
Mitotic count (/high-power field)				
mean (range)	2.9 (0–7)	3.1 (0–10)	2.8 (0–10)	NS/NS
MIB-1, %, mean (range)	58.8 (30–90)	61.8 (30–80)	63.1 (20–90)	NS/NS
GCB:non-GCB	17:9	18:20	5:16	NS/ < 0.01
EBV-positive, n (%)	1/25 (4%)	1/14 (7.1%)	1/20 (5%)	NS/NS

IPI: International prognostic index; HI/H, high-intermediate/high; GCB, germinal center B-cell type; CNS, central nervous system; NS, not significant.

according to the previously described method with some modifications [23]. Briefly, we synthesized a 30-base oligonucleotide probe; 5′-AGACACCGTCCTCACCACCCGGGACTTGTA-3′, which was the sense and antisense for a portion of the EBER-1 gene, a region of the EBV genome that is actively transcribed in latently infected cells. The Raji cell line was used as a positive control. The hybridizing mixture containing sense or antisense probe after RNase treatment was used as a negative control. The presence of EBV genomes was evaluated in 25 SEDLBCL cases and in 14 nodal and 20 CNS DLBCL cases as controls. When the in situ hybridization yielded positive signals in the nuclei of more than 1% of the proliferating cells, such cases were defined as EBV-positive.

2.4. Clonality analysis with use of Ig gene rearrangement (Gene Scan analysis) and BCL2-IgH gene rearrangement

One to five sections (4–10 μm) were cut from the paraffin-embedded samples, deparaffinized with xylene, washed with 70% and absolute ethanol, and subsequently digested in lysis buffer (50 mM Tris–HCl, 10 mM EDTA, 150 mM NaCl, 0.5% SDS and 0.4 mg/l proteinase K) at 55 °C overnight. DNA was extracted according to phenol–chloroform extraction-based protocol, followed by ethanol precipitation, and was redissolved in TE buffer. Immunoglobulin (Ig) gene rearrangement was assessed by 8 PCRs with 41 primers according to BIOMED-2 protocols (4 multiplex PCRs and 1 single PCR with 28 primers for Ig heavy chain (IgH) gene; 2 multiplex PCRs with 10 primers for Ig kappa light chain (Igκ) gene; 1 multiplex PCR with 3 primers for Ig lambda light chain (Igλ) gene) [22]. For this, fluorescence-labeled (6-FAM, VIC, NED, PET), custom-made primers were purchased from Applied Biosystems (Tokyo, Japan). When the PCR amplification was not sufficient because of the small amount of extracted DNA or fragmentation of DNA, we modified the PCR condition of BIOMED-2 protocols (Table 2). The amplified PCR products were mixed and diluted to ×16 or ×32 volumes with distilled water. Diluted samples (0.5 μl) were added to 11.5 μl Hi-Di formamide containing 0.5 μl internal size standard (Gene Scan-600 LIZ; Applied Biosystems). After denaturation at 95 °C for 3 min, the samples were cooled with ice-cold water, and analyzed using ABI PRISM 310 genetic analyzer with DS-33 dye-set and software v. 3.1. (Applied Biosystems). For detection of BCL2-IgH chimera gene generated by t(14;18)(q32;q21), BIOMED-2 PCR protocol for MBR, 3′MBR and mcr was applied as described previously [22]. The amplified PCR products were electrophoresed in 5.0% or 6.6% polyacrylamide gel based on fragment sizes. Samples for clonality analysis were not available in 10 SEDLBCL cases.

Table 2
Summary of the PCR protocols for the original and modified BIOMED-2 PCR reactions.

	Original BIOMED-2	Modified BIOMED-2
PCR reaction mix		
Template DNA	40 ng/50 μL	20 ng/50 μL
dNTP	200 μM	No change
Buffer ($MgCl_2$)	1.5 mM	No change
Primer	0.2 μM	0.5 μM
AmpliTaq gold	1 U/50 μL	2.5 U/50 μL
PCR run parameters		
Denature	30 s	No change
Annealing	30 s	No change
Extention	30 s	No change
Cycles	35	40

2.5. Follow-up

SEDLBCL patients were followed until July 2009. The follow-up period for survivors ranged from 4.6–49 (average 26.1) months. Sixteen of 27 patients were alive at the end of the observation period. The Kaplan–Meier estimated survival rate for the SEDLBCL at 4 years was 58.0%.

2.6. Statistical analysis

Differences in the frequencies of various clinical and pathologic factors between SEDLBCL and control DLBCL cases were compared using the Chi-square test or the Fisher's exact probability test. Differences in mean values were compared with the *t* test or the Mann–Whitney test. Survival curves and overall survival rates were calculated using the Kaplan–Meyer method and were compared by the log-rank test. Multivariate analysis was performed with the Cox proportional hazard regression model.

3. Results

3.1. Clinical findings

The clinical and pathologic findings of SEDLBCL are summarized in Table 1. One patient suffering from psoriasis was treated with cyclosporine A for six years, and SEDLBCL developed. One patient suffered from uterus cancer and another from large bowel cancer. In the remaining patients, there were no findings that suggested the presence of immunodeficient conditions. Three patients had a history as carrier of hepatitis B virus. Five patients suffered from chronic hepatitis caused by hepatitis C virus, with liver cirrhosis in one. There were no significant differences in age, sex ratio, and serum LDH level between SEDLBCL and control DLBCL cases. When compared to nodal DLBCL, the frequency of patients with high performance status (PS 2–4) is higher in SEDLBCL. When compared to CNS DLBCL, the frequency of patients with advanced stage (stage 3/4), 2 or more extranodal lesions, high IPI score (high-intermediate and high risk groups), and ratio of GCB-type to non-GCB type is higher in SEDLBCL. Back pain was the commonest symptom (70.4% of patients), followed by weakness of the lower limbs (66.7%), sensory disturbance (59.3%), dysfunction of bladder (29.6%) and bowel (22.2%), and weakness of the upper limbs (11.1%). Roentgenographic examination revealed the involvement of thoracic, lumbar, and other areas in 48.1%, 18.5%, and 7.4% of cases, respectively. Multiple lesions involving the thoraco-lumbar, cervico-thoracico, lumbo-sacral, and thoraco-lumbo-sacral areas were found in three, two, one, and one case. Bone infiltration was found in 7 cases.

3.2. Histologic and immunohistochemical findings

There were no significant differences in histologic features between the SEDLBCL and control groups. Minute to small necrotic foci were occasional in three SEDLBCL cases. Finely fibrous tissue in the background of the lesions was found in 16 (59.3%) of 27 SEDLBCL cases and in 16 (41.0%) of 39 nodal DLBCL cases. The difference was not statistically significant. The mean mitotic count in one high-power field and MIB-1 labeling index among large lymphoid cells in SEDLBCL, nodal and CNS DLBCL were 2.9, 3.1 and 2.8, and 58.8, 61.8 and 63.1, respectively.

Immunohistochemically, the large lymphoid cells were $CD20^+$ and $CD3^-$. According to the criteria proposed by Hans et al. [6], SEDLBCL could be categorized into GCB ($CD10^+$ or $CD10^-$/bcl-6^+/

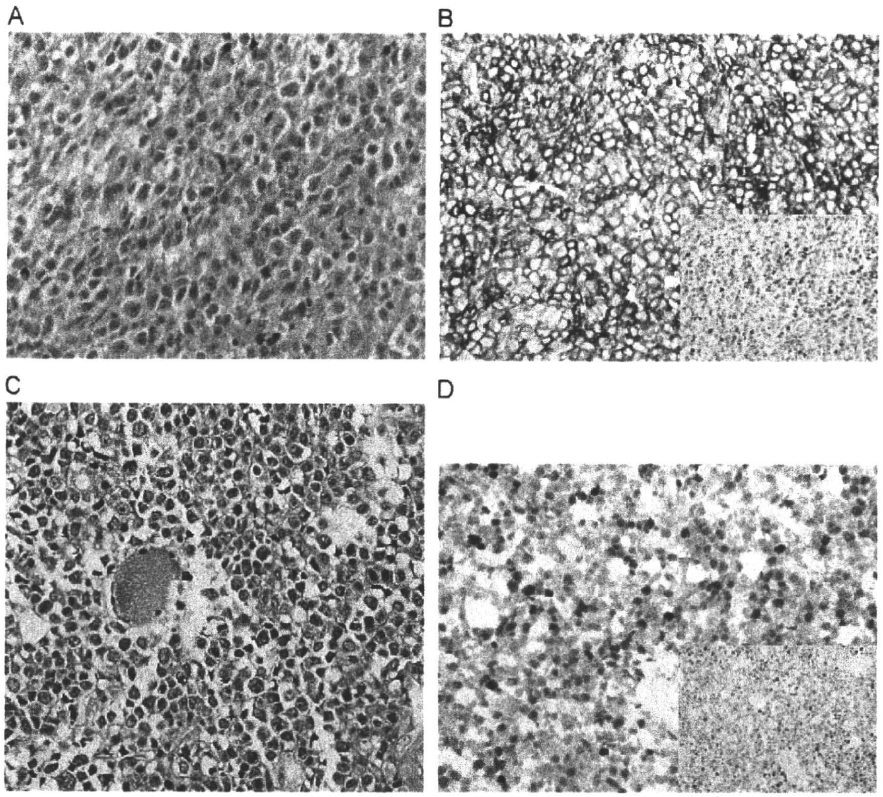

Fig. 1. (A) Diffuse large B-cell lymphoma of germinal center B-cell (GCB) type. Proliferating cells have an oval to round nucleus with occasional slight indentation, in which one to several rather small nucleoli are discernible. H&E. (B) Proliferating cells show strong immunoreactivity for CD10. Inset: they also show immunoreactivity for bcl-6. (C) Non-GCB type. There was a diffuse proliferation of large lymphoid cells with rather rich, basophilic cytoplasm and occasional prominent nucleoli mimicking immunoblasts. H&E. (D) Proliferating cells show strong nuclear staining for MUM-1. Inset: they also show immunoreactivity for bcl-6. All ×400.

MUM1$^-$) and non-GCB (CD10$^-$/bcl-6$^+$ or CD10$^-$/bcl-6$^-$/MUM1$^+$) type (Fig. 1). The ratio of the GCB to the non-GCB subgroup was significantly higher in SEDLBCL (17:9) than in CNS DLBCL (5:16) ($P < 0.01$).

3.3. *In situ hybridization*

In situ hybridization with EBER-1 probe revealed positive signals in the nucleus of large lymphoid cells in 1 (4%) of 25 SEDLBCL cases. The EBV-positive rate was similar between cases with SEDLBCL and the control groups.

3.4. *Molecular genetic study*

Genotypic study was performed in 17 cases with SEDLBCL. All cases showed monoclonal rearrangement of Ig genes with at least one primer. Monoclonal bands for both IgH and Ig light chain (IgL) genes were found in 11 cases, only for IgH gene in 3, and only for IgL gene in 3. Monoclonal rearrangement of BCL2-IgH gene was detected in 2 (11.8%) of 17 cases examined. Tumor cells in these two cases showed positive immunoreactivity for CD10.

3.5. *Prognostic factors*

The results of the univariate analysis are shown in Table 3. The stage of disease showed a marginal significance for prognosis (P=0.060). Multivariate analysis for age, sex, serum LDH level, PS, stage, extranodal involvement, IPI, GCB/non-GCB, and therapy (chemotherapy or the combination of chemotherapy and radiotherapy) revealed that none of them significantly affected the prognosis of the patients.

4. Discussion

In previous reports, spinal epidural involvement by malignant lymphoma has been described in 0.1% and 3.3% of cases [11]. The frequency was considerably lower in the present series, i.e., in 33 of 3307 cases (0.1%). Although it has been reported that T-cell lymphomas are occasionally found among NHL involving spinal epidural space [3,8,10,12,14,17], NHLs in the present series were composed exclusively of B-cell lymphomas, the vast majority being DLBCL. In the SEDLBCL presented here, age distribution and sex ratio were rather similar to those reported previously [2,5,7–9,12,17].

At diagnosis, approximately 60% of the SEDLBCL patients presented here had advanced stages of disease (stages III–IV). As clinicians regarded the spinal epidural space as the main lesion, it was extirpated for histologic examination. This might lead to the hypothesis that spinal epidural involvement is a manifestation of systemic DLBCL, an aggressive lymphoma, or local spread of DLBCL from the vertebral bones or paravertebral lesion. Another possibility would be a development of *de novo* DLBCL in the spinal epidural space. Russell and Rubinstein state that native lymphoid cells are derived from mesodermal cells in the spinal epidural space, and it is conceivable that they could follow a transformation cascade to produce primary SEML [16]. On the other hand, formation of lymphoid tissue in the chronically inflamed tissue might provide a basis for the development of malignant lymphoma consisting mostly of the B-cell type. Under such a

Table 3
Univariate analysis for overall survival in patients with diffuse large B-cell lymphoma of spinal epidural space.

Characteristic	Number of patients	OS (%)	P
Age, years		4-Year OS	
Age≦60	8	75.0	NS
Age > 60	19	50.1	
Sex		4-Year OS	
Male	16	68.2	NS
Female	11	50.5	
Serum LDH level		4-Year OS	
Normal or lower	10	75.0	NS
Higher than normal	16	50.9	
Performance status		3-Year OS	
Ambulatory (0–1)	6	50.0	NS
Not ambulatory (2–4)	21	58.5	
Ann Arbor stage		3-Year OS	
Stage ½	11	78.7	0.060
Stage ¾	16	35.8	
Extranodal involvement		3-Year OS	
0–1 Site	14	65.0	NS
> 1 Sites	13	55.9	
International prognostic index		4-Year OS	
L/LI	7	85.7	NS
HI/H	19	45.4	
GCB/non-GCB		2-Year OS	
GCB	17	75.1	NS
Non-GCB	9	50.0	
Chemo alone/Chemo+RT		4-Year OS	
Chemo alone	15	61.3	NS
Chemo+RT	12	55.6	

OS: overall survival; L/LI, low/low-intermediate; HI/H, high-intermediate/high; GCB, germinal center B-cell type; Chemo alone, chemotherapy alone; Chemo+RT, combined chemotherapy and radiotherapy; NS, not significant.

condition, the formed lymphoid tissue is referred to as mucosa-associated lymphoid tissue (MALT), and the lymphoma originating from it is a marginal zone B-cell lymphoma. Indeed, the present series of spinal epidural NHL includes a case of marginal zone B-cell lymphoma. Among the current SEDLBCL cases, the history included narrowing of the lumbar vertebral canal, tuberculosis, pleuritis, interstitial pneumonia, or psoriasis vulgaris in a total of five cases.

DLBCL is the most common lymphoma worldwide, and comprises heterogenous groups of diseases showing a wide range of response patterns to treatment. There were no significant differences in histologic features between SEDLBCL and nodal/CNS DLBCL, except for the ratio of the GCB to the non-GCB type as discussed later. Based on the gene expression profiles, Alizadeh et al. categorized the DLBCL cases into germinal center and activated B-cell signatures, with a more favorable prognosis for the former than for the latter group [1]. Hans et al. proposed to categorize DLBCL into GCB and non-GCB types based on the immunohistochemical findings [6]: $CD10^+$ or $CD10^-$/$bcl\text{-}6^+$/$MUM1^-$ as GCB and $CD10^-$/$bcl\text{-}6^-$ or $CD10^-$/$bcl\text{-}6^+$/$MUM1^+$ as non-GCB type. There are no reports categorizing SEDLBCL as GCB or non-GCB type. The ratio of GCB and non-GCB cases in the present cases of SEDLBCL (17:9) was higher than that in a previous report on the ordinary type of DLBCL (about 1:1) [15]. The ratio in SEDLBCL was significantly higher than that in CNS DLBCL (5:16) ($P < 0.01$). It has been reported that DLBCL of the GCB type had a more favorable prognosis than that of the non-GCB type [1,6,18]. The SEDLBCL with the GCB type showed a rather favorable prognosis compared to those with the non-GCB type, although the difference was not statistically significant (log-rank, $P > 0.05$): 2-year survival rate was 75.1% and 50.0%, respectively (Table 3).

The EBV-positive rate in the ordinary DLBCL has been reported to account for approximately 10% worldwide [19], but it is really much lower in Osaka, Japan, i.e., less than 5% [24]. An EBV-positive rate in SEDLBCL in a large series of cases has not been reported to date. The EBV-positive rate in the present SEDLBCL cases (4%) was rather similar to that in ordinary DLBCL, indicating that a role of EBV for the development of SEDLBCL is unlikely.

Univariate analysis revealed that stage of disease showed a marginal significance for prognosis (P=0.060). Multivariate analysis revealed that none of the clinicopathologic factors was useful for predicting the overall survival of the SEDLBCL. This might be due to the relatively small number of cases analyzed in the present study.

In conclusion, SEDLBCL is different from nodal and CNS DLBCL, but an association with EBV is unlikely in every group.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

[1] A.A. Alizadeh, M.B. Eisen, R.E. Davis, et al., Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling, Nature 403 (2000) 503–511.
[2] C. Bachmeyer, F. Kazerouni, B. Langman, L. Daumas, P. Hessler, [A rare cause of cauda equina syndrome: primary epidural lymphoma] [Article in French], Presse Med 34 (2005) 1082–1083.
[3] M. Boukobza, C. Mazel, E. Touboul, Primary vertebral and spinal epidural non-Hodgkin's lymphoma with spinal cord compression, Neuroradiology 38 (1996) 333–337.
[4] B.D. Cheson, S.J. Horning, B. Coiffier, et al., Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group, J. Clin. Oncol. 17 (1999) 1244–1253.
[5] A. Chiodo, Spinal cord injury caused by epidural B-cell lymphoma: report of two cases, J. Spinal Cord Med. 30 (2007) 70–72.
[6] C.P. Hans, D.D. Weisenburger, T.C. Greiner, et al., Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray, Blood 103 (2004) 275–282.
[7] V. Köseoglu, A.E. Kürekçi, R. Akin, et al., Primary epidural non-Hodgkin's lymphoma with cervical location in an HIV-negative child: case report, J. Child Neurol. 13 (1998) 520–522.
[8] M.K. Lyons, B.P. O'Neill, P.J. Kurtin, W.R. Marsh, Diagnosis and management of primary spinal epidural non-Hodgkin's lymphoma, Mayo Clin. Proc. 71 (1996) 453–457.
[9] K. Masuda, Y. Mochida, J. Fujii, et al., Primary cervical epidural malignant lymphoma with rheumatoid arthritis: a case report, Mod. Rheumatol. 17 (2007) 239–242.
[10] W.A. Mohammed, R. Doshi, Spinal epidural malignant lymphoma presenting with spinal cord compression, Clin. Neuropathol. 14 (1995) 237–240.
[11] V. Monnard, A. Sun, R. Epelbaum, et al., Primary spinal epidural lymphoma: patients' profile, outcome, and prognostic factors: a multicenter rare cancer network study, Int. J. Radiat. Oncol. Biol. Phys. 65 (2006) 817–823.
[12] J. Mora, N. Wollner, Primary epidural non-Hodgkin lymphoma: spinal cord compression syndrome as the initial form of presentation in childhood non-Hodgkin lymphoma, Med. Pediatr. Oncol. 32 (1999) 102–105.
[13] B. Petit, I. Roche, F. Paraf, et al., [Epidural non-Hodgkin's lymphoma presenting as a spinal cord compression] [Article in French], Ann. Pathol. 21 (2001) 123–128.
[14] A. Raco, L. Cervoni, M. Salvati, R. Delfini, Primary spinal epidural non-Hodgkin's lymphomas in childhood: a review of 6 cases, Acta Neurochir. (Wien) 139 (1997) 526–528.
[15] A. Rosenwald, G. Wright, W.C. Chan, et al., The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma, N. Engl. J. Med. 346 (2002) 1937–1947.
[16] D.S. Russell, L.J. Rubinstein, in: Pathology of Tumours of the Nervous System, fifth edition, Williams & Wilkins, Baltimore, 1989.
[17] K. Schwechheimer, A. Hashemian, G. Ott, H.K. Müller-Hermelink, Primary spinal epidural manifestation of malignant lymphoma, Histopathology 29 (1996) 265–269.

[18] L.D. Sjö, C.B. Poulsen, M. Hansen, M.B. Møller, E. Ralfkiaer, Profiling of diffuse large B-cell lymphoma by immunohistochemistry: identification of prognostic subgroups, Eur. J. Haematol. 79 (2007) 501–507.
[19] H. Stein, R.A. Warnke, W.C. Chan, et al., Diffuse large B-cell lymphoma, not otherwise specified, in: S.H. Swerdlow et al.(Ed.), WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, fourth edition, World Health Organization Classification of Tumours, IARC Press, Lyon, France, 2008, pp. 233–237.
[20] The International Non-Hodgkin's Lymphoma Prognostic Factors Project, A predictive model for aggressive non-Hodgkin's lymphoma, N. Engl. J. Med. 329 (1993) 987–994.
[21] The Non-Hodgkin's Lymphoma Classification Project, A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma, Blood 89 (1997) 3909–3918.
[22] J.J. Van Dongen, A.W. Langerak, M. Brüggemann, et al., Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 concerted action BMH4-CT98-3936, Leukemia 17 (2003) 2257–2317.
[23] L.M. Weiss, E.S. Jaffe, X.F. Liu, Y.Y. Chen, D. Shibata, L.J. Medeiros, Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma, Blood 79 (1992) 1789–1795.
[24] A. Yamauchi, S. Fujita, J. Ikeda, et al., Diffuse large B-cell lymphoma in the young in Japan: a study by the Osaka lymphoma study group, Am. J. Hematol. 82 (2007) 893–897.

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Clinical and Economic Evaluation of First-line Therapy with FOLFIRI or Modified FOLFOX6 for Metastatic Colorectal Cancer

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Objective: Recently, significant progress in treatment of metastatic colorectal cancer has been achieved. Either FOLFIRI (fluorouracil, leucovorin and irinotecan) or modified FOLFOX6 (fluorouracil, leucovorin and oxaliplatin, oxaliplatin dose 85 mg/m^2) is selected as first-line therapy in clinical practice in Japan. However, economic burden of colorectal cancer is considerable.

Methods: Analysis was made for all patients who were treated with FOLFIRI or modified FOLFOX6 for metastatic colorectal cancer. Regimen of FOLFIRI was compared with modified FOLFOX6 under consideration from clinical and economic standpoints. Progression free survival, response, toxicity and cancer care cost in patients with metastatic colorectal cancer was analyzed. Direct costs based on the fee schedule of the Japanese national health insurance were calculated.

Results: Median progression free survival was 7.7 months for FOLFIRI versus 8.4 months for modified FOLFOX6 ($P = 0.48$). Overall cost for first four cycles was ¥756 284 for FOLFIRI and ¥1 081 162 for modified FOLFOX6 ($P < 0.0001$). All grade alopecia was significantly more frequent with FOLFIRI than with modified FOLFOX6 ($P = 0.04$). All grade neuropathy was more observed with modified FOLFOX6 than FOLFIRI ($P = 0.0002$).

Conclusions: FOLFIRI is inexpensive in the initial stage of treatment which a number of patients can receive chemotherapy than modified FOLFOX6 as first-line therapy for metastatic colorectal cancer in Japanese national insurance system.

Key words: costs and cost analysis – FOLFIRI protocol – FOLFOX-6 protocol – colorectal neoplasms

INTRODUCTION

Cancer is a major public health problem in Japan as well as the USA and European countries. Currently, one of three deaths in Japanese is due to cancer. Especially, the incidence of colorectal cancer (CRC) is rapidly increasing and CRC is the highest cause of cancer deaths in women, and the third highest cause in men (1). In addition, almost half of patients diagnosed with CRC will develop metastatic disease (2). Recently, significant progress in treatment of metastatic colorectal cancer (mCRC) has been achieved with development of chemotherapy regimens containing fluorouracil (5-FU), irinotecan and oxaliplatin (3). Additionally, targeted monoclonal antibodies, including bevacizumab and cetuximab, have improved treatment outcome (4–6). In Japan, however, bevacizumab and cetuximab were approved for metastatic or recurrent CRC in 2007 and in 2009, respectively. Either FOLFIRI (fluorouracil, leucovorin and irinotecan) or modified (m) FOLFOX6 (fluorouracil, leucovorin and oxaliplatin, oxaliplatin dose 85 mg/m^2) has been selected as first-line therapy in clinical practice until 2009. The result of

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GERCOR study, comparing FOLFIRI with FOLFOX6 (fluorouracil, leucovorin and oxaliplatin, oxaliplatin dose 100 mg/m^2), indicated that there was no statistically significant difference in median progression free survival (PFS) as first-line therapy (7). The choice of first-line therapy has been mainly decided according to physician's favor and toxicity profiles of these regimens.

Although development of chemotherapy for mCRC has prolonged overall survival, new therapeutic options dramatically increased the cost of treatment (8,9). Elevating cost of cancer care, especially cancer drug costs has been recognized as serious problem based on long recession in Japanese society. There are few researches for cost of cancer chemotherapy in Japan and most of the pharmacoeconomic reports are carried out based on model analysis. To make decision in clinical practice, however, it is necessary to take not only cost of anticancer drugs but also cost of supportive care into consideration. The objective of our analysis is to compare FOLFIRI with mFOLFOX6 in mCRC patients under consideration from clinical and economic standpoints in the context of Japanese clinical practice.

PATIENTS AND METHODS

This was a retrospective study of all patients who were treated for mCRC at Saitama Medical University International Medical Center-Comprehensive Cancer Center (SMU-CC) between April 2007 and January 2009. This analysis was approved by the Institutional Review Board of Saitama Medical University International Medical Center.

Selection of Patients

All patients received as first-line therapy either FOLFIRI or mFOLFOX6 at SMU-CC in clinical practice were included. Patients were required to have histologically proven adenocarcinoma of the colon or rectum; metastatic or recurrent disease; at least one bi-dimensionally measurable lesion; to be between 20 and 75 years of age; and a World Health Organization (WHO) performance status of 0–2. Patients receiving fewer than four cycles of chemotherapy for a reason other than disease progression or death and having already received initial chemotherapy as first-line therapy for CRC at other hospital were excluded from this analysis.

Chemotherapeutic Regimens

FOLFIRI regimen consisted of l-leucovorin (l-LV) 200 mg/m^2 as a 2-h infusion, and irinotecan 180 mg/m^2 given as a 90-min infusion, followed by bolus 5-FU 400 mg/m^2 and a 46-h infusion 5-FU 2,400 mg/m^2. mFOLFOX6 regimen consisted of the same l-LV plus 5-FU regimen, with the addition of oxaliplatin 85 mg/m^2 given as a 2-h infusion, concurrent with l-LV. Granisetron and dexamethasone were administered to prevent acute emesis. These regimens were repeated every 2 weeks. In all cases, 5-FU continuous infusion was given using a portable disposable pump on outpatient basis. Each oncologist considering of patient's preference decided the choice of regimen. Treatment was continued until unacceptable toxicity, patient refusal to continue chemotherapy, tumor progression or death.

Clinical Assessment

PFS was defined as time duration from the start date of Cycle 1 to tumor progression. We also assessed tumor response by using Response Evaluation Criteria in Solid Tumors (RECIST) (10). Toxicity was evaluated according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (11). Relative dose intensity was calculated based on the ratio of the drug doses actually delivered in the originally expected time over the expected dose in the expected time.

Economic Analysis

We carried out cost-minimization analysis based on the assumption that effectiveness of FOLFIRI and mFOLFOX6 was similar (7). Generally, costs were collected over the total duration of patient survival. However, it is difficult to evaluate costs of overall survival because the choice of second- and third-line therapies for mCRC is differ widely in individuals. Therefore, we collected costs during PFS to evaluate two regimens as first-line therapy. Primary outcome of this cost analysis was costs for first four cycles (8 weeks) because fist evaluation of chemotherapy was performed after four cycles and almost all patients were likely to receive full-dose chemotherapy in four cycles.

This analysis was conducted from the perspective of the health care payer. We calculated direct costs based on the fee schedule of the Japanese national health insurance. Hospital and outpatient resources related to chemotherapy and adverse events were collected until unacceptable toxicity, patient refusal to continue chemotherapy, tumor progression or death. Overall costs included all direct costs associated with hospitalization for chemotherapy or for management of adverse events, anticancer drugs and antiemetics, additional prescribed drugs for adverse events, infusions on out-patient basis, visits to health professionals due to adverse events or follow-up and all examinations. Additional prescribed drugs for adverse events contained outpatient drug costs, estimated based on the fee schedule of the Japanese national health insurance. We did not include traveling costs of each patient.

Statistical Analysis

Differences in quantitative parameters, including economic data, were tested using the non-parametric Mann–Whitney test. Differences in qualitative parameters were tested using the χ^2 test or Fisher's exact test. PFS was estimated by the Kaplan–Meier method, and values were compared using the

Table 1. Patient characteristics

	FOLFIRI ($n = 30$)	%	mFOLFOX6 ($n = 24$)	%	P value
Sex					
Male	21	70	16	67	0.79
Female	9	30	8	33	
Age (years)					
Median	58		63		0.1
Range	42–73		47–75		
WHO performance status					
0	27	90	16	67	
1	3	10	8	33	0.046
Primary site[a]					
Colon	12	40	18	75	0.03
Rectum	17	57	6	25	
Multiple	1	3	0	0	
Metastatic site					
Liver	13	43	12	50	–
Lung	12	40	7	29	
Other	19	63	12	50	
No. of sites					
1	14	47	9	38	0.5
≥2	16	53	15	62	
Adjuvant chemotherapy					
Yes	8	27	5	21	0.75
No	22	73	19	79	
Body surface area (m^2)					
Median	1.58		1.58		0.88
Range	1.27–1.78		1.26–1.86		

[a]Comparing colon with rectum.

log-rank test. P value of <0.05 was considered as statistically significant. All statistical analyses were carried out using the SPSS statistical software (version 17.0).

RESULTS

From April 2007 to January 2009, 247 patients with metastatic or recurrent CRC visited department of medical oncology at SMU-CC to receive first-line chemotherapy. A total of 193 patients were excluded, 161 patients had already received initial chemotherapy at other hospital, 18 patients did not receive FOLFIRI or mFOLFOX6, 14 patients received fewer than four cycles of chemotherapy. In total, 54 patients were included in this analysis, 30 patients received FOLFIRI and 24 patients received mFOLFOX6. Characteristics of 54 included patients were reported in Table 1. The patients were well balanced between two regimens, except for performance status and primary site.

Table 2. Clinical outcome

	FOLFIRI ($n = 30$)	mFOLFOX6 ($n = 24$)	P value
Median progression free survival (months)	7.7	8.4	0.48
Overall response rate (%)	47	42	0.71
Complete response (%)	7	0	
Partial response (%)	40	42	
Stable disease (%)	37	50	
Progression disease (%)	16	8	
Cycles[a]	12 (3–24)	8.5 (4–26)	0.48
Visits[a]	26 (5–35)	20 (8–52)	0.86
Relative dose intensity (%)			
Irinotecan dose intensity[a]	68 (10–92)	–	
Oxaliplatin dose intensity[a]	–	62 (17–100)	
Hospitalization for chemotherapy			
Patients (%)	36.7	37.5	0.95
Length of stay (days)[b]	1.8 ± 2.8	2.2 ± 3.3	0.75
Hospitalization for adverse event			
Patients (%)	3.3	0	–
Additional prescribed drug			
Antibiotics (%)	36.7	37.5	0.95
Antidiarrheics (%)	40.0	41.7	0.90
Antiemetics (%)	93.3	92.7	0.61
Hematopoietic growth factor (%)	3.3	4.2	0.87

[a]Data are median (range).
[b]Data are mean ± standard deviation.

Clinical Outcome

Clinical data were shown in Table 2. Median PFS was 7.7 months for FOLFIRI versus 8.4 months for mFOLFOX6 ($P = 0.48$). Overall response rates were 47% with FOLFIRI versus 42% with mFOLFOX6. There were no statistically significant difference in number of treatment cycles and visits between two regimens. One patient received FOLFIRI was hospitalized for febrile neutropenia. Relative dose intensity for irinotecan was 68% and for oxaliplatin was 62%. Frequency of common toxicities was shown in Table 3. All grade alopecia was significantly more frequent with FOLFIRI than with mFOLFOX6. All grade neuropathy was more observed with mFOLFOX6.

Economic Analysis

Cancer care costs were compared in Table 4. Overall cost for first four cycles of FOLFIRI and mFOLFOX6 were ¥756 284 and ¥1 081 162, respectively ($P < 0.0001$). Overall cost until disease progression was ¥1 867 377 for FOLFIRI

Table 3. Frequency of common toxicities (maximum toxicity per patient)

Toxicity	FOLFIRI ($n = 30$)				mFOLFOX6 ($n = 24$)				*P* value (all grade)
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
Neutropenia	6	4	6	3	2	7	5	0	0.90
Thrombocytopenia	1	0	0	0	4	1	0	0	0.08
Nausea	14	9	1	0	14	3	0	0	0.43
Vomiting	11	5	1	0	6	2	0	0	0.09
Diarrhea	13	6	0	0	9	3	0	0	0.32
Mucositis	9	0	0	0	11	0	0	0	0.23
Fatigue	23	1	0	0	17	4	0	0	0.71
Alopecia	23	1	0	0	12	1	0	0	0.04
Neuropathy	9	1	0	0	17	3	0	0	0.0002

Table 4. Cancer care cost

	FOLFIRI (¥)	mFOLFOX6 (¥)	*P* value
Hospitalization	92 500 (0–427 550)	77 035 (0–211 940)	0.82
Visits	14 350 (4900–28 650)	14 000 (6300–43 150)	0.92
Additional prescribed drug	65 798 (4814–612 813)	55 679 (3890–299 538)	0.37
Laboratory test	101 655 (17 260–186 740)	76 235 (22 610–185 940)	0.40
Diagnostic imaging	130 665 (31 110–265 930)	130 165 (32 000–306 210)	0.46
Chemotherapy			
For first four cycles	604 025 (252 380–841 720)	858 645 (450 650–1 367 250)	<0.0001
Until disease progression	1 432 955 (369 190–2 904 800)	1 665 675 (611 060–4 187 790)	0.046
Overall			
For first four cycles	756 284 (450 904–1 077 216)	1 081 162 (636 406–1 599 466)	<0.0001
Until disease progression	1 867 377 (458 954–3 663 292)	2 064 952 (769 533–4 782 598)	0.22

Data are median (range).

and ¥2 064 952 for mFOLFOX6 ($P = 0.22$). Chemotherapy cost accounted for more 80% of overall cost in each regimen. Other economic parameters had no statistically difference between two groups.

DISCUSSION

Incidence of CRC is increasing and CRC as well as lung cancer and gastric cancer is one of the most important malignancies in Japan. Regardless with prolonged survival in patients with CRC, economic burden of CRC is considerable around the world (8,9). On the other hand, Japan has been maintained excellent national health insurance system for all the people, however, substantial increase in cost of hearth care, especially cancer care cost causing a serious financial problem to Japanese society.

SMU-CC is newly established hospital in April 2007. SMU-CC is only one cancer center that belong to medical school in Japan and 330 beds are available in the treatment of cancer patients. We carried out clinical and economic evaluation of first-line chemotherapy for patients with CRC in SMU-CC in clinical practice setting. Although current analysis was performed retrospectively, all the patients who met selection criteria were covered. In addition, we calculated direct costs based on the Japanese national health insurance record, which also covers all the direct cost for each patient except traveling cost.

To make clinical decision, medical oncologist must take into account for several factors, such as efficacy, toxicity and cost of the treatment. Especially, cancer drug cost has received increasing attention. However, not only drug cost but also other medical fee including supportive care such as antiemetics, granulocyte colony stimulating factor and

antibiotics, radiographic diagnostics, blood cell counts, serum biochemistry and hospitalization fee, which induced by selected chemotherapeutic regimen must be took into account. In our analysis, there was no significant difference in PFS between two regimens. This result is similar to the result of GERCOR study (7). Drug induced toxicity is also the important factor whether patient can continue chemotherapy. Frequency of visits is similar between two groups, but there was difference of toxicity profiles between two regimens. Alopecia was more frequently observed with FOLFIRI. Neuropathy was more profound with mFOLFOX6 than FOLFIRI. This difference of toxicity profiles between two regimens, however, did not have influence on total cost, because there exist no established supportive treatment for both alopecia and neuropathy.

For first four cycles, mFOLFOX6 was clearly more expensive than FOLFIRI ($P < 0.0001$) in Japanese health care insurance system. However, in overall cost, there was no statistically significant difference between two regimens ($P = 0.22$). We consider the fact that the decrease of chemotherapy cost with mFOLFOX6 was greater than FOLFIRI as main reason for this result because chemotherapy cost accounted for more 80% of overall cost in each regimen. Relative dose intensity for irinotecan was 68% and for oxaliplatin was 62%. Neuropathy is the major toxicity with oxaliplatin. When neuropathy is appeared and patients complain the severity, oncologists tend to reduce oxaliplatin dose or omit oxaliplatin administration from regimen (12,13). Therefore, the decrease of chemotherapy cost with mFOLFOX6 will become pronounced over time. This result indicates that FOLFIRI is inexpensive in the initial stage of treatment which a number of patients can receive chemotherapy than mFOLFOX6 as first-line therapy for CRC.

We have several limitation of this analysis as follows; the data of this analysis is retrospectively obtained from clinical practice, relatively small sample size may result in a lack of statistical power, selection of treatment regimen was left to oncologist and patient's choice and there may exist selection bias, costs of expensive targeting agents including cetuximab and bevacizumab were not prescribed in the patients cohorts, we analyzed only first-line chemotherapy and no information of the drug and supportive care cost by salvage treatment and palliative care, which are too complicated to analyze, and we collected only direct costs, not including indirect costs.

In Japan, medical oncologists have not really recognized cost of cancer care. Obviously, we have stressed efficacy priority over cost to improve patient's quality of life. However, we should also consider efficacy, toxicity and cost of chemotherapy. Recently, American Society of Clinical Oncology (ASCO) published 'Guidance Statement: The Cost of Cancer Care' addressing that patient–physician discussions regarding the cost of care are an important component of high-quality care (14). We calculated cancer management cost based on clinical practice. We must also make prospective cost-effective analysis in Phase III trial in the future.

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Conflict of interest statement

None declared.

References

1. Ministry of Health, Labor and Welfare [Internet]. Japan: The Association. Available from:http://www.mhlw.go.jp/.
2. Saunders M, Iveson T. Management of advanced colorectal cancer: state of the art. *Br J Cancer* 2006;95:131–8.
3. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005;352:476–87.
4. Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005;23:3502–8.
5. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008;26:3523–9.
6. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–17.
7. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–37.
8. Schrag D. The price tag on progress—chemotherapy for colorectal cancer. *N Engl J Med* 2004;351:317–9.
9. Jansman FG, Postma MJ, Brouwers JR. Cost considerations in the treatment of colorectal cancer. *Pharmacoeconomics* 2007;25:537–62.
10. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
11. Japan Clinical Oncology Group. Japanese translation of common terminology criteria for adverse events (CTCAE), and instructions and guidelines. *Int J Clin Oncol* 2004;9(Suppl 3):S1–S82 (in Japanese).
12. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer–a GERCOR study. *J Clin Oncol* 2006;24:394–400.
13. Maindrault-Goebel F, Tournigand C, Andre T, Carola E, Mabro M, Artru P, et al. Oxaliplatin reintroduction in patients previously treated with leucovorin, fluorouracil and oxaliplatin for metastatic colorectal cancer. *Ann Oncol* 2004;15:1210–4.
14. Meropol NJ, Schrag D, Smith TJ, Mulvey TM, Langdon RM, Jr, Blum D, et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. *J Clin Oncol* 2009;27:3868–74.

Mebio Clinical Report

mTOR阻害剤と転移性腎細胞がん治療の進化

第1回 mTOR－細胞内の標的因子－

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執印太郎（高知大学医学部泌尿器科学教室教授）

mTORとは

mTORは、mammalian target of rapamycinの略であり、rapamycinの標的という意味で名付けられたTOR（target of rapamycin）という蛋白質のなかで哺乳類にみられる細胞内分子（分子量289kDa）のことである。マクロライド系抗生物質の一つであるrapamycinは、モアイ像で有名なイースター島の土壌から単離された放線菌から作られたもので、同島のポリネシア語名の「Rapa Nui」のRapaと、「放線菌から得られた抗生物質」を意味する接尾語のmycinとを組み合わせてrapamycinと名付けられた。シクロスポリン、FK506に続く第三の免疫抑制剤として使用されていた経緯がある。ちなみにシクロスポリン、FK506の標的はカルシニューリンであり、rapamycinの標的はmTORである。PI3K（phosphatidylinositol 3-kinase）-AKTシグナル伝達経路の下流に位置するmTORは、アミノ酸の存在下でS6K1（p70 ribosomal protein S6 kinase 1）と4EBP1（eIF4E -binding protein 1）のリン酸化を介して、翻訳開始、蛋白質合成を促進して、細胞増殖を正に制御するserine/threonine protein kinaseである（**図1**、**2**）。最近ではtemsirolimus（CCI779）やエベロリムス（RAD001）のようなrapamycin誘導体が腎細胞がんに抗腫瘍効果を示しているため注目されている。またrapamycin誘導体は生体における副作用が少ないことがその特徴とされ、新規の分子標的治療薬として期待されている[1,2]。

mTORの役割

mTORの関わる細胞内シグナル伝達経路は、酵母を中心に多く研究されている。その経路はヒトを含む哺乳類の細胞でもよく保存されている。一般に“細胞増殖cell proliferation”は、細胞分裂cell division（細胞数の増加：increase in cell number）と細胞成長cell growth（細胞サイズの増大：increase in cell size）の2つに分類される。細胞分裂周期の制御機構において、CDKs（cyclin-dependent kinases）が中心的な役割を担っていることが知られているが、細胞成長の制御機構において、この役割を担っていると考えられている分子がmTORである。mTORは細胞内でmTORC1（mTOR complex 1）とmTORC2（mTOR complex 2）として存在している。mTOR結合蛋白raptorを含むmTORC1は4EBP1をリン酸化することで翻訳開始を促進し、S6K1をリン酸化することで蛋白質合成を促進して、細胞増殖を正に制御している（**図1**、**2**）。mTOR結合蛋白rictorを含むmTORC2はAKTをリン酸化することで、細胞増殖を正に制御する役割をもっている。mTORC1はrapamycinの標的となりうるが、mTORC2はrapamycinの標的とならない[3]。

mTORとがん

mTORは、細胞内で単一の蛋白として存在するのではなく、細胞膜から

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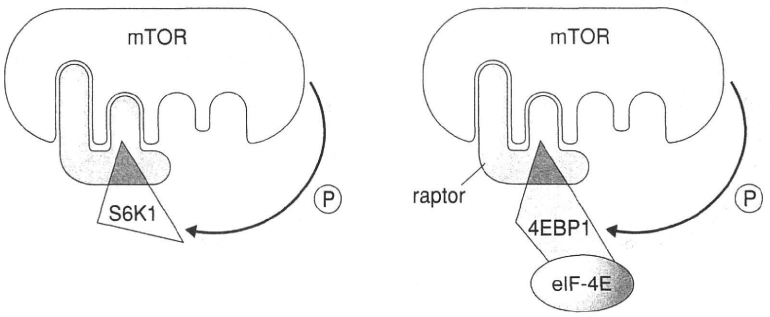

図1　mTORによるS6K1、4EBP1のリン酸化

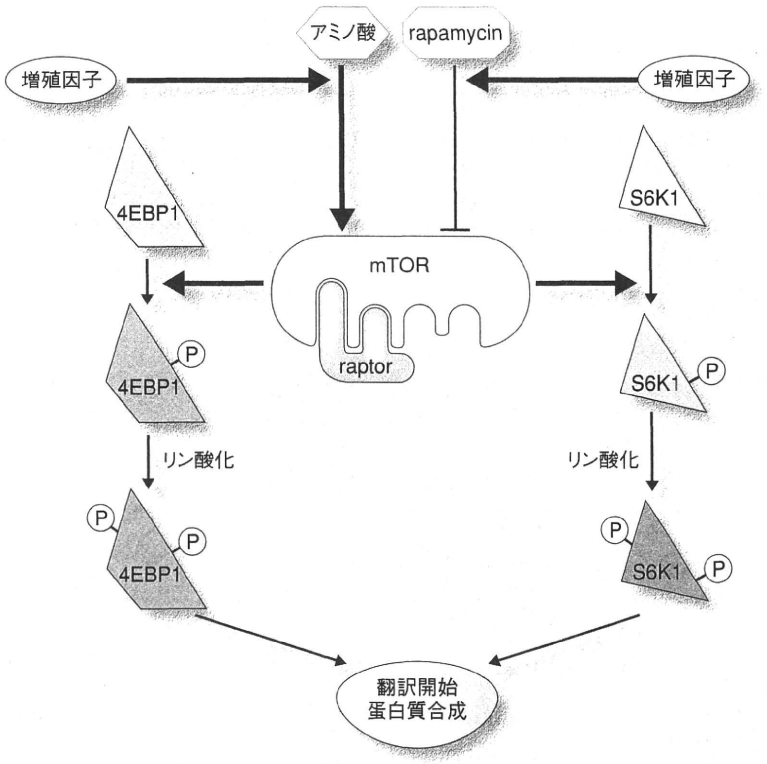

図2　蛋白質の翻訳開始を制御するmTORC1の伝達経路

細胞質内への一連のシグナル経路、すなわち、インスリンなどの増殖因子群、PI3K、PTEN、PDK1、AKT、TSC1/2（TSC1/TSC2 complex）、mTORを含む細胞増殖経路の一つとして存在している（**図3**）。

細胞外からのインスリン、そのほかの増殖因子や、それらの受容体からの増殖刺激を受けると、PI3K→PTEN→PDK1→AKT→TSC1/2→mTORの経路で、最終的にはmTORは活性化される仕組みとなっている。この経路は、PTENの異常などにより多くのがんで活性化されているとされる。また、これとは別にrictorを含むmTORC2はAKTを活性化するようにpositive feedbackを行っている。

mTORを標的とした腎細胞がん治療

1．mTOR阻害剤作用機序

アミノ酸が多い環境、すなわち栄養的によい生体環境では、4EBP1とS6K1

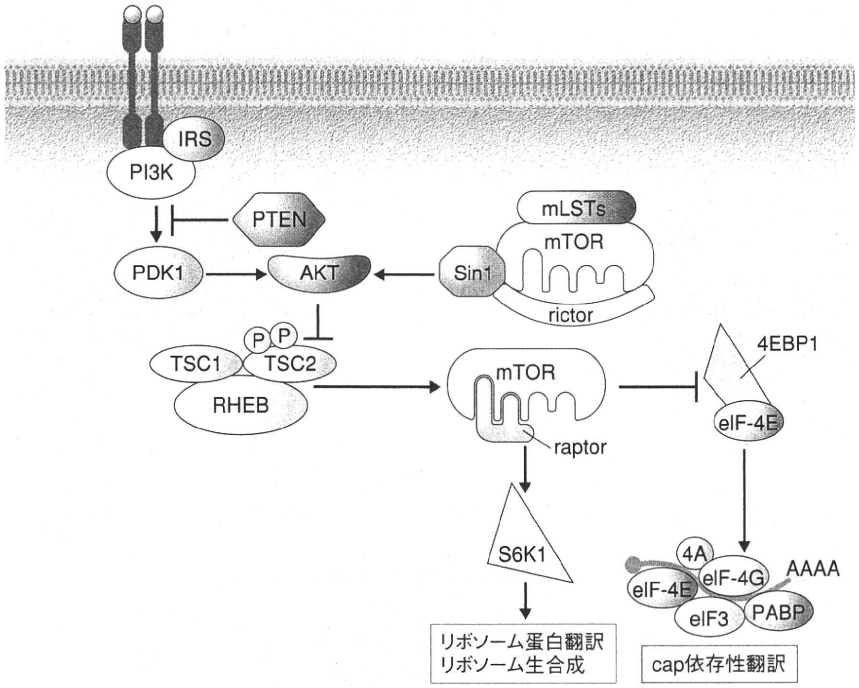

図3　インスリンなどの増殖因子、PI3K、PTEN、AKT、TSC1/2、mTORを含む細胞増殖のシグナル経路

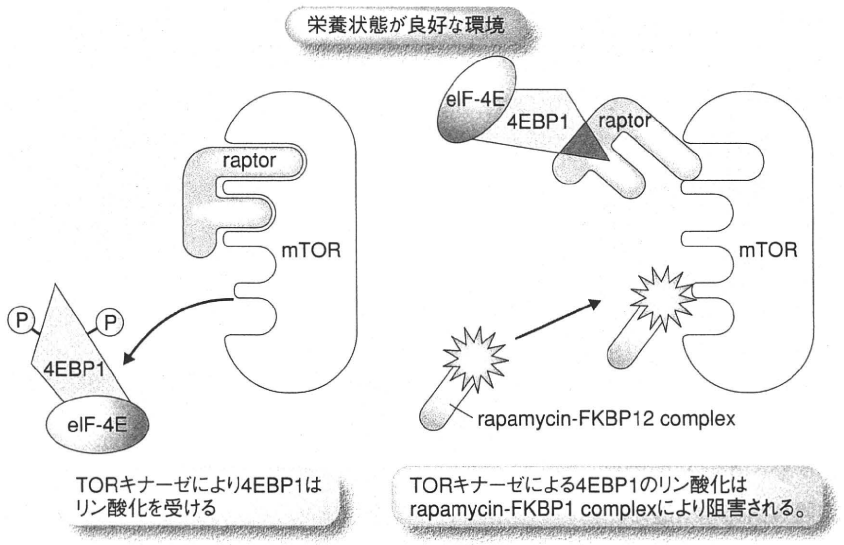

図4　RapamycinはFKBP12と結合してmTORのserine / threonine kinaseを阻害

はmTORによりリン酸化を受けて、結果として相対的に蛋白質合成の強い促進が起こる。この経路は腎臓がんを含む多くのがんで活性化されていると考えられる[1)]。Rapamycinは**図4**のようにFKBP12(FK506-binding protein 12kDa)と複合体を形成してmTORのリン酸化ドメインに結合し、リン酸化活性を抑える作用をもつ。これにより蛋白質合成の強い促進による細胞増殖は抑制される。

mTORC1はrapamycinによりリン