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Acute Treatment of Ruptured Cerebral Aneurysm

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Subarachnoid hemorrhage in most cases is the bleeding from a cerebral aneurysm, and the rupture of cerebral aneurysm is estimated to occur at the frequency of 20 per 100,000 cases.[1] About 35% of patients with subarachnoid hemorrhage die within 8 hours of an attack.[2] There is a data set showing that the overall death rate 30 days after onset is 58%.[3] Despite the efforts of modern medicine, this condition still records a very high death rate and is considered a social problem. Trying to improve the treatment outcome of patients with subarachnoid hemorrhage is a crucial mission bestowed upon us neurosurgeons.

Important causes of poor prognosis in patients with subarachnoid hemorrhage include cerebral infarction due to cerebral vasospasm and rebleeding. The paper by Ohwaki et al. in this issue of the Journal is considered significant, as it analyzed prognostic factors in patients receiving aggressive early surgery and cisternal drainage to treat cerebral vasospasm as a means of preventing these causes of poor prognosis. However, there is some ambiguity as to the reason why subjects were limited to Fisher group 3 patients. The authors were right in saying that Fisher group 3 patients comprised a high-risk group for cerebral vasospasm, but the results could have been more informative if they had included comparison with other groups and examination in all patients with subarachnoid hemorrhage.

The paper claimed that age was the only factor dictating the outcome of patients receiving early surgery and adequate treatment for vasospasm. However, prognosis of any disease generally worsens with age, and age is considered merely a representative of many factors. It is probable that various other factors, such as complications with respiratory and cardiovascular disorders, might be involved. Age is a factor that cannot be modified by physicians or surgeons. It would be more helpful if we could identify some factors associated with the poor prognosis in a group of aged patients after successful prevention of cerebral vasospasm. An analysis from this aspect could have made this paper more significant.

This paper reported a lack of significant differences in terms of initial damage. However, the fact may be that the condition at the time of the first examination may often affect prognosis. Further study using a larger number of cases seems to be required in this respect. While the outcomes were classified into good (good recovery and moderate disability) and poor (severe disability, persistent vegetative state, and death) based on the Glasgow Outcome Scale, it might be inappropriate to include moderate disability in the "good" category. More detailed evaluation of outcomes using the modified Rankin Scale is considered necessary, as it would also allow more accurate analysis of prognostic factors.

Despite the development and improvement of new treatment methods, subarachnoid hemorrhage still results in high rates of death and residual disabilities. As the authors of this paper pointed out, prognosis can be poor even in the cases where aggressive treatment was successful in preventing cerebral vasospasm and rebleeding. The study by Ohwaki et al. was a valuable attempt to shed light on this fact. Further investigation to develop more effective preventive methods is required to improve the outcome of the present treatment.

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Outcome in Subarachnoid Hemorrhage After Early Surgery

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Abstract

Background Following subarachnoid hemorrhage (SAH), numerous factors including neurological conditions, rebleeding and vasospasm influence the outcome. Advances in neurosurgical management, such as early surgery and aggressive vasospasm treatment, have improved the outcome. To achieve more effective management and improve outcome further, however, the identification of important factors for the deleterious consequences of SAH is essential. The aim of this study was to identify prognostic factors in patients with a high risk of vasospasm, who were candidates for early surgery.

Methods We assessed 81 patients with Fisher group 3 who underwent early surgery. We provided cisternal irrigation combined with the head-shaking method to prevent vasospasm. Outcome was assessed 6 months after the onset of SAH according to the Glasgow Outcome Scale. The impacts of clinical factors on outcome were assessed, including sex, age, neurological grade, timing of surgery, cerebral infarction due to vasospasm, and chronic hydrocephalus.

Results Patients with poor outcome (severe disability, persistent vegetative state, and death) were 16 (20%). Poor outcome was associated with older age (mean ± SD; 68 ± 9 vs. 57 ± 12; $P = 0.0003$) and the occurrence of hydrocephalus (56% vs. 29%; $P = 0.042$). Logistic regression analysis revealed that only older age was independently associated with poor outcome (odds ratio, 2.35 per 10 years of age; 95% confidence interval, 1.18 to 4.71) after controlling for neurological grade, timing of surgery, and hydrocephalus.

Conclusions The results of this study indicate that older age has an important impact on poor outcome under conditions permitting early surgery.

Key words Subarachnoid hemorrhage, Outcome, Cisternal irrigation, Elderly

Introduction

Despite considerable advances in neurosurgical management, the outcome of patients with subarachnoid hemorrhage (SAH) remains poor. It has been estimated that 10 to 20% of patients suffering from SAH die before arriving at hospital. Although approximately 60% of patients are treated extensively, only 30–40% of all the patients show good recovery.[1–5] Following SAH, numerous factors influence the outcome. The level of consciousness on admission is a major determinant of outcome.[5–8] Even best management would not improve the outcome of patients with too severe primary brain damage due to the initial hemorrhage. Among patients surviving the initial hemorrhage, rebleeding is the major cause of morbidity and mortality.[6,9] Clinical state permitting, therefore, early surgery is performed to reduce this risk. After surgery, vasospasm is the most important factor affecting outcome.[6]

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Cisternal irrigation appears to decrease the incidence of vasospasm significantly.[10] We have provided cisternal irrigation combined with the head-shaking method for patients with a high risk of vasospasm (Fisher group 3) to prevent vasospasm. Although cisternal irrigation with the head-shaking method decreased the incidence of vasospasm significantly,[11] some patients had poor outcome. To achieve more effective management and improve outcome further, the identification of important factors for the deleterious consequences of SAH is essential. Although it is useful to determine the risk factors for poor outcome in patients with a high risk of vasospasm, who are candidates for early surgery, few reports are available on this issue. The aim of this study was to identify prognostic factors in patients with a high risk of vasospasm, who underwent early surgery.

Methods

Patient population

When the clinical state permitted, early operation was performed for patients with SAH. The severity of SAH was classified by the CT appearance according to Fisher's criteria.[12] Among patients who were admitted to Teikyo University Hospital between January 1996 and December 2000, 82 patients with Fisher group 3 underwent clipping surgery within 72 hours of the onset. One patient died of hepatic cell cancer before the assessment time of 6 months after SAH. The charts of the remaining 81 patients were reviewed retrospectively.

Methods of treatment

Normovolemic hemodilution and controlled mild hypertension were used in patients after the operation. We provided cisternal irrigation with urokinase combined with the head-shaking method to prevent vasospasm for patients with Fisher group 3 after clipping surgery.[11] Cisternal irrigation was started just after the surgery. Lactated Ringer's solution containing urokinase (60,000 IU/500 ml) was infused through a ventricular tube set below 25 cm H_2O from the external auditory meatus. The intracranial pressure control system was usually set at a height of 5–10 cm H_2O from the external auditory meatus. The head of a patient was then rested on the head-shaking device (Neuroshaker, Mizuho Ika Kogyo, Tokyo, Japan), and was shaken periodically at a rate of 1–1.5 c/s. Cisternal irrigation with head-shaking was terminated when the total amount of urokinase reached 420,000 IU or high-density areas in the Sylvian fissure disappeared in the CT scan. When patients showed one of the initial symptoms due to vasospasm after termination of this therapy, additional treatments, which included intrathecal injection of nicardipine 2 mg and/or intraarterial injection of papaverine 40–80 mg,[13,14] were given immediately. Almost all the patients received nizofenon[15] (n = 73) and/or fasudil hydrochloride[16] (n = 51). Ventriculo-peritoneal shunts were performed for all patients with chronic hydrocephalus.

Statistical analysis

The outcomes of the patients were assessed 6 months after the onset of SAH, by clinic visit or telephone interview, according to the Glasgow Outcome Scale (GOS).[17] The outcome was dichotomized into good (good recovery and moderate disability) and poor (severe disability, persistent vegetative state, and death).

The neurological condition was graded according to the classifications of the World Federation of Neurosurgical Societies (WFNS).[18] The WFNS grade was divided into three categories (1, 2–3, and 4–5) because previous studies found that the outcome differs most significantly between patients with grade 1 and 2.[19,20] We used the preoperative WFNS grade as a measure of neurological grade. Intracerebral hematoma (ICH) and massive intraventricular hemorrhage (IVH) were assessed by CT scan on admission. The timing of surgery was counted from noon of the day when accurate onset time was unknown (n = 14). The site of the aneurysm was classified as anterior or posterior circulation. Cerebral infarction on CT scan due to vasospasm was evaluated about 2–4 weeks after onset considering its distribution and the clinical course. Chronic hydrocephalus was defined as cases requiring shunt operation. Shunt operations were performed for all patients who had symptoms such as disorientation, gait disturbance, and urinary incontinence when ventricular enlargements on the CT scans were present from 3 weeks to 2 months after the onset of SAH.

The chi square test or Fisher's exact test was used to compare the two groups (good and poor GOS) for the categorical variables. Wilcoxon's

rank sum test or t-test was used for the continuous variables. A logistic regression model was used to investigate whether any clinical prognostic factor was associated with GOS. The factors with P values of <0.15 were used in logistic regression analysis. The preoperative WFNS grade was forced in the model because it was considered to be an important prognostic factor. Values of $P<0.05$ were deemed significant. Data analysis was performed using the Statistical Analysis System (SAS Institute Inc).

Results

The patient population consisted of 29 males (36%) and 52 females (64%). The ages ranged from 30 to 87 years with a mean of 58.7 years. Preoperatively, there were 27 subjects in WFNS grade 1 (33%), 28 in grade 2 (35%), five in grade 3 (6%), 19 in grade 4 (23%), and two in grade 5 (2%). Regarding the site of aneurysm, their frequency was: anterior communicating/anterior cerebral artery aneurysms (32%), internal carotid artery aneurysms (31%), middle cerebral artery aneurysms (21%), and vertebrobasilar artery aneurysms (11%), in descending order. Cerebral infarction on CT scan occurred in only two patients. Fifty-four (67%) had made a good recovery, 11 (14%) were moderately disabled, 12 (15%) were severely disabled, one (1%) was in a vegetative state, and three (4%) died. The distribution of outcome according to the WFNS grade is depicted in Table 1.

Table 2 illustrates the statistical relationship

Table 1 Preoperative WFNS grade and outcome

		GOS	
		Good n=65	Poor n=16
WFNS grade, n (%)	1	24 (89)	3 (11)
	2	23 (82)	5 (18)
	3	4 (80)	1 (20)
	4	13 (68)	6 (32)
	5	1 (50)	1 (50)

WFNS: World Federation of Neurosurgical Societies; GOS: Glasgow Outcome Scale; Good: good recovery and moderate disability; Poor: severe disability, persistent vegetative state, and death

Table 2 Relationship between clinical factors and outcome

		GOS		P value
		Good n=65	Poor n=16	
Sex	Female	42 (65)	10 (63)	0.87
WFNS grade	1	24 (37)	3 (19)	0.18
	2–3	27 (42)	6 (38)	
	4–5	14 (22)	7 (44)	
IVH	Yes	8 (12)	2 (13)	1
ICH	Yes	4 (6)	2 (13)	0.34
Aneurysm	Posterior	8 (12)	1 (6)	0.68
Infarct	Yes	1 (2)	1 (6)	0.36
Hydrocephalus	Yes	19 (29)	9 (56)	0.042
Age, y	mean ± SD	57 ± 12	68 ± 9	0.0003
Timing of surgery, hr	median (min–max)	19.0 (1.5–62.0)	22.5 (6.5–51.5)	0.11

Values are n (%) unless otherwise stated. WFNS: World Federation of Neurosurgical Societies; GOS: Glasgow Outcome Scale; IVH: intraventricular hemorrhage; ICH, intracerebral hemorrhage; Good: good recovery and moderate disability; Poor: severe disability, persistent vegetative state, and death

Table 3 Logistic regression analysis predicting poor outcome

	OR	95% CI
WFNS grade		
1	1	—
2–3	1.41	0.26–7.57
4–5	3.39	0.61–18.76
Timing of surgery (per hr)	1.02	0.98–1.07
Hydrocephalus	1.69	0.46–6.19
Age (per 10 years of age)	2.35	1.18–4.71

WFNS: World Federation of Neurosurgical Societies; OR: Odds ratio; CI: Confidence interval

between GOS and the predictor variables. Older age and the occurrence of hydrocephalus were associated with GOS ($P=0.0003$ and $P=0.042$, respectively).

A logistic regression model for predicting GOS was constructed using the preoperative WFNS grade and the variables that had values of $P<0.15$, including age, hydrocephalus, and timing of surgery. The logistic regression analysis revealed that only age was independently associated with poor GOS (odds ratio [OR] = 2.35 per 10 years of age; 95% confidence interval [CI], 1.18 to 4.71) (Table 3). A nonsignificant increased risk of poor GOS was observed in the long interval between onset and surgery (OR = 1.02; 95% CI, 0.98 to 1.07), WFNS grade 2–3 and 4–5 (vs. grade 1; OR = 1.41; 95% CI, 0.26 to 7.57 and OR = 3.39; 95% CI, 0.61 to 18.76, respectively), and the occurrence of hydrocephalus (OR = 1.69; 95% CI, 0.46 to 6.19).

Discussion

In the present study, we found that older age was independently associated with poor outcome of aneurysmal SAH patients who underwent early surgery, adjusting for different prognostic factors. The preoperative WFNS grade, timing of surgery, and hydrocephalus had no significant association with GOS in the logistic regression analysis.

Although several studies found a significant association between age and poor outcome, certain factors including neurological grade were also shown to be significant.[6,7,21,22] In our study, only age was a significant predictor of the outcome. The discrepancy may be due in part to differences in the inclusion criteria and vasospasm treatment. In our study, only patients who underwent early surgery were used in the analyses. Cerebral infarction caused by vasospasm occurred in only two patients (2%) owing to aggressive vasospasm treatment including cisternal irrigation with the head-shaking method. The report of Lanzino et al. pointed out that the aging brain had a less optimal response to the initial bleeding.[21] For elder patients, physical function declines in a short time. They may also have many preexisting medical problems. An infectious disease is often complicated because of an impaired immune system. Although older age seems to represent various factors, we cannot clarify how these factors are associated with poor outcome. Further studies are needed to clarify how older age is associated with poor outcome and to examine preventative measures.

In the future, older patients will be indicated for aggressive treatment when neurosurgical treatment advances. One of the most expected procedures for aneurysmal SAH treatment is coil embolization. It will be approved widely for SAH patients with various clinical conditions. However, coil embolization may not be suitable for elderly patients because of the difficulty of catheterization. As the number of elderly people grows, it is increasingly important to identify prognostic factors in elderly patients and determine indications for treatment including coil embolization.

A significant association between neurological grade and outcome has often been shown.[5–8,22] In our study, the WFNS grade was divided into three categories (1, 2–3, and 4–5) because previous studies found that the outcome differs most significantly between patients with grade 1 and 2.[19,20] Nevertheless, the results of our study indicate that the WFNS grade is not associated with GOS. The number of patients with WFNS grade 5 was small in our study because most of them were not candidates for early surgery. The proportion of good outcome in patients with WFNS grade 4 seems to be relatively high as shown in Table 1. Outcome may be related to age more strongly than the WFNS grade under conditions permitting early surgery.

In this study, chronic hydrocephalus was defined as cases that required shunt operations. We

used MEDOS shunt valve systems (Codman/Johnson and Johnson) in all patients with chronic hydrocephalus. Because this system can adjust the pressure delicately, adjustment of the size of the cerebral ventricle can be performed satisfactorily. Despite this system used, chronic hydrocephalus was associated with poor GOS ($P = 0.043$). After adjusting for different prognostic factors, however, the significant association did not persist. Because shunt operation usually improves the symptoms of hydrocephalus, this result seems to be reasonable. Hydrocephalus occurred more often in patients of older age or with a poor WFNS grade (data not shown).

We can expect that the GOS of elderly patients is more likely to be categorized into good recovery considering their age because slight loss of function is more common in elderly persons. However, the results show that older age was inversely related to favorable outcome, so if this bias exists, the true association between age and outcome is even stronger.

Certain limitations of our study must be acknowledged. This series of early surgery is small and selected. It is conceivable that only those patients thought to have a better chance of recovery were offered early surgery, as suggested by the relatively young age and good clinical conditions. Despite the decreased incidence of rebleeding and vasospasm, however, patients who have undergone early surgery and aggressive vasospasm treatment do not always show a good recovery. The identification of important prognostic factors in these patients is essential. In addition, the population was limited to only patients who received cisternal irrigation with head-shaking. These findings may not be applicable to the SAH population as a whole including patients who received various treatments for preventing vasospasm. Further studies are needed with a large population that includes SAH patients with various clinical states to clarify the risk factors for poor outcome, in addition to seeking the determinants of outcome in elderly patients.

In conclusion, multiple logistic regression analysis indicated that only age was independently associated with poor outcome adjusting for different prognostic factors. The results of this study suggest that older age is the most important prognostic factor under conditions permitting early surgery.

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Efficient Interval of Colorectal Cancer Screening Using Immunological Fecal Occult Blood Testing and Flexible Sigmoidoscopy

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Abstract

Purpose The use of annual fecal occult blood testing (FOBT) plus flexible sigmoidoscopy (FS) at 5-year intervals is recommended in Western countries as a screening procedure for colorectal cancer. However, no adequate scientific basis for the interval of screening tests has been provided. In this regard, we examined the efficient interval and method of serial screening tests, based on the results of the second test in subjects who showed no abnormalities in their initial FOBT combined with FS.

Subjects and Methods A total of 45,729 subjects who showed no abnormalities in their initial immunological FOBT (IFOBT) plus FS underwent a second screening test. The second test revealed 55 cases of colorectal cancer (29 with intramucosal cancer, 26 with invasive cancer). For these 55 cases, the odds ratio (OR) of the rate of detection of colorectal cancer for each screening interval (years) was obtained, after adjusting for the screening method (IFOBT alone vs. a combination of IFOBT and FS), method of IFOBT (one-day procedure vs. two-day procedure), results of IFOBT (negative vs. positive), and gender and age of the subjects.

Results In comparison with the 1-year interval (OR = 1), there was no significant increase in OR up to the screening interval of three years, but the overall OR increased significantly to 3.40 (95% confidence interval [CI], 1.57–7.40) and 3.91 (95% CI, 1.74–8.80) for intervals of 4 years and 5 years, respectively. In cases of invasive cancer, there was no significant increase in OR until after 3 years, but the OR was significantly increased at 4 years, to 4.09 (95% CI, 1.40–11.94). When the method of the second screening test was the combination of IFOBT and FS, the OR in comparison with IFOBT alone (OR = 1) was 1.09 (95% CI, 0.60–1.98) as a whole and 0.60 (95% CI, 0.26–1.41) for invasive cancer, showing no significant increase.

Conclusion When an initial screening test consisting of IFOBT and FS is negative, an interval of three years until the second screening test is considered acceptable, enabling efficient screening. A second screening test comprising IFOBT alone may be adequate for efficient screening. If annual IFOBT is continued, FS at 5-year intervals is considered to be unnecessary.

Key words Colorectal cancer, Colorectal cancer screening, Fecal occult blood testing, Sigmoidoscopy, Screening interval

Introduction

Clinical guidelines for colorectal cancer screening in the US recommend implementation of annual fecal occult blood testing and flexible sigmoidoscopy (FS) at 5-year intervals for asymptomatic subjects aged 50 years or older who have average risk of developing colorectal cancer.[1,2] Recently, an increasing number of institutions

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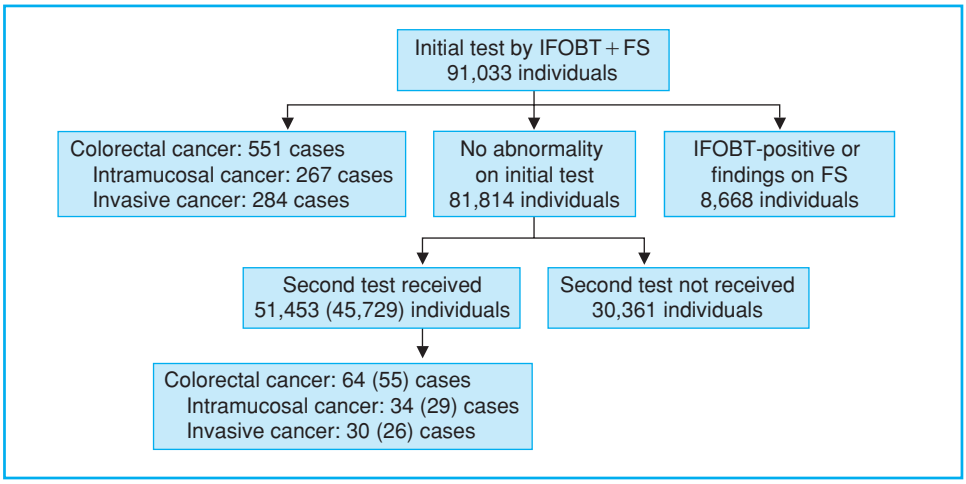

Fig. 1 Analysis of the subjects of colorectal cancer screening
IFOBT: Immunological fecal occult blood testing
FS: Flexible sigmoidoscopy
( ): Number of individuals who received the second test within 5 years

in Japan have been using FS in addition to FOBT in the primary screening stage in general health checkups.[3,4] However, no adequate scientific basis has been provided for annual FOBT and FS at the 5-year intervals adopted for health checkups using a combination of FOBT and FS. In Western countries, a chemical approach is used for FOBT. In contrast, a more sensitive and comparably specific immunological approach (immunological fecal occult blood testing, IFOBT) is used in Japan.[5] To date, few investigations have been carried out to determine an optimal interval of implementing screening tests that combine IFOBT and FS.[6] It remains unclear whether IFOBT and FS should be repeated annually and at 5 years in subjects who have undergone an initial screening test consisting of IFOBT and FS.

In this regard, we examined the efficient interval and method of subsequent screening for colorectal cancer in subjects who had undergone an initial screening test comprising IFOBT and FS. Our investigation used the measure of the rate of detection of colorectal cancer in the second screening test following negative results on the initial test.

Subjects and Methods

The present retrospective study was based on the results of colorectal cancer screening performed in our hospital. The subjects were those who received the initial primary screening test for colorectal cancer comprising IFOBT and FS in our hospital between April 1985 and March 1997. Individuals who received IFOBT or FS alone as the initial screening test were, therefore, excluded from the study. The subject was regarded as having no abnormalities on FS-combined IFOBT when the results of IFOBT were negative and no findings of cancer or polyps were obtained by FS. A total of 91,033 individuals underwent initial screening by IFOBT and FS, and 81,814 of them exhibited no abnormalities. Of these 81,814 individuals, 51,453 received at least one subsequent screening test (Fig. 1). The results of the second screening test in those who had no abnormalities in the initial test were analyzed. In principle, when the test revealed no abnormalities, close examination of the entire large bowel was not carried out in the same year as the initial screening test using FS combined with IFOBT. The subjects included men and women at a ratio of about 2:3, with a mean age of 58.4 ± 9.7 years for men and 58.9 ± 10.8 years for women at the time of the initial screening test. Individuals who had a history of colorectal cancer or adenoma, who had inflammatory bowel disease such as ulcerative colitis or Crohn's disease, or who had a family history of familial adenomatous polyposis were excluded from the

study. A flexible colonoscope was used for FS (a fiberscope with an effective length of 100 cm was used until March 1992, and an electronic endoscope 130 cm in length was used thereafter). In principle, the rectum and sigmoid colon were observed by colonoscopy. Observation was not combined with biopsy or other endoscopic treatments. When colonoscopy revealed a tumor suggestive of cancer or a polyp measuring 5 mm or greater, the subject was regarded as FS-positive and later subjected to closer examination mainly by total colonoscopy. For IFOBT, a one-day procedure was generally used until March 1992, and thereafter a two-day procedure was employed. Submucosal invasive cancer and advanced cancer with a risk of metastasis were dealt with collectively as invasive cancers. To exclude the effect of the number of screening tests, analysis in the present study was restricted to the initial and second screening tests.

The initial screening test using FS-combined IFOBT disclosed 551 cases of cancer (detection rate, 0.61%) comprising 267 cases of intramucosal cancer (m cancer) (0.29%) and 284 cases of invasive cancer (0.31%) (Fig. 1). Among 51,453 individuals who showed no abnormalities on the initial screening test, 64 cases of cancer (34 cases of m cancer and 30 cases of invasive cancer) were found on the second screening test, which consisted of IFOBT alone in 31,725 individuals and FS-combined IFOBT in 19,728 individuals. Interval cancers, i.e., cancers detected when patients visited medical institutions because of perceived symptoms, were not included in the present analysis. No case of interval cancer was found in these 51,453 individuals between the day after the initial screening test and the day before the second screening test, according to our investigations of the available medical records or the interview sheets filled out by the subjects themselves or their families. Since the focus of the present study was on the efficacy of screening tests consisting of IFOBT and FS, rectal cancer and sigmoid colon cancer, which can be directly detected by FS (because the colonoscope can reach the rectum and sigmoid colon), and cancer of the colon more proximal than the descending colon, which are likely to be detected by close examination based on positive results of IFOBT, were handled together without differentiation.

The interval between the initial screening test by FS-combined IFOBT and the second screening test was classified as 0 year (less than 0.5 year), 1 year (0.5 or more but less than 1.5 years), 2 years (1.5 years or more but less than 2.5 years), 3 years (2.5 years or more but less than 3.5 years), 4 years (3.5 years or more but less than 4.5 years), and 5 years (4.5 years or more but less than 5.5 years), and 6 years or more (5.5 years or more). Since the number of subjects decreased markedly as the number of years increased beyond 6 years, those who received the second screening test after 6 years were excluded from analysis. Therefore, a total of 55 cases of colorectal cancer (including 26 cases of invasive cancer) detected in 45,729 individuals whose screening interval fell in the 5-year or shorter categories were analyzed in the present study.

First, with attention focused on the interval between the initial and second screening tests, the rate of detection of colorectal cancer at the 1-year interval was compared with that obtained at longer intervals, regardless of whether the method of the second screening test was IFOBT alone or FS-combined IFOBT. Next, a similar comparison was made, taking the method of screening into consideration. Whether advanced cancer might increase as the interval between screening tests increased was examined in terms of Dukes classification of invasive cancer in relation to each screening interval. Differences in the rates of detection of colorectal cancer between interval categories of one year and longer and between IFOBT alone and FS-combined IFOBT in each interval category were analyzed by χ^2 test or Fischer's direct probability test as appropriate. The percentages of subjects who received IFOBT alone and those on combined IFOBT and FS in one-year and longer interval categories were compared by χ^2 test. Relation with Dukes classification of invasive cancers was examined by the Kruskal-Wallis test.

In addition, odds ratios (OR) of the rates of detection of colorectal cancer in relation to the screening interval were obtained by multivariate analysis consisting of logistic regression analysis using the explanatory variables of method of screening, IFOBT procedure, results of IFOBT, and gender and age of the subjects, and the objective variable of type of colorectal cancer detected. The results of IFOBT were included as an explanatory variable because 1,520 (8.9%) of 17,172 individuals who underwent FS-combined IFOBT were IFOBT-positive and would have

Table 1 Number of individuals who received the second screening test in relation to the method of screening and the screening interval

	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	Total
IFOBT alone	16,509 (84.2%)	6,064 (61.2%)	2,640 (33.2%)	1,970 (38.2%)	1,374 (44.3%)	28,587 (62.4%)
IFOBT + FS	3,107 (15.8%)	3,841 (38.8%)	5,312 (66.8%)	3,185 (61.8%)	1,727 (55.7%)	17,172 (37.6%)
Total	19,616	9,905	7,952	5,155	3,101	45,729

( ): Percentage of individuals who received IFOBT alone or IFOBT + FS

Table 2 Number of colorectal cancers detected by the second screening test in relation to the method of screening and the screening interval

		1 yr	2 yrs	3 yrs	4 yrs	5 yrs	Total
IFOBT alone	Intramucosal cancer	5	2	1	2	1	11
	Invasive cancer	5	1	3	3	2	14
IFOBT + FS	Intramucosal cancer	2	2	4	4	6	18
	Invasive cancer	2	1	3	4	2	12

been subjected to closer examination even if FS had not been combined. Therefore, the results of IFOBT were added as an explanatory variable to achieve adjustment.

Statistical analysis was carried out with StatView for Windows software (version 5.0, SAS Institute, Cary, NC, USA). Differences were considered statistically significant at significance a level of less than 5%.

Results

Rates of detection of colorectal cancer on the second screening test in relation to screening interval

Table 1 shows the number and percentage of subjects in relation to screening interval between the initial and second screening test and the method of screening. When the screening interval was 1 year, the percentage of subjects who underwent IFOBT alone was as high as 84.2%, whereas the percentage of those who received FS-combined IFOBT was significantly higher for 2-year or longer screening intervals ($P<0.0001$ for each screening interval). In particular, when the screening interval was 3 years or longer, the percentage of subjects who underwent FS-combined IFOBT exceeded 50%. Table 2 shows the number of colorectal m cancers and invasive cancers detected, in relation to screening interval.

Figure 2 shows the rate of detection of colorectal cancer in relation to screening interval. There was no significant increase in overall colorectal cancers until 2 years after the initial test; the detection rate tended to be higher at 3 years ($P=0.094$) and significantly higher at 4 or more years. The rate of detection of invasive cancer up to 3 years after the initial screening test showed no significant difference, but became significantly higher at 4 years ($P=0.0144$). The detection rate tended to be higher at 5 years than at one year ($P=0.052$).

Figure 3 shows the rate of detection of overall colorectal cancer on the second screening test in relation to the method of screening and the screening interval. In cases of screening test by IFOBT alone, there was no significant increase in detection rate until after 3 years, but the detection rate was significantly increased ($P=0.016$) at 4 years and tended to be increased ($P=0.072$) at 5 years. In cases of screening tests by combined IFOBT and FS, there was no significant difference until after 4 years from the result at 1 year, but the detection rate was significantly higher at 5 years ($P=0.028$). There was no significant difference in detection rate at any screening interval

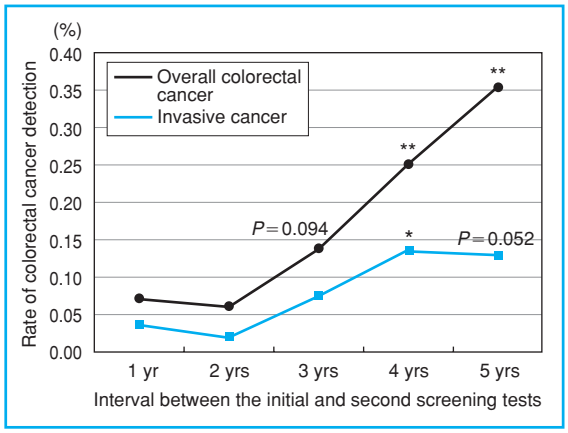

Fig. 2 Rates of detection of colorectal cancer on the second screening test in relation to the interval from the initial test

Comparison with the 1-yr interval. *$P<0.05$ **$P<0.01$

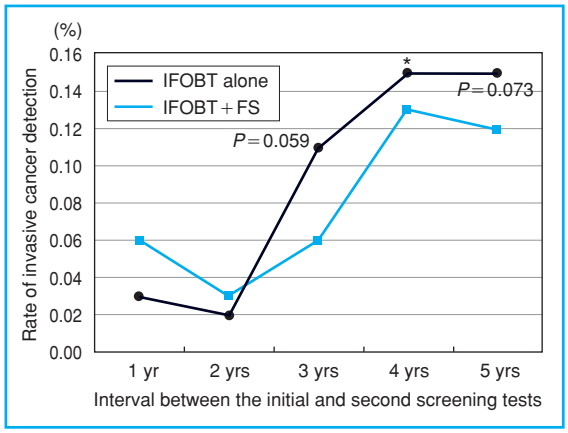

Fig. 4 Rates of detection of invasive cancer on the second screening test in relation to the method screening

Comparison with the 1-yr interval. *$P<0.05$ **$P<0.01$

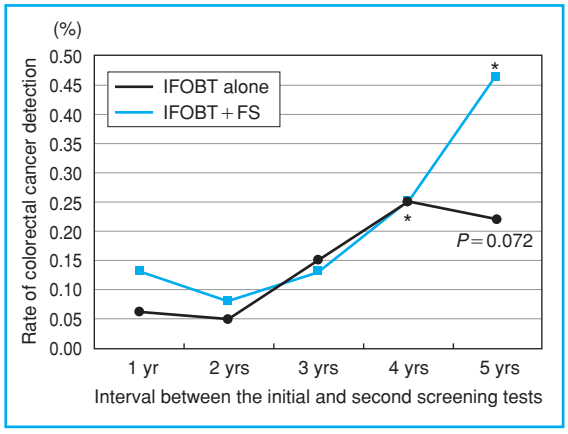

Fig. 3 Rates of detection of colorectal cancer on the second screening test in relation to the method of screening and the screening interval

Comparison with the 1-yr interval. *$P<0.05$ **$P<0.01$

Table 3 Dukes classification of invasive cancer in relation to the screening interval

	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Dukes A	2	1	2	4	1
Dukes B	3	1	3	1	2
Dukes C	2	0	1	2	1
Total	7	2	6	7	4

(Kruskal-Wallis test, $P=0.894$)

in relation to whether or not FS was combined with IFOBT.

Figure 4 shows the rate of detection of invasive cancer on the second screening test in relation to the method and interval of screening. In cases of IFOBT alone, there was no significant increase in detection rate until 2 years. The rate of detection tended to be increased at three years ($P=0.059$) and was significantly increased at four years ($P=0.03$). The detection rate also tended to be high at five years ($P=0.073$). In cases of combined IFOBT and FS, the detection rate was higher, but not significantly, at 4- and 5-year intervals than at one year. There was no significant difference in detection rate between IFOBT alone and combined IFOBT and FS at any screening interval.

Table 3 shows Dukes classification of the invasive cancers detected at each screening interval. There was no particular correlation between the screening interval and Dukes classification of the detected cancers; advanced cases were not notably increased as the screening interval became longer.

Of 26 individuals who were found to have invasive cancer on the second screening test, 25 (96.2%) had positive results on IFOBT. The only invasive cancer negative on the 2-day procedure of IFOBT was a sigmoid colon cancer that tested positive for FS at the 4-year screening interval. Of 29 individuals with m cancer, 15 (53.6%) were positive for IFOBT. Seven individuals were

Table 4 Details of the subjects of the second screening test

Explanatory variable		No. of cases	(%)
Screening interval	1 yr	19,616	42.9
	2 yrs	9,905	21.7
	3 yrs	7,952	17.4
	4 yrs	5,155	11.3
	5 yrs	3,101	6.8
Method of screening	IFOBT alone	28,557	62.5
	IFOBT + FS	17,172	37.6
IFOBT procedure	One-day procedure	37,730	82.5
	Two-day procedure	7,999	17.5
Results of IFOBT	Negative	42,842	93.7
	Positive	2,887	6.3
Gender	Men	16,876	36.9
	Women	28,853	63.1
Age	Mean (yrs)	58.3 ± 10.1	

found to have m cancer at the 1-year screening interval. Five (71.4%) of them were positive for IFOBT, and the remaining two negative cases were rectal cancer and sigmoid colon cancer.

Investigation of the ratio of colorectal cancer detection rates by multivariate analysis

Table 4 shows the number of subjects in relation to the respective screening intervals, methods of screening, results of IFOBT, and gender and mean age of the subjects.

Table 5 shows the odds ratio for the rate of detection of overall colorectal cancer in relation to the screening interval, and Table 6 similarly shows the odds ratio for the rate of detection of invasive cancer. The odds ratio of the rate of cancer detection at each screening interval against the value obtained at the 1-year interval was calculated. In comparison with the 1-year interval (OR = 1), the odds ratio of the rate of detection of overall colorectal cancer at the 3-year interval was 1.97 (95% confidence interval [CI], 0.87–4.45), showing no significant increase. However, the odds ratio increased significantly to 3.40 (95% CI, 1.57–7.40) at the 4-year interval and to 3.91 (95% CI, 1.74–8.80) at the 5-year interval. In cases of invasive cancer, the OR was 2.52 (95% CI, 0.82–7.71) for the 3-year interval, which was not significantly increased. However, the OR of 4.09 (95% CI, 1.40–1.45) obtained for the 4-year interval was significantly higher. The OR for the 5-year interval was also high, 3.05 (95% CI, 0.87–10.66). With regard to the method of screening, in comparison with IFOBT alone (OR = 1), the OR for combined IFOBT and FS was 1.09 (95% CI, 0.60–1.98) for overall colorectal cancer and 0.60 (95% CI, 0.26–1.41) for invasive cancer, showing no significant difference. In comparison with the 1-day procedure of IFOBT (OR = 1), the OR of the 2-day procedure was 1.19 (95% CI, 0.62–2.28) for overall colorectal cancer and 0.86 (95% CI, 0.33–2.21) for invasive cancer, showing no significant difference. With regard to the results of IFOBT, the OR of positive to negative cases (OR = 1) was 35.71 (95% CI, 19.52–65.31) for overall colorectal cancer and 373.17 (95% CI, 50.22–2773.19) for invasive cancer, showing a significant increase. In comparison with men (OR = 1), the OR of women was 0.75 (95% CI, 0.44–1.28) for overall colorectal cancer and 0.91 (95% CI, 0.42–2.01) for invasive cancer, showing a slight, but not significant, decrease. As age increased by one year, the OR for overall colorectal cancer increased significantly to 1.04 (95% CI, 1.01–1.07). In cases of invasive cancer, the OR also increased, but not significantly, to 1.03 (95% CI, 0.99–1.07).

Discussion

The benefit of colorectal cancer screening by chemical FOBT at 1- or 2-year intervals in reducing the mortality from colorectal cancer

Table 5 Ratio of the rate of cancer detection in relation to the screening interval (overall colorectal cancer)

Explanatory variable		Odds ratio	(*P* value)	95% confidence interval
Screening interval	1 yr	1		
	2 yrs	0.90	0.82	0.34–2.35
	3 yrs	1.97	0.10	0.87–4.45
	4 yrs	3.40	0.002	1.57–7.40
	5 yrs	3.91	0.001	1.74–8.80
Method of screening	IFOBT alone	1		
	IFOBT＋FS	1.09	0.77	0.60–1.98
IFOBT procedure	One-day procedure	1		
	Two-day procedure	1.19	0.60	0.62–2.28
Results of of IFOBT	Negative	1		
	Positive	35.71	0.0001<	19.52–65.31
Gender	Men	1		
	Women	0.75	0.28	0.44–1.28
Age		1.04	0.007	1.01–1.07

(Logistic regression analysis)

Table 6 Ratio of the rate of cancer detection in relation to the screening interval (invasive cancer)

Explanatory variable		Odds ratio	(*P* value)	95% confidence interval
Screening interval	1 yr	1		
	2 yrs	0.65	0.59	0.14–3.17
	3 yrs	2.52	0.11	0.82–7.71
	4 yrs	4.09	0.01	1.40–11.94
	5 yrs	3.05	0.08	0.87–10.66
Method of screening	IFOBT alone	1		
	IFOBT＋FS	0.06	0.24	0.26–1.41
IFOBT procedure	One-day procedure	1		
	Two-day procedure	0.86	0.75	0.33–2.21
Results of IFOBT	Negative	1		
	Positive	373.17	0.0001<	50.22–2773.19
Gender	Men	1		
	Women	0.91	0.82	0.42–2.01
Age		1.03	0.13	0.99–1.07

(Logistic regression analysis)

has already been demonstrated epidemiologically.[7–10] The efficacy of FS has been strongly suggested by a number of case-control studies.[11,12] Colonoscopy is advantageous in that it allows direct observation of the large bowel. Therefore, not only colorectal cancer but also adenomatous polyps can be detected with high accuracy. The view that most colorectal cancers result from canceration of adenomas is widely supported.[1,13] Therefore, it is considered that endoscopic resection of adenomatous polyps at the time of colonoscopic observation can suppress the development of adenoma-derived cancer, leading to a decrease in mortality from colorectal cancer.[1,14,15] The period in which an adenoma develops into an advanced cancer is generally considered to be

at least 5 years or, more likely, about 10 years.[1,13] Selby et al., who examined the efficacy of FS by the case-control study approach, demonstrated that sigmoidoscopy repeated at an interval of 10 years or more would be effective for reducing deaths from colorectal cancer located within the area reachable by the endoscope.[11] Rex et al. proposed that 5-year intervals would be appropriate for screening by FS in asymptomatic individuals aged 50 years or older who have average risk of developing colorectal cancer if the initial screening test has revealed no abnormality.[16]

Based on the above scientific data, annual FOBT, FS once every 5 years, or a combination of annual FOBT and FS once every 5 years are recommended for colorectal cancer screening in Western countries.[1,2,17,18]

We have employed community-based mass screening for colorectal cancer using a combination of FS and IFOBT,[19,20] and we recommend that annual IFOBT combined with FS once every 3 years be implemented when there is no abnormality in the initial screening using combined IFOBT. Recently, we have been recommending annual IFOBT and FS once every 5 years, based on reference to related guidelines issued in Western countries.[1,2] However, in actuality, our recommendation of annual IFOBT combined with FS once every 3 or 5 years is not fully observed. A preliminary survey prior to the present study disclosed that there were many individuals who had not undergone the second screening test or in whom the screening interval was prolonged. In a high percentage (84.3%) of the individuals who received the second screening test 1 year after the initial test using FS-combined IFOBT, the second screening test comprised IFOBT not combined with FS. As the screening interval increased, the proportion of screening using IFOBT alone decreased, whereas combined IFOBT and FS accounted for a significantly higher percentage (Table 1). In particular, when the interval was 3 years, the percentage of FS-combined IFOBT was the highest, at 66.8%. The corresponding percentage was 61.8% for the 3-year interval and 55.7% for the 5-year interval, demonstrating that more than half the total subjects received combined IFOBT as the second screening test. Thus, a substantial number of individuals were found not to receive annual IFOBT after the initial screening test, but to receive a combination of IFOBT and FS within 3–5 years; this finding was the stimulus for the present study.

In the present study, the benefit of the initial colorectal cancer screening test comprising IFOBT and FS was examined from the aspect of the rate of detection of colorectal cancer in relation to screening interval. In addition, we also examined whether subsequent annual IFOBT and FS once every 5 years constitute a necessary means of efficient screening when no abnormality is found in the initial screening test using FS-combined IFOBT.

Although colonoscopy often reveals the presence of a number of adenomatous polyps that are negative on FOBT, it has not been established to what extent they should be endoscopically resected, how to perform surveillance after resection, and whether post-resection subjects should be regarded as a high-risk group. When the results of FOBT are positive, closer examination of the entire large bowel by colonoscopy or contrast enema radiography is generally performed.[5] Therefore, it is difficult to evaluate the benefit of screening by combined IFOBT and FS because the results of such close examination are also involved as confounding factors. In this regard, in order to minimize these issues, the subjects of our study were restricted to those who had no abnormality on a screening test comprising IFOBT combined with FS from among all subjects of colorectal cancer screening.

Initially, the rates of cancer detection at the second screening test carried out after different time intervals were compared (Fig. 2). In comparison with the 1-year interval, there was no significant increase in the detection rate for the 2-year interval, but the rate tended to be increased at the 3-year interval, and was significantly increased at intervals of 4 years or longer. In cases of invasive cancer, there was no significant difference in detection rate at the 2- or 3-year interval compared with the 1-year interval, but the rate obtained at the 4-year interval was significantly higher than that at the 1-year interval. The detection rate also tended to be higher at the 5-year interval than at the 1-year interval. In no case did prolonged screening intervals lead to the detection of more advanced cancers (Table 3). Since colorectal cancers include m cancers, which are cancers of an earlier phase, it is considered reasonable that the detection rate tended to be increased at the 3-year interval.

Based on the above findings, it is considered that, within a period of three years, there would be no significant difference in the detection rate, whether the second test is performed at the 1-year or longer intervals. Table 1 shows the numbers of individuals who received the second screening test comprising IFOBT alone or a combination of IFOBT and FS in relation to the interval from the initial screening test. The percentage of those who received IFOBT was significantly higher for the 1-year interval than for 2-year or longer intervals. Therefore, when the screening interval is 2 years or more, it seems that FS is more likely to be combined with IFOBT than in cases of a 1-year interval, resulting in a higher possibility for FS to detect IFOBT-negative cancers and thus a higher rate of overall cancer detection. Taking this into account, it is advantageous to use FS in combination with IFOBT in the initial screening test. In addition, when attention is focused on the results of IFOBT in cases of invasive cancer detected on the second screening test, it is apparent that one case of IFOBT-negative cancer was found at a screening interval of 4 years. This supports the idea that IFOBT alone, without combining FS, would be appropriate for the second screening as long as the interval from the initial screening test consisting of IFOBT plus FS is 3 years or less.

Next, we examined whether IFOBT alone would be appropriate as the second screening test in individuals who exhibited no abnormalities on the initial screening test consisting of IFOBT plus FS. In this regard, the rates of detection of colorectal cancer were analyzed according to the method of the second screening test, i.e., IFOBT alone and FS-combined IFOBT in relation to the screening interval. For overall colorectal cancer (Fig. 3), the detection rate by IFOBT alone did not increase significantly until 3 years after the initial screening test; the detection rate was significantly higher at the screening interval of 4 years. When the second screening test comprised FS-combined IFOBT, there was no significant difference in the detection rate until 4 years after the initial test, but the detection rate was significantly higher at the screening interval of 5 years. At any screening interval, there was no significant difference in the detection rate of colorectal cancer between IFOBT alone and FS-combined IFOBT. For invasive cancer (Fig. 4), the detection rate by IFOBT alone did not increase significantly until 2 years after the initial test. The detection rate tended to increase at the 3-year interval and showed a statistically significant increase at the 4-year interval. When the second screening test consisted of a combination of IFOBT and FS, the detection rate was higher at 4- and 5-year intervals than at the 1-year interval, but it did not reach statistical significance because of the relative lack of subjects. At any screening interval, there was no significant difference in the detection rate of colorectal cancer between IFOBT alone and FS-combined IFOBT. Based on the finding that there was no significant difference in the rate of cancer detection between IFOBT alone and combined IFOBT and FS, it is considered that IFOBT alone is appropriate for the second screening test, without need for the concomitant use of FS.

For further objective evaluation, the rates of cancer detection were examined by logistic regression analysis after adjusting for the method of screening, IFOBT procedure, IFOBT results, and gender and age of the subjects. For overall colorectal cancer, the odds ratio of the detection rate for the 1-year interval (OR = 1) increased to 1.97 (95% CI, 0.87–4.45) at the 3-year interval, but there was no statistically significant difference. Since the number of subjects who received the second screening test 3 years after the initial test was only 7,952, the statistical power was considered inadequate to detect statistically significant differences. The OR was 3.40 (95% CI, 1.57–7.40) at the 4-year interval and 3.91 (95% CI, 1.74–8.80) at the 5-year interval; these values were significantly higher. In cases of invasive cancer, the OR increased to 2.52 (95% CI, 0.82–7.71) at the 3-year interval, but the increase was not statistically significant. As with overall colorectal cancer, the number of subjects was considered too small to provide sufficient power to detect statistically significant differences. The OR was significantly increased at the 4-year interval to a value of 4.09 (95% CI, 1.40–11.94). Based on these findings, the 3-year interval is considered to provide efficient screening tests. In comparison with IFOBT alone (OR = 1), the OR for combined IFOBT and FS was 1.10 (95% CI, 0.60–1.98) for overall colorectal cancer and 0.60 (95% CI, 0.26–1.41) for invasive cancer, indicating no significant difference between the methods of screening. When similar analysis was carried out using m cancer as the objective vari-

able (data not shown), the OR for FS-combined IFOBT was increased to 1.78 (95% CI, 0.77–4.11), but no significant difference was detected because of insufficient power. This also indicates that the second screening test requires IFOBT alone and not concomitant FS. In relation to the procedure of IFOBT, the OR of the 2-day procedure vs. the 1-day procedure was 1.19 (95% CI, 0.62–2.28) for overall colorectal cancer and 0.86 (95% CI, 0.33–2.21) for invasive cancer, indicating no significant difference between the two procedures. The sensitivity of IFOBT is reported to be 50% for m cancer and 71% for invasive cancer, using the 1-day procedure, whereas the corresponding values are 74% for m cancer and 85% for invasive cancer when the 2-day procedure is used.[5,21] These figures appear to explain why no significant difference was detected when the 1- and 2-day procedures were incorporated as explanatory variables. In relation to the results of IFOBT, the OR of positive cases against negative cases (OR = 1) was 35.71 (95% CI, 19.52–65.31) for overall colorectal cancer and 373.17 (95% CI, 50.22–2773.19) for invasive cancer, showing a statistically significant increase. Overall colorectal cancer was found in 40 (1.39%) of 2,887 individuals positive for IFOBT and 15 (0.035%) of 42,842 individuals negative for IFOBT. Invasive cancer was found in 25 (0.87%) IFOBT-positive individuals and one (0.002%) negative individual. These figures may explain the high OR values persisting even after adjustment for other explanatory variables. In comparison with men (OR = 1), the OR of women was lower, 0.75 (95% CI, 0.44–1.28) for overall colorectal cancer and 0.91 (95% CI, 0.42–2.01) for invasive cancer, but the difference was not statistically significant. With regard to age, the OR for overall colorectal cancer increased significantly to 1.04 (95% CI, 1.01–1.07) as the age of subjects increased by one year. The OR for invasive cancer also increased to 1.03 (95% CI, 0.99–1.07), but the difference was not statistically significant. These results are considered to be consistent with the fact that the detection rate in screening for colorectal cancer is higher in individuals of advanced age than in younger people and in men than in women.[22]

The results of the present study indicate that if no abnormality is found by the initial screening test using a combination of IFOBT and FS, an interval of 3 years to the second test allows efficient screening for colorectal cancer because no significant difference was found in the rates of cancer detection at 1- and 3-year intervals. In addition, there seems to be no need to combine FS in the second screening test. IFOBT alone would be sufficient.

Meanwhile, some cases of invasive cancer were found even when the second screening test was carried out at the 1-year interval, although the detection rate was just 0.036%. These cases are likely to have been overlooked by the preceding FS-combined IFOBT. To detect these cancers, implementation of IFOBT the year after the initial screening test using a combination of IFOBT and FS and annually thereafter is considered effective, and, in this case, implementation of FS once every 5 years would be unnecessary.

In Japan, the current general tendency is hesitation in introducing concomitant FS into the screening test for colorectal cancer in view of various issues such as cost-effectiveness and processing capacity.[23] An initial screening test using a combination of IFOBT and FS followed by annual IFOBT may prove to be a solution to this issue.

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Original Article

Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening

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Abstract

Background To clarify the limitations of immunologic fecal occult blood tests (IFOBT) as a screening method for colorectal cancer (CRC), we analyzed data from a total colonoscopy (TCS) and an IFOBT independently performed in asymptomatic average-risk adults, undergoing a complete medical check-up on a single day.

Methods Colonoscopic screening examinations were performed by IFOBT on 7,797 asymptomatic adults enrolled for a complete medical check-up at our hospital between July 1998 and July 2002.

Results A total of 19 cancers and 53 large adenomas (10 mm or more in diameter) were detected using TCS: 18 in early stages of cancer and 1 in advanced stages of cancer. The sensitivity of IFOBTs for cancer was 52.6% and for large adenoma was 24.5%. Seven cancers (36.8%) were found in the proximal colon, and 34 large adenomas (64.2%). Of the 12 cancers found in the distal colon, 7 (58.3%) had a positive IFOBT. On the other hand, 3 of the 7 proximal cancers (42.9%) had a positive IFOBT. The positive rates of IFOBT for large adenoma found in the distal and proximal colon were 7 out of 19 (36.8%) and 6 out of 34 (17.6%) respectively. There was a tendency for lesions in the proximal colon to have a lower IFOBT positive rate than those in the distal colon. From the results above, approximately one half of both cancers and large adenomas would have been missed using just IFOBT as a screening test.

Conclusion The sensitivity of IFOBT for screening for cancers and large adenomas was lower in the proximal colon than in the distal colon.

Key words Asymptomatic subjects, Total colonoscopy, Colorectal cancer screening, Fecal occult blood test, Complete medical check-up

Introduction

The mortality and morbidity from colorectal cancer (CRC) continues to increase in Japan as well as in the Western world.[1] At the present time, methods to primarily prevent CRC have not yet been established, so secondary prevention is very important. Several large prospective randomized controlled studies have shown that fecal occult blood test (FOBT) plays an important role as a secondary preventive measure.[2–4] However, the FOBT method is not sufficient to obtain survival benefit or to detect cancers at an early stage. To counteract these disadvantages, a more sensitive modality is necessary, such as total colonoscopy (TCS). The aim of the present study is to clarify the problems of an immunologic fecal occult blood test (IFOBT) based on a comparison of data obtained from TCS and IFOBT independently performed on a patient in a single day.

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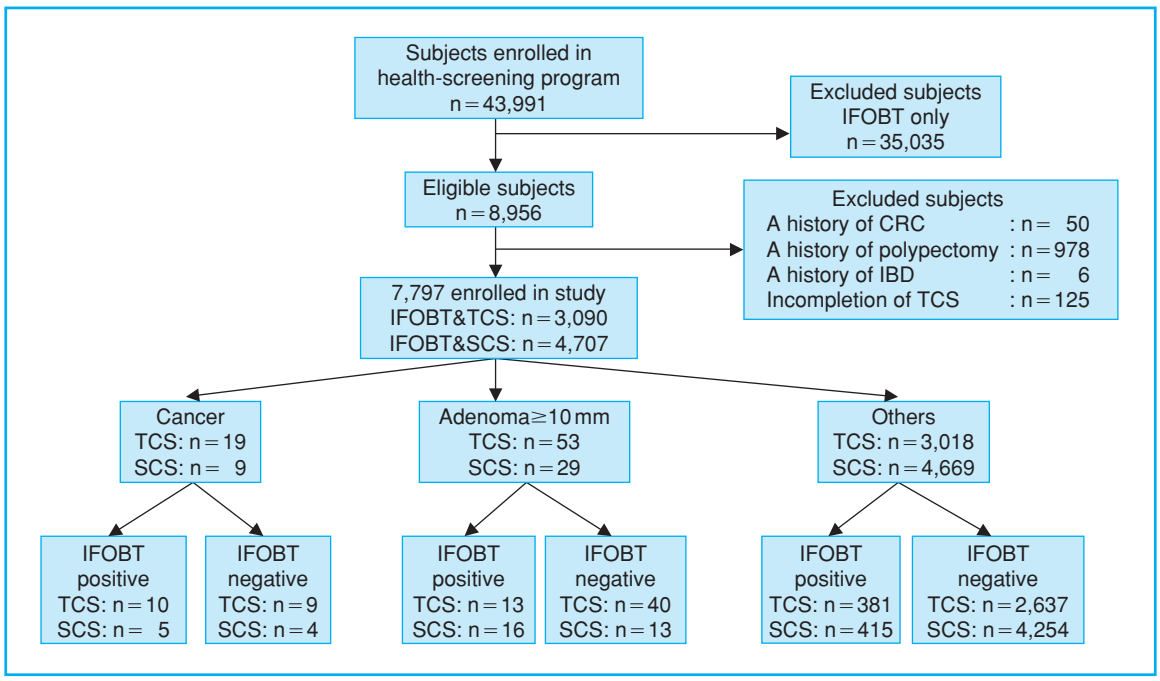

Fig. 1 Study profile

IFOBT: immunologic fecal occult blood test; TCS: total colonoscopy; SCS: sigmoidoscopy; CRC: colorectal cancer; IBD: inflammatory bowel diseases

Materials and Methods

Study subjects (Fig. 1)

We performed a cross-sectional analysis of asymptomatic adults who underwent both a colonoscopic examination and an IFOBT, independently performed in a single day in complete medical check-up conducted at our hospital in the period from July 1998 through July 2002. The study was approved by the institutional review board of Akita Red Cross Hospital. Of 43,991 subjects enrolled for a complete medical check-up at our hospital, 8,956 were screened by both IFOBT and colonoscopy at their request. A total of 7,797 (87.1 percent) of examinations were included in this analysis. Of the total of 7,797 colonoscopic examinations, 3,090 consisted of TCS and 4,707 consisted of sigmoidoscopy (SCS). The average age of the subjects was 52.7 ± 7.9 years (mean age ± SD) (TCS; 53.4 ± 8.2 years, SCS; 52.5 ± 7.6 years) and the male-female ratio was 3.4:1 (TCS; 5.6:1, SCS; 2.8:1). The subjects were excluded from the study if they met the following criteria: 1) a personal history of CRC and colonoscopic treatment of colorectal neoplasm, 2) a history of altered bowel habits or rectal bleeding, or 3) a known history of inflammatory bowel diseases (IBD), familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). The analysis was based on data obtained from colonoscopic examinations (TCS and SCS), pathologic findings and IFOBT of 7,797 examinees.

Study procedures

Eligible subjects received a polyethylene glycol-based electrolyte solution for bowel preparation. Two stool samples from each of the two consecutive days before bowel preparation were sent for IFOBT. As a rule, colonoscopies were performed with no use of conscious sedation. All lesions found were photographed and their sites, size, morphological findings and classification of pit pattern were recorded by the study doctors. In our study, all the endoscopists had substantial experience with colonoscopy.

Histological evaluation

All retrieved lesions were sent to pathological

Table 1 Results of IFOBT in relation to total colonoscopic findings

	Cancer (early/advanced)	Large adenoma (adenoma≥10 mm)	Small adenoma (adenoma<9 mm)	Others
IFOBT positive (n=404)	10 (9/1)	13	37	344
IFOBT negative (n=2,686)	9 (9/0)	40	216	2,421
Overall (n=3,090)	19 (18/1)	53	253	2,765

IFOBT: immunologic fecal occult blood test

Table 2 Sensitivity, specificity, positive predictive value and negative predictive value of IFOBT for cancer and large adenoma

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Cancer	52.6%	87.2%	2.5%	99.7%
(95% CI)	(30.1–75.1)	(86.0–88.4)	(1.0–4.0)	(97.5–99.9)
Large adenoma (adenoma≥10 mm)	24.5%	87.1%	3.2%	98.5%
(95% CI)	(12.9–36.1)	(85.9–88.3)	(1.5–4.9)	(98.0–99.0)

IFOBT: immunologic fecal occult blood test; CI: confidence interval

laboratories in our center for processing. Interpretation of the histopathological features was performed by a single pathologist who had considerable experience in gastroenterologic pathology. In cases having some kind of tumor, the classification of the tumor was based on the most advanced lesions. The distal part included the sigmoid colon and the rectum. The proximal part included the descending colon and all proximal portions of the colon. Early colorectal cancer has been defined as intramucosal carcinoma and carcinoma invading the submucosal layer in Japan. Advanced colorectal cancer was defined as a lesion in which malignant cells had infiltrated beyond the submucosal layer.[5]

Statistical analysis

Management of the study database and all statistical analyses were performed by StatView for Windows software (Version5.0, SAS Institute, Cary, NC, USA).

The results were shown as rates or proportions. χ^2 test was used to compare proportions. Statistical significance was taken as $P<0.05$. Descriptive statistical analyses included the calculation of rates and proportions for categorical data and means and standard deviation for continuous data.

Results

We assessed the sensitivity of IFOBT as a screening test. Of the 3,090 subjects who underwent TCS, 404 (13.1%) had positive IFOBT results. Cancer was detected in 19 subjects. 10 had positive IFOBT results. Among all the 53 subjects with large adenoma (10 mm or more in diameter), 13 had positive IFOBT results. The sensitivity of IFOBT for cancer was 52.6%, the specificity was 87.2%, and the positive predictive value was 2.5%. As for large adenomas, the sensitivity was 24.5%, the specificity was 87.1%, and the positive predictive value was 3.2% (Table 1, 2).

Nineteen cancer subjects would have been diagnosed using TCS as a screening test: 18 in the early stages of cancer and 1 in advanced stage cancer. Twelve (63.2%) subjects had cancers in the distal colon, and 7 (36.8%) in the proximal colon. Among 53 subjects with large adenoma, 34 (64.2%) were found in the proximal colon

Table 3 Relation between location and IFOBT positive rate of cancer and large adenoma found among the subjects who underwent TCS

	Distal colon	Proximal colon	Overall	*P* value
Cancer	12	7	19	
IFOBT positive (%)	7 (58.3)	3 (42.9)	10	$P=0.7125$
Large adenoma (adenoma≥10 mm)	19	34	53	
IFOBT positive (%)	7 (36.8)	6 (17.6)	13	$P=0.2340$

IFOBT: immunologic fecal occult blood test; TCS: total colonoscopy

Table 4 The Rate of detection of cancer and large adenoma of TCS and SCS

Variable	Overall (n=7,797)	TCS (n=3,090)	SCS (n=4,707)	*P* value
The rate of detection of cancer (%)	28 (0.36)	19 (0.615)	9 (0.191)	$P=0.0043$
early cancer (%)	27 (0.35)	18 (0.583)	9 (0.191)	$P=0.0375$
advanced cancer (%)	1 (0.01)	1 (0.032)	0	—
The rate of detection of Large adenoma (adenoma≥10 mm) (%)	82 (1.05)	53 (1.72)	29 (0.62)	$P<0.0001$

TCS: total colonoscopy; SCS: sigmoidoscopy

and 19 (35.8%) were in the distal colon.

Of the 12 cancers found in the distal colon, 7 (58.3%) had positive IFOBT results. On the other hand, 3 out of 7 cancers (42.9%) in the proximal colon had positive IFOBT results. The rate of positive IFOBT results for large adenomas which were found in the distal and proximal colon were 7 out of 19 (36.8%) and 6 out of 34 (17.6%) respectively. Cancers and large adenomas in the proximal colon tended to have a much lower rate of positive IFOBT results than those in the distal colon (Table 3).

The rate of detection of cancer in the TCS group was 19/3,090 (0.615%) consisting of 18/3,090 (0.583%) of early colorectal cancers and 1/3,090 (0.032%) of advanced colorectal cancers, and that in SCS group was 9/4,707 (0.191%) consisting of 9/4,707 (0.191%) of early stage cancers and 0/4,707 (0%) of advanced stage cancers. The difference in the detection rate between TCS and SCS reached statistical significance. The corresponding figures for large adenoma were 53/3,090 (1.72%) of the subjects who received TCS and 29/4,707 (0.62%) of the subjects who received SCS. A statistically significant difference was also found for the detection rate of large adenoma between two groups (Table 4).

There were no complications among the 3,090 subjects who underwent TCS examinations and the 263 subjects who underwent colonoscopic treatment. Colonoscopies are usually performed at our center without intravenous sedation. None of the subjects in this study required the use of medication for conscious sedation. The completion rate for total colonoscopy was 96.1% under these conditions.

Discussion

The purpose of this study was to clarify the limitations of IFOBT as a screening test for CRC by examining the data of the rate of detection and location of cancers and large adenomas, and the relation between the location and the sensitivity of IFOBT for average-risk asymptomatic adults. In large randomized controlled studies in the West[2,3,4] there is evidence that as a screening test chemical FOBT can reduce the mortality of

CRC in the screened group. However, it is not clear whether screening with the FOBT method would have given individuals the benefit of a complete medical check-up. That is to say, to obtain longer survival after detection of colorectal cancer or the higher rate of detection of cancers in the early stage, we need more sensitive modalities than IFOBT can provide. Based on the results of this study, the sensitivity of IFOBT for cancer (large adenoma) was 52.6% (24.5%). In addition more than half of colorectal neoplasms were underdiagnosed with use of IFOBT alone as a screening test. The sensitivity of IFOBT for cancer in this study was much lower than that previously reported.[6] This may be due to the result that most of the cancers detected in complete medical check-up at our hospital were not advanced cancers, but early stage cancers.

Many people have pointed out that a significant number of colorectal neoplasms have been underdiagnosed with use of chemical FOBT alone due to its low sensitivity in detecting colonic neoplasms.[7,8,9] Therefore, the use of SCS has been recommended as a more sensitive screening strategy. Analyses from case-control studies[10,11] also suggested that SCS examination reduced the mortality of cancer. However, two recent studies[12,13] confirm that sigmoidoscopic screening would fail to detect a substantial proportion of asymptomatic colorectal cancers or polyps associated with a high risk of cancer. As 64.2% of large adenoma (36.8% of cancer) was found in the proximal colon from the result obtained in this study, about half of the sum of cancer and large adenoma would be missed using SCS alone as a primary screening procedure. Even combining SCS with IFOBT, 52.8% of large adenoma (21.1% of cancer) would have been missed because the IFOBT-positive rates were lower for proximal large adenoma (17.6%) and cancer (42.9%). In short, it is impossible to detect the lesions in the proximal colon using SCS, and yet IFOBT has difficulty in finding lesions in the proximal colon because of its lower sensitivity. Thus, TCS has been recommended as a screening modality since it can not only detect colonic neoplasms with a high degree of accuracy, but also accurately examine the entire colon.[14] However, before TCS can be widely used as a primary screening modality, there are several problems to solve: manpower, cost-effectiveness, technical factors and so on.

In summary, this study demonstrates the lower positivity of IFOBT for colonic lesions in the proximal colon as compared with in the distal colon. A complete medical check-up is needed to be of benefit to individuals, rather than mass screening. Therefore, we believe that a screening modality that enables us to accurately examine the entire colon, such as TSC, is desirable for complete medical check-up.

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Review Article

Issues in the Usages of New Anti-rheumatic Drugs in Japan

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Abstract

Rheumatoid arthritis (RA) is an inflammatory disease with its principal lesions appearing in the synovial membranes of joints. Historically, the objectives of the treatment were improvement of activity of daily living (ADL) and quality of life (QOL). However, the objective has now shifted to prevention of joint destruction due to the following reasons: 1) early diagnosis of RA has become possible; 2) early intervention with disease-modifying antirheumatic agents (DMARDs) has exhibited high efficacy; and 3) biological agents have been introduced. However, in Japan, as compared with the U.S. and Europe, there are disparities in the use of DMARDs and biological agents, and in their adverse effects. Physicians should acknowledge these disparities when providing treatment.

Key words Rheumatoid arthritis, Disease-modifying antirheumatic drugs, Biological agents, Methotrexate, Leflunomide, Interstitial pneumonitis

Introduction

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease with polyarthritis as the cardinal symptom. Lesions mainly preside in the synovial membranes of joints. However, when arthritis continues, it progressively destroys the cartilage and bones resulting in decline or loss of joint function. Furthermore, RA often affects other organs such as the lung. Persistence of inflammation can induce secondary amyloidosis. In addition, recent epidemiological studies showed that RA causes frequent cardiovascular complications due to atherosclerosis and the lifespan of affected patients is approximately 10 years shorter than that of healthy individuals.

The incidence of RA is approximately 1% of the population worldwide. However, due to the global increase of aged population, including Japan, RA are expected to increase in future. With this background, the World Health Organization (WHO) declared the decade beginning in 2000 the "Bone and Joint Decade," and is taking measures to suppress bone and joint diseases including RA.

Paradigm Shift in Ultimate Goal of RA Treatment

The treatment of RA has been focused on relieving the inflammation, improving ADL, and sustaining and ameliorating QOL of RA patients. However, now that early diagnosis of RA has become possible, and therapeutic drugs with high efficacy such as methotrexate (MTX) and biological agents have been introduced, remission of the disease and delaying or inhibiting destruction of the cartilage and bones can be realized. Consequently, the main objective of current treatment has become prevention of joint destruction which can be obtained from complete remission of the disease, leading the American College of Rheumatology (ACR) to advocate positive treatment algorism to prevent joint destruction in 2002.[1]

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Treatment Guidelines of American College of Rheumatology (ACR)

The basis of traditional RA therapies was the so-called pyramid therapy. In other words, treatment began with nonsteroidal anti-inflammatory drugs (NSAIDs). When inflammation could not be controlled with NSAIDs, then antirheumatic agents (DMARDs) or corticosteroids were subsequently initiated. The concept of this therapy was based on the hypothesis that "bone destruction in RA will not occur in early stages of the disease."

However, recent studies in the U.S. and in Europe have introduced surprising evidence that "bone destruction in RA progresses the most in 1 to 3 years after the onset of the disease."[2] As a result, treatment guidelines presented by American College of Rheumatology (ACR) in 2002 have knocked the bottom out of the traditional pyramid therapy. The characteristics of the guidelines are to establish the diagnosis as early as possible, to assess the disease activity and presence of radiographic damage, and to promptly initiate proper treatment including DMARDs, NSAIDs, and corticosteroids. Initiation of DMARDs treatment is suggested to begin within 3 months of diagnosis when the disease is not yet controlled. After 3 months, the efficacy of the initial treatment needs to be reevaluated. If the treatment is found to be ineffective, it is recommended to administer stronger DMARDs, mainly MTX, by rheumatologists. If the efficacy of MTX is not sufficient, other DMARDs such as leflunomide will be used instead, or combination therapy of MTX and other DMARDs are advised. Furthermore, if the situation allows, biological agents will be considered. This positive treatment algorism has become the world trend.

Issues of MTX in Japan

In the U.S. and Europe, MTX is a first-line agent for severe, active RA. Not only is MTX effective in controlling or retarding joint destruction, but it is also proven to improve the lifespan of RA patients. In addition, prolonged administration of other DMARDs often cause progressive reduction or lack of efficacy (escape phenomenon), and is a reason for discontinuation of the remedies. However, with MTX, escape phenomenon is rare.[3]

The dosing regimen of MTX significantly differs between the Western countries and Japan. In the U.S. and Europe, it starts at 7.5 mg/week with gradual increase to the maximum of 20 to 25 mg/week. On the other hand, in Japan, it starts at 4 to 6 mg/week with maximum of 8 mg/week. However, remission is often observed only after the administration of more than 8 mg even among Japanese patients. For this reason many rheumatologists advocate that the legal dosage of MTX should be increased. In addition, in Japan, MTX cannot be used as the first-line drug because of the drug package insert stating that MTX can be used "only when at least more than 1 kind of DMARDs is ineffective." However, patients with rapid progression should be treated with sufficient doses of MTX from the early stages to prevent further joint damage. The dosing regimen and indication of MTX should therefore be reconsidered in Japan.

Issues of Leflunomide in Japan

Leflunomide is a pyrimidine synthesis inhibitor. Due to its strong inhibitory effects of controlling the disease and halting joint destruction, it was approved and put on the market in the U.S. in 1998, in European countries in 1999, and in Japan in September 2003. However, in Japan, in January 2004, fatal cases of interstitial pneumonitis were reported. Interstitial pneumonitis was complicated between 2 weeks to a couple of months after institution of leflunomide. Postmarketing surveillance disclosed that preexisting lung lesions, the elderly over 60, and hypoalbuminemia were identified as risk factors. In addition, there was no correlation between the occurrence of interstitial pneumonitis and the dosage of leflunomide, thus assuming an allergenic mechanism may be implicated in the pathogenesis. However, it is still possible that opportunistic infections such as *Pneumocystis jiroveci* might be included in some of these cases. Exacerbation of interstitial pneumonitis with leflunomide is generally rapid and progressive. In particular, chest X-rays which are compatible with diffuse alveolar damage (DAD) have a poor prognosis.[4] Incidence of interstitial pneumonitis with leflunomide is approximately 1%, while the mortality rate is high as approximately 30%. This incidence is approximately 80 to 100 times higher when compared with that of Western countries. However, it remains to be

clarified why interstitial pneumonitis is complicated in such a high frequency and mortality with the use of leflunomide in Japan. Detailed investigations including genetic polymorphism will shed a light on its pathogenesis.

Issues of Biological Agents in Japan

Two types of biological agents are currently approved in Japan: infliximab,[5] which is a chimeric monoclonal antibody against TNF-α, and etanercept,[6] which is a soluble TNF receptor. Both have inhibitory effects against TNF-α which is a known inflammatory cytokine. The most significant benefit of these TNF-α inhibitors is to inhibit the progression of joint destruction. Among these, infliximab is used in more than 10,000 cases in Japan, and the results of a post-marketing surveillance study are being released. On the other hand, there are not yet sufficient results of post-marketing surveillance for etanercept is provided because of its late appearance in the market.

In Japan, infliximab must be used in combination with MTX in cases in which disease activity is not controlled with more than 6 mg/week of MTX alone.[7] Physician's global assessment with the use of infliximab indicated a marked response in about 30% of the patients and moderate response in more than 50% suggesting its dramatic efficacy. In addition, rapid and sustained response are of characteristic profiles of infliximab.

One of the issues using infliximab in Japan is the association of infectious diseases. Especially, pneumonia is observed in approximately 2% of the cases with administration of infliximab. Risk factors such as diabetes, advanced age, and preexisting lung diseases are identified in postmarketing surveillance. Infliximab tends to be used in advanced and longstanding cases of RA with multiple organ involvement in Japan, and this may explain high frequency of pneumonia.

Globally, Japan is a country with high prevalence of tuberculosis (TB), leading to increased frequency of complicated cases of TB with infliximab, i.e. 0.3%. Since the occurrence of TB is more frequent within the 3rd administration from the onset of the treatment, an exacerbation of previous TB rather than a new TB infection can be speculated. Prior to start infliximab, all patients should be screened for TB by examining previous history of or exposure to TB, tuberculin reaction, and chest radiograph. Patients with an abnormal chest radiograph and/or strongly positive tuberculin test should receive isoniazid (INH) 0.3 g/day one month prior to the onset of the infliximab administration for 6 to 9 months as a prophylactic measure.

Pneumocystis pneumonia is seen in about 0.4% of the cases with administration of infliximab, a much higher frequency than in the U.S. or Europe. Reasons for this are still unknown. However, in Japan, there is a risk of *Pneumocystis* pneumonia even in cases with MTX, which may suggest that racial and environmental differences are involved in its pathogenesis.

Conclusion

The ultimate goal of RA treatment has shifted to prevention of joint destruction.[8] However, in Japan, MTX cannot be used as a first-line drug and its dosage is limited. In addition, leflunomide is not an alternative for MTX at present because of frequent and fatal complication of interstitial pneumonitis. Furthermore, although biological agents have shown remarkable efficacy compared with cases in the U.S. and Europe, opportunistic infections such as pneumonia, TB and *Pneumocystic* pneumonia are observed in higher incidence than in the U.S. or Europe. Consequently, it is vital to periodically monitor adverse effects and to detect them at early stages in the course of treatment. In addition, physicians are required to have sufficient clinical knowledge to undergo proper risk management upon complication of adverse effects.

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HIV Encephalopathy

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Abstract

HIV encephalopathy is one of the most complex viral diseases. HIV-infection is mainly restricted to macrophages and microglia in HIV-infected brains, although HIV-induced damage extends to neurons and oligodendrocytes. Accumulating evidences suggest that HIV-encoded factors and other host factors are involved in the development of this disease: however, the precise mechanism remains unclear. In order to investigate this mechanism, we developed an HIV-1-infected human cell-transplanted mouse model (hu-PBMC-NOD-SCID mouse) and a coculture system with HIV-1-infected macrophages and murine or rat brain cells. Using these models, we have successfully determined that certain host factors are involved in the neuronal damage. Additionally, we are developing a screening system to identify the host factors that provide protection against HIV-1-induced encephalopathy. Our study will contibute to the development of a new therapeutic strategy for HIV encephalopathy and other CNS diseases.

Key words HIV encephalopathy, Macrophage, hu-PBMC-NOD-SCID mouse, A lentiviral screening system, Host factors, CNS diseases

Introduction

The human immunodeficiency virus type 1 (HIV-1) causes acquired immunodeficiency syndrome (AIDS) by the destruction of the immune system.[1–3] However, the target tissues are not restricted to those of the immune system. This virus invades the central nervous system (CNS) and induces a neurological disease called HIV encephalopathy. Most cases of this disease are diagnosed several years after the primary infection, and by then, the number of $CD4^+$ cells in the peripheral blood is significantly lower. The clinical symptoms of this disease include cognitive, behavioral, and motor dysfunction: these symptoms are characteristically found in subcortical dementia and commonly develop over a period of few months. In the early stage, forgetfulness and reduced concentration are frequently encountered and these are typically followed by short-term memory loss, carelessness and mental slowing. Motor disturbance in the form of leg weakness is sometimes observed at this stage. These symptoms often occur along with behavioral symptoms such as personality changes. Ataxia, tremor, pyramidal sign, and paresis are also found. On disease progression, the patient shows behavioral changes such as social withdrawal, apathy, akinetic and mute state.

New Problems After the Introduction of HAART

In 2004, approximately 40 million people worldwide were estimated to be already infected with HIV. However, a very effective anti-viral therapy called highly active antiretroviral therapy (HAART) that comprises a combination of HIV reverse transcriptase and protease inhibitors has been available since around 1997. Following the availability of this therapy, the number of deaths

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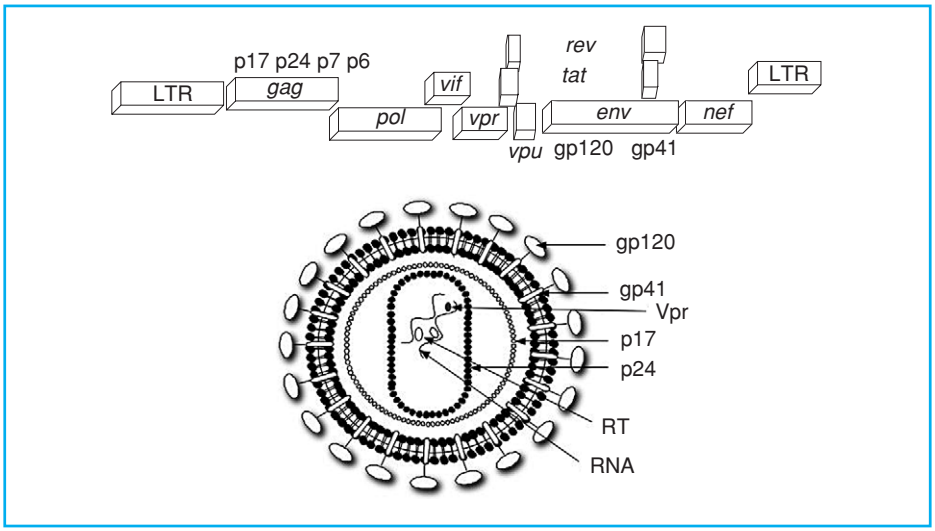

Fig. 1 The HIV-1 provirus and the virion structure

The genome consists with the LTRs (long terminal repeat), structural genes (*gag*, *pol*, and *env*), regulatory genes (*tat* and *rev*), and accessories genes (*nef*, *vif*, *vpr*, and *vpu*). The virion consists with Gag, Pol, Env, Vpr, and an RNA dimmer.

occurring due to AIDS has decreased, particularly in advanced countries. Although the incidence of HIV encephalopathy has markedly decreased due to this therapy,[4] in 2004, it was estimated that approximately 3 million patients worldwide continued to die of AIDS. Further, a less severe form of HIV encephalopathy that comprises a milder cognitive and motor disorder (MCMD) is now a potentially serious problem.[5] This syndrome is characterized by a much less pronounced state of memory loss and a decrease in computational and other higher cortical functions. The clinical presence of MCMD has been thought to be associated with the extent of pathological changes observed in the CNS due to HIV invasion. A potential explanation for the development of MCMD is that low level viral replication, as shown even in cases of highly HAART regimens, leads to the gradual progression of neurodegenerative damage.

The CNS of young children appears to be more vulnerable to the effect of HIV than that of adults. This is probably because in young children, the CNS is still in the developmental stage and contains many undifferentiated cells. The progression of pediatric AIDS is rapid and children do not respond to HAART. In addition, clinical analysis reveals that congenitally HIV-infected children frequently develop progressive encephalopathy, which is complicating microcephaly, spastic paraparesis, and delayed developmental milestones. After the introduction of HAART in many areas, the maternal-fetal transmission of HIV has been reduced successfully, thereby reducing the prevalence of progressive encephalopathy.

Currently, more than 6,500 people in Japan have been confirmed to be infected with HIV, and the number of HIV-infected persons is gradually increasing at a rate of 780 patients per year. Although the number of HIV encephalopathy patients clearly decreased after the introduction of the HAART, new problems such as the emergence of HAART-resistant viruses and the side effects of HAART are becoming apparent. Since subclinical MCMD patients appear to be increasing in many countries, HIV encephalopathy may also become a serious disease in Japan.

HIV and HIV Encephalopathy

HIV is virologically classified into HIV-1 and HIV-2. HIV-1 was initially isolated from a French patient in 1983, and subsequently, it has been identified as the causative agent of AIDS in many other countries. Currently, the HIV-1 epidemic has spread worldwide. It has been demonstrated that HIV-1 originated from chimpanzees:

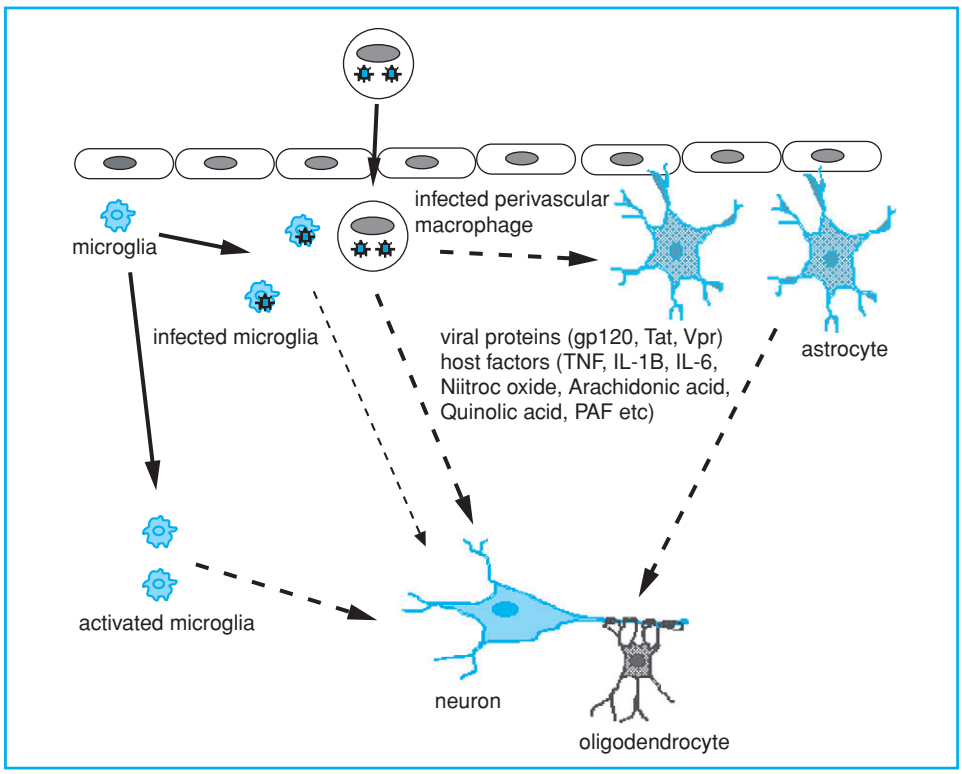

Fig. 2 Pathogenesis of HIV encephalopathy

Perivascular macrophages and microglia are responsible for producing HIV. They release viral proteins such as gp120, Tat, and Vpr and other host factors. Simultaneously, microglia and astrocytes are activated by these factors. Neuroprotective and neurodestructive factors coexist in this pathogenesis.

however, infected chimpanzees are resistant to the development of this disease. In 1986, HIV-2 was independently isolated from some patients in West Africa. Interestingly, in the case of HIV-2, it has been demonstrated that it originated in a small monkey species, such as the mangabee, and its potential for causing pathogenesis or acting as a pathogen in humans was clearly low. HIV-1 belongs to the retrovirus family, and its virion structure comprises 100-nm ball-like particles. Two viral RNAs, viral structural proteins, core protein p24, matrix protein p17, nucleocapsid p7, and the accessory protein Vpr are packed into its capsid, and the capsid is enveloped by two viral-encoded glycoproteins, namely, gp120 and gp41, and a plasma membrane-derived lipid (Fig. 1). When the HIV particles attach to the target human cells, gp120 on the viral surface specifically binds to the CD4 molecule on the plasma membrane of the target cells and subsequently to CXCR4 or CCR5, which are the physiological receptor molecules for different chemokines. In vivo, HIV replicates in the $CD4^+$ T cells and macrophages because both these cells express CD4 and CXCR4 or CCR5. Although these receptor positive cells get distributed in many lymphoid tissues such as the peripheral blood and lymph nodes, they rarely reside in the healthy brain. An examination of the autopsy samples of HIV encephalopathy patients revealed that HIV was predominantly found in the macrophages and microglia but not in the $CD4^+$ T cells located near the vessels. It is thought that the $CD4^+$ T cells are depleted in the peripheral blood at the time of development of HIV encephalopathy, and that they invade the brain very little. The typical pathological features of parenchymal infections include the activation of macrophages and astrocytes, cortical and central atrophy, diffuse myelin pallor, multinucleated giant cells, and microglial nodules. Furthermore, the macrophage-tropic virus, which uses CCR5

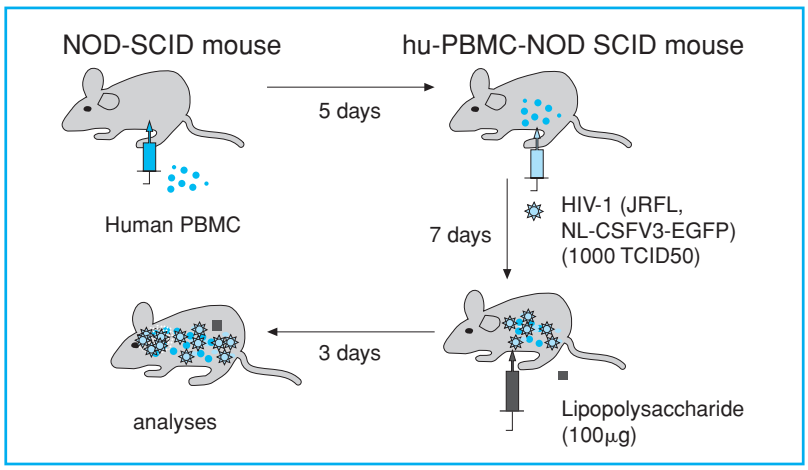

Fig. 3 A murine model using the hu-PBMC-NOD SCID mouse for HIV encephalopathy

Human peripheral blood monocytes were intraperitoneally transplanted into the immunodeficient NOD-SCID mouse. Macrophage-tropic HIV-1 and lipopolysaccharide were then intraperitoneally injected into the mouse.

as a coreceptor, is frequently isolated from the HIV-infected brain.[6] However, the T-tropic virus, which uses CXCR4, could not be detected. Interestingly, HIV does not replicate in neurons and oligodendrocytes, which are found to be severely damaged in the infected brains. Therefore, it has been postulated that macrophages and microglia are the key cell types that are affected in HIV, while the neurons and glia cells are damaged by the factors released from the infected macrophages and microglia in the infected brain. HIV-encoded proteins and host factors from the macrophage and glial cells may mutually influence the function and fates of neurons. Based on studies using an animal model, it is thought that HIV can enter the brain early after systemic infection. Although the CNS is physiologically separated by the blood-brain barrier (BBB), the mechanism of action of the BBB in HIV-infected brains and the critical factors that lead to the development of HIV encephalopathy remain unclear.

Several chemokines and their receptors have been the focus of the studies on the pathogenesis of HIV encephalopathy.[7] It has been reported that CXCL8 (IL-8), CXCL10 (IP10), CXCL12 (SDF-1α, β), CCL2 (MCP1), CCL3 (MIP1α), CCL4 (MIP1β), CCL5 (RANTES), CCL7 (MCP3), and CX3CL1 (Fractalkine) are involved in the development of HIV encephalopathy. CXCR1, CXCR2, CXCR3, CXCR4, CCR1, CCR2, CCR3, CCR5, and CX3CR1 are known to be expressed in the CNS and might have a various role in maintaining the balance between neuroprotection and neurodegeneration.

The infection of perivascular macrophages and microglia may cause a disruption in the normal neurological functions either by producing viral proteins, such as gp120,[8] Tat, and Vpr,[9] or by exerting an indirect or bystander effect via some neurotoxic factors.[10–12] In addition, it has been proposed that after the inflammatory process, due to the establishment of a self-sustaining chain reaction, viral infection might play a more limited role in the degenerative process. Although both these mechanisms are not mutually exclusive and might coexist, the bystander theory is probably more consistent with most of the evidence (Fig. 2).

Recently, a hypothesis that the CXCR4-using X4 virus emitted to the neurons has been suggested.[13] Although the X4 virus may act as a neurotoxic factor in vitro thus far, there is little evidence indicating that the X4 virus plays a critical role in the human CNS. HIV-1 has certain characteristics that differ from other simian-related viruses, namely, simian immunodeficiency virus (SIV) and simian human immunodeficiency virus (SHIV): the latter is a recombinant virus that is obtained by replacing the SIV envelope with an HIV envelope. The X4 virus frequently infects the neurons in SIV- and SHIV-infected models.

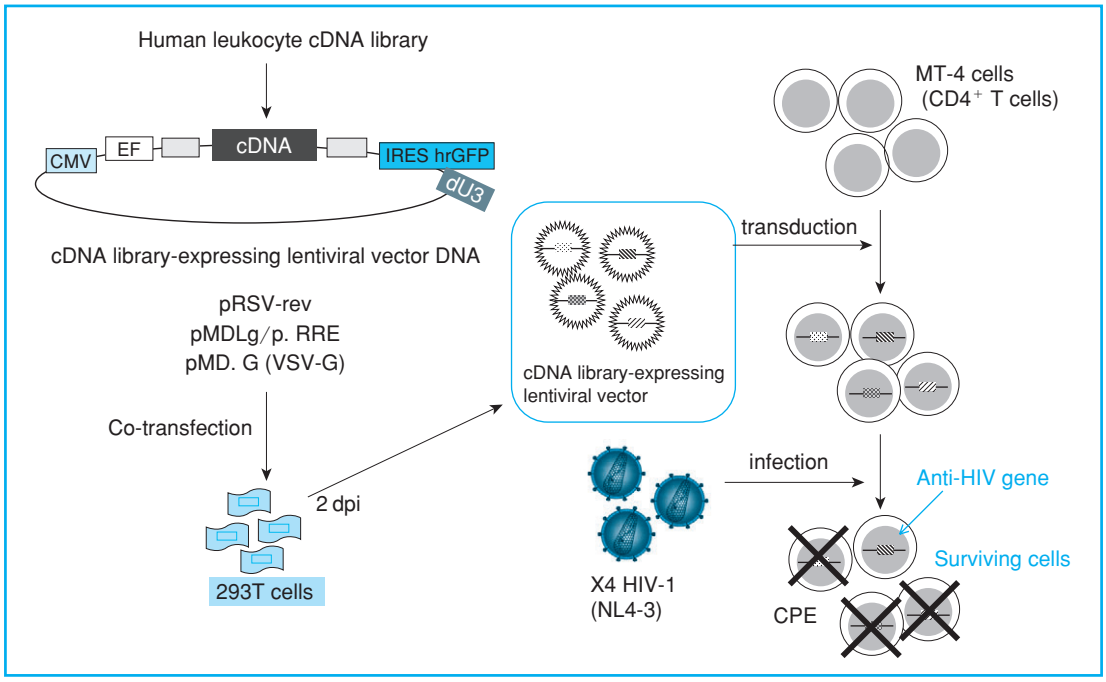

Fig. 4 The screening system used for the detection of the anti-HIV gene

A human leukocyte cDNA library was inserted into a vector and cotransfected with packaging plasmids into 293 T cells. The supernatant were transduced into MT-4 cells. They were infected with NL4-3 and the survivor cells were collected and analyzed.

By contrast, in the case of HIV-1, only the viruses using CCR5 have been found in the infected brain.

New Models of HIV Encephalopathy

We have developed an animal model of HIV encephalopathy. We used the NOD-SCID mouse, which represented severe immunodeficiency acquired through heredity, and produces human chimeric mice by the intraperitoneal transplantation of human peripheral blood mononuclear cells (PBMCs). HIV-1, which uses CCR5, was then inoculated intraperitoneally. After establishing systemic HIV-1 infection, a bacterial component lipopolysaccharide was injected intraperitoneally (Fig. 3). Infiltration of human T cells and macrophages was induced in the mouse brain and many of these cells were found to be infected with HIV-1. Further, the astrocytes and microglia were activated. Importantly, the apoptosis of neurons was frequently detected near the human macrophages infected with HIV-1. On the other hand, using the X4 virus, we observed that significant neuronal death was not detected in the brain. The TRAIL molecule, which is one of the death-inducing ligands, was found to be predominantly expressed in the HIV-1-infected macrophages in the brain. When a neutralizing antibody against human TRAIL was injected intraperitoneally, neuronal apoptosis was significantly inhibited. This suggests that the TRAIL molecule is important for guiding the apoptosis of neurons in HIV encephalopathy.[12] Therefore, we propose that the TRAIL molecule may play a role in HIV encephalopathy. Our proposal was further confirmed by the examination of human pathological autopsy samples and cultured human neurons.[14,15]

Based on these results, we are focusing on the analysis of HIV pathogenesis in the CNS using small animals such as mice and rats. These animals are very useful in neuroscientific studies because a considerable amount of scientific knowledges has been amassed using these animals. Several experiments using the cells of these small animals have been reported in HIV research.[16]

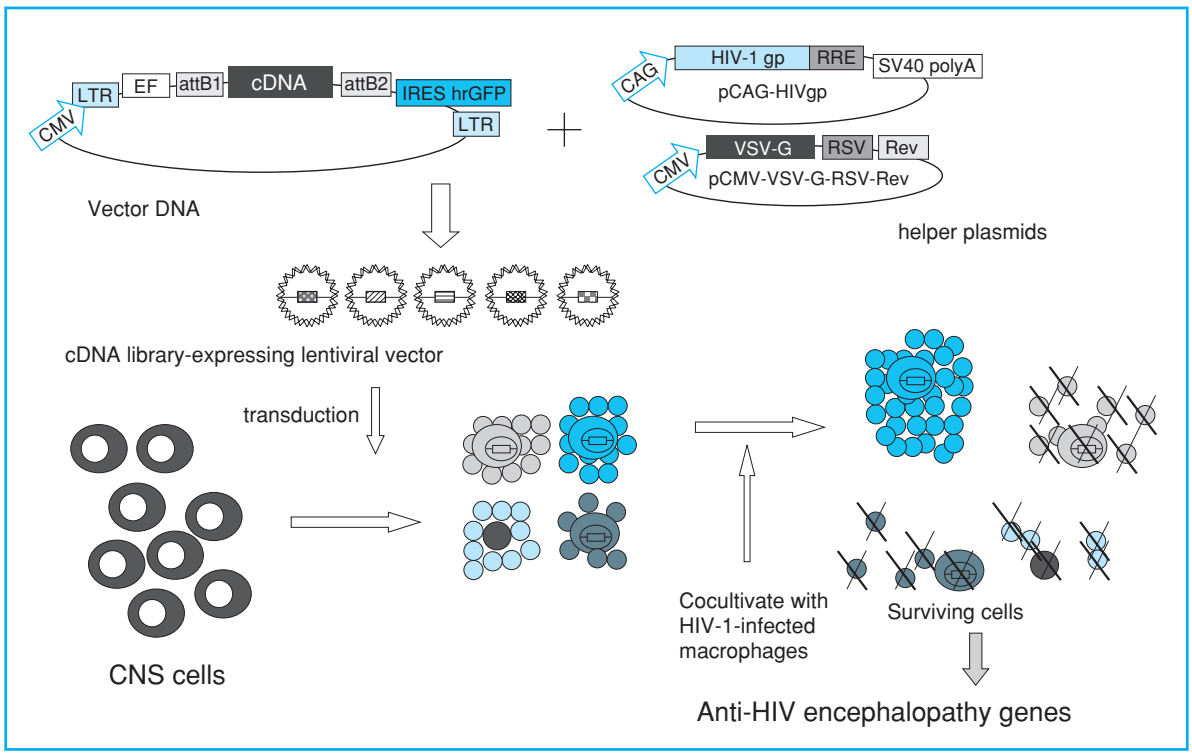

Fig. 5 The analyzing system of anti-HIV encephalopathy genes
The viral vectors expressing the rat brain cDNA were collected, transduced into the CNS cells, and cocultivated with HIV-1-infected macrophages. The surviving cells were then collected and analyzed.

Novel investigations have been carried out to determine the factors associated with this virus using a lentiviral vector system; this system was originally generated from HIV itself. We transduced the human leukocyte cDNA library into a human T cell line and then infected them with X4 HIV-1. After analyzing the gene that provides anti-HIV activity in the surviving cells, the CD14 gene[17] and an N-terminal deletion mutant of CD63 gene, namely CD63dN, were isolated (Fig. 4). CD14 appears to partially inhibit HIV-1 entry and provides resistance to HIV-1-induced cytopathic effect. CD63dN inhibits the surface expression of CXCR4. CD14 is one of the marker molecules of monocytes, and although the expression of CXCR4 can be seen in these cells, X4 virus cannot replicate efficiently in these cells. Further, since CD63 downregulates the activity of CXCR4 and the expression of CD63 is augmented in activated macrophages and microglia, it was suggested that CD63 might preferentially inhibit X4 HIV-1 infection in the infected brain. This explanation may be supported by the fact that it is difficult to detect X4 HIV-1 in the HIV-1-infected brain.

Further, we are trying to identify the genes that function against the cytopathic effect of HIV encephalopathy. An organic culture of the rat brains was cocultivated with the human macrophages with HIV infection. RNA was then collected from the samples of this culture, and was analyzed using a microarray system. Based on this analysis, the cDNA of a candidate gene was transduced into the rat brain cells and was cocultivated with HIV-infected human macrophages (Fig. 5). These experiments are currently in progress.

Conclusion

To date, the research on HIV encephalopathy has been carried out by analyzing the brain tissues of clinical specimens and by infecting experimental animals with SIV or SHIV. In addition to these

models, a novel approach has been initiated using small animals such as mice and rats. Based on previous reports, it is thought that many host factors as well as viral factors are closely involved in the pathogenesis of the HIV encephalopathy, and the elucidation of its mechanisms is very important. Further, new types of researches that aim at identifying additional host factors have been initiated by using a lentiviral vector. They can be applied to devise powerful new medical treatments. Finally, it is important to improve these systems using small experimental animals and lentivirus for various central nervous system diseases.

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Case Report

A Case of Stage IV Gastric Cancer: Long-term remission achieved with S-1 mono-chemotherapy

JMAJ 49(5・6): 219–223, 2006

Yutaka Suzuki,*1 Naruo Kawasaki,*1 Yoshio Ishibashi,*1 Naoto Takahashi,*1 Hideyuki Kashiwagi,*1 Kazuo Koba,*2 Mitsuyoshi Urashima,*2 Katsuhiko Yanaga*1

Abstract

S-1 is a recently developed agent that reduces the gastrointestinal toxicity of 5-fluorouracil without affecting its antitumor activity. We encountered a patient with advanced gastric cancer, who responded to S-1 mono-chemotherapy and has maintained complete remission for over 4 years. The case was of a 61-year-old man who presented with abdominal pain in July 2001 and was diagnosed with stage IV gastric cancer (T4N2M0). Curative surgery such as gastrectomy was not appropriate, and mono-chemotherapy with S-1 was administered. This was given for 4 consecutive weeks at a dose of 120 mg/day, followed by a 2-week rest period; 18 courses were administered until September 2003. These cases suggest that a subgroup of patients with advanced gastric cancer may attain a complete response with S-1 chemotherapy, with or without gastrectomy.

Key words Stomach neoplasms, Drug therapy, TS-1, S-1

Introduction

S-1 is a drug containing three components, tegafur, an oral anticancer agent that is a prodrug of 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP), and monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate (Oxo).[1–3] This combination reduces the gastrointestinal toxicity of 5-FU without affecting its antitumor activity.[1–3] The safety of S-1 and maximum tolerable dose has been determined through phase I clinical trials.[4–11] Moreover, the efficacy of S-1 as mono-chemotherapy[12–14] or in combination with cisplatin[15–17] against advanced gastric cancer has been measured through phase II clinical trials. However, although the response rate was 20–50%, patients rarely attain a complete response to S-1 mono-chemotherapy.[12–14] In addition, the median survival time and 1-year survival rates of patients with advanced gastric cancer treated with S-1 are 6 to 12 months and 33 to 36%, respectively.[18–20] We encountered a patient with advanced gastric cancer, who was administered S-1 mono-chemotherapy at home as a palliative treatment. Against our prediction, the patient responded completely to S-1 and has maintained remission for more than 4 years after starting chemotherapy.

Reporting as a case report was directly explained to both patients by Y.S., and consent was obtained from both patients.

Case

A 61-year-old man presented with abdominal pain on July 19, 2001. Upper gastrointestinal series (Fig. 1A; upper panel) and endoscopy

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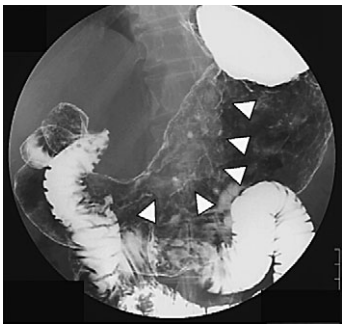
Before chemotherapy (July 2001)



After chemotherapy (March 2005)

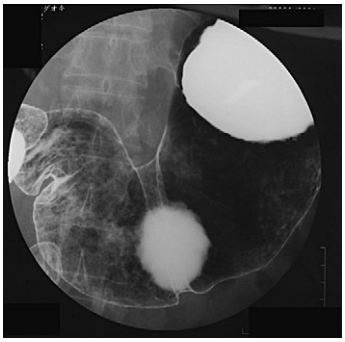
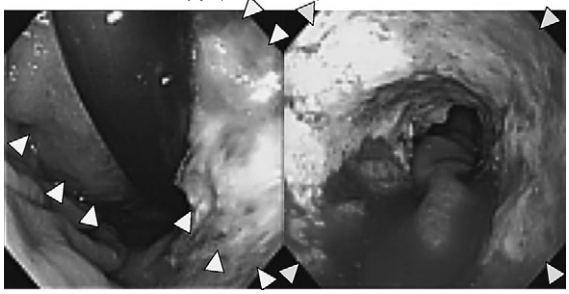
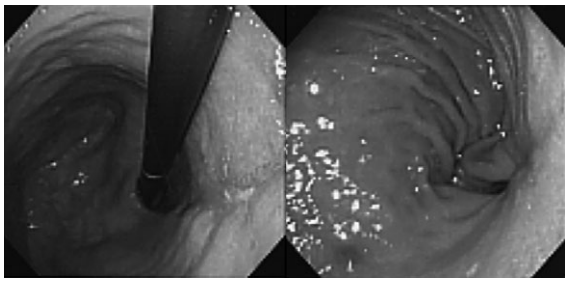


Fig. 1A Upper gastrointestinal series
Arrows present existence of tumor.

Before chemotherapy (July 2001)



After chemotherapy (December 2001)



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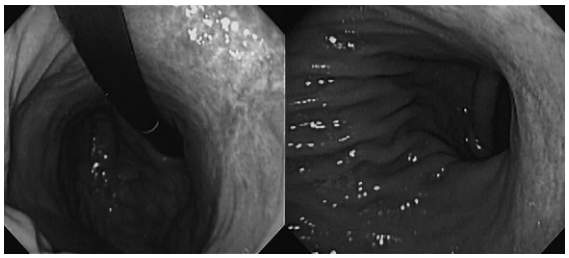
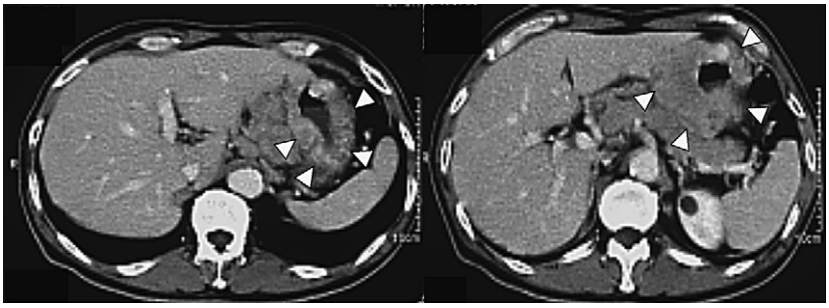


Fig. 1B Upper gastric endoscopy
Arrows present existence of tumor.

(Fig. 1B; upper panel) demonstrated an ulcerative lesion extending along the lesser curvature of the stomach from the cardia to the pyloric region. Examination of a biopsy specimen showed adenocarcinoma with undifferentiated histology. Moreover, abdominal computed tomography (CT) suggested direct invasion of cancer to the pancreatic body, lymph node metastases (mainly on the lesser curvature side of the gastroesophageal junction), as well as diffuse invasion of the gastric wall (Fig. 1C; upper panel). Laparotomy performed on July 30 2001 confirmed the following findings: 1) tumor invasion extending out of the stomach wall and adjacent to both the great omentum and lesser omentum; 2) direct invasion into the pancreas; 3) enlarged lymph nodes at multiple sites; and 4) class II cells in ascetic fluid. The patient was accordingly diagnosed as having stage IV (T4, more than N2M0) gastric cancer. Hence, curative therapy including gastrectomy was not considered beneficial for this patient, and the only surgical intervention performed was the construction of a button-type jejunal fistula at approximately 20 cm anal to the Treitz' ligament to support enteral nutrition.

Mono-chemotherapy with S-1 was started from August 12, 2001. One course consisted of S-1 (TS-1®, Taiho Pharmaceutical Co., Ltd, Saitama, Japan) for 4 consecutive weeks at a dose of 120 mg/day, followed by a 2-week rest period. A total of 18 courses was administered until September 10, 2003. After the first two courses of S-1, the gastric wall appeared thinner, lesser curvature lymphadenopathy had reduced, and the pancreatic lesion had been replaced by fat tissue (Fig. 1C, lower panel). Upper gastrointestinal endoscopy performed on December 12, 2001, after four courses of S-1, revealed

Before chemotherapy (June 2001)



After chemotherapy (October 2001)

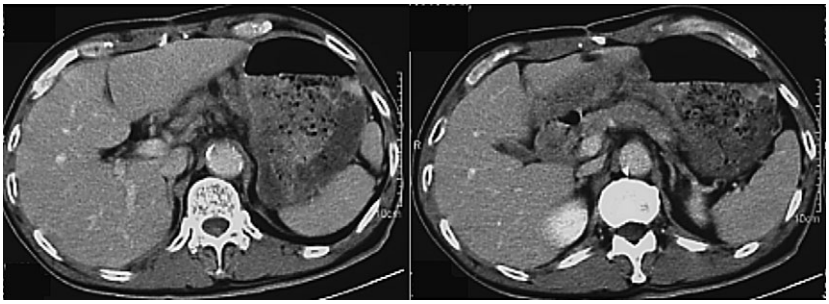


Fig. 1C Abdominal CT
Arrows present existence of tumor.

remarkable shrinkage of the lesser curvature tumor. Moreover, its appearance had changed to resemble an H2 stage gastric ulcer (Fig. 1B, middle panel). Cancer cells were not detected in biopsy specimens from plausible lesions. Therefore, the patient was considered to have achieved a complete response after 4 courses of S-1 mono-chemotherapy, without either gastrectomy or radiotherapy. After completion of the 18th course of S-1 treatment on September 11, 2003, the patient has remained in good health without any anticancer therapy. No sign of recurrence has been noted on upper gastrointestinal endoscopy with biopsy repeated every four months for nearly 2 years. Serum levels of CEA and CA 19-9 remained within normal limits before and after the chemotherapy. Recent findings with upper gastrointestinal series (Fig. 1A; lower panel) and endoscopy (Fig. 1B; lower panel) are also shown.

During 18 courses of S-1, all adverse events (which included pigmentation of the skin and nails) were minor and classified as grade I. The patient remains in complete remission as of September 26, 2005.

Discussion

We have reported a patient with advanced gastric cancer who responded well to S-1 mono-chemotherapy and has maintained complete remission for 4 years after starting treatment. Since S-1 was released on the Japanese market in 1999, many case reports have demonstrated the marked effectiveness of this drug on advanced gastric cancer, similar to that observed in the present two cases.[21–44] However, this seems to contrast with response patterns shown by phase II clinical trials. Phase III clinical trials comparing the effectiveness of S-1 with continuous 5-FU infusion as the reference arm have not yet reached a final conclusion,[45] and it hence remains unknown whether S-1 is superior to 5-FU in terms of survival of patients with advanced gastric cancer. However, S-1 may induce a complete response in a certain subgroup of patients with advanced gastric cancer. The treatment effects of S-1 mono-chemotherapy for gastric cancer can be determined by the status of thymidylate synthase gene expression.[46] In lung cancer, specific single poly-

morphisms have been demonstrated to predict responses to gefitinib.[47,48] Exploring such molecular markers to predict a complete response to S-1 may a clinically beneficial future direction.

Eighteen courses of S-1 for the patient could be administered at home, without disrupting the patient's occupational routine. To overcome anorexia after starting S-1, we concurrently administered enteral nutrition through a jejunal fistula created at operation. We believe this device enables us to continue S-1 chemotherapy at home as long as possible and results in maximum tumor shrinkage.

In conclusion, we encountered a patient with advanced gastric cancer who exhibited a complete response to S-1 mono-chemotherapy and has maintained remission for more than 4 years after starting treatment.

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Transoesophageal Echocardiography for Perioperative Haemodynamic Monitoring of Breast Carcinoma Patients with Neoadjuvant Chemotherapy

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Abstract

Both Transoesophageal echocardiography (TOE) and Transthoracic echocardiography (TTE) are valuable for monitoring in patients at risk from haemodynamic disturbance. However, TTE is impracticable in patients undergoing surgical procedure of breast carcinoma. We reported one case showing that TOE was valuable for monitoring a breast cancer patient who displayed a neoadjuvant chemotherapy-induced myocardial dysfunction during surgery.

Key words Transoesophageal echocardiography, Myocardial function, Breast cancer, Neoadjuvant chemotherapy

Introduction

Both Transoesophageal echocardiography (TOE) and Transthoracic echocardiography (TTE) are valuable for perioperative monitoring in patients at risk of haemodynamic disturbance.[1] When patients underwent mastectomy or breast-conserving surgery, transthoracic echocardiography (TTE) was impracticable during surgery. We reported one case showing that TOE could monitor chemotherapy-induced myocardial dysfunction during surgery and may be an alternative method of perioperative monitoring in breast cancer patients with neoadjuvant chemotherapy.

Case Report

A 65-year-old woman with primary left breast carcinoma (T2N0M0) received neoadjuvant chemotherapy consisting of 4 cycles of doxorubicin (adriamycin, ADM) and docetaxel (taxotere, TXT). Her physical examination was normal. She had no past or family history of cardiovascular disease. TTE, electrocardiogram (ECG) and chest X-ray revealed no abnormalities before starting neoadjuvant chemotherapy. The patient also underwent TTE and ECG just before surgery and they showed no abnormalities. On the operative day, general anesthesia was induced with 200 mg of thiamylal sodium. Inhaled anesthetic (100 ml of sevoflurane) was administered for maintenance of general anesthesia under endotracheal intubation. After endotracheal intubation, ECG showed bigeminy and trigeminy. We performed TOE (5.0 MHz probe, SSD 5500, Aloka, Tokyo, Japan) during surgery as a monitoring of the myocardial function. We calculated EF by Simpson's method. The median EF value

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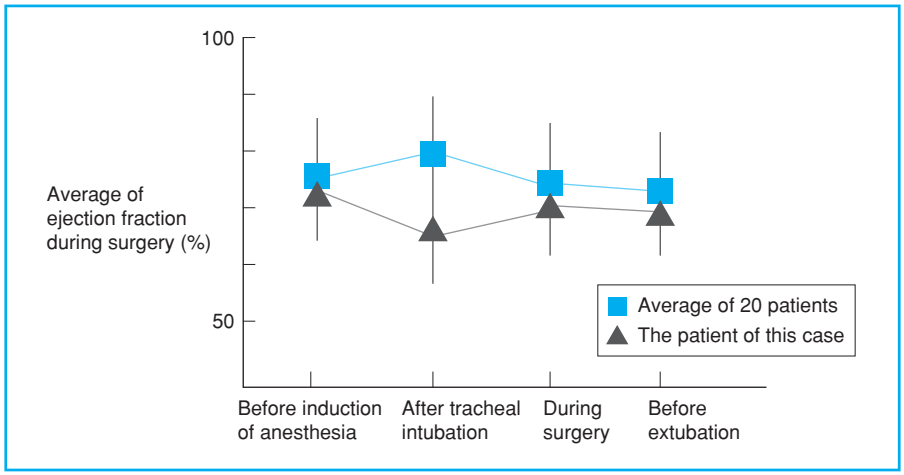

Fig. 1 The change of ejection fraction during surgery

during surgery was 60% and that was lower than the value of preoperative EF by TEE (Fig. 1). During surgery, course observation was selected except for careful ventilation with 10L/min of oxygen. The patient underwent modified mastectomy for 95 minutes. The volume of blood loss during surgery was 45 ml. After surgery, incomplete AV Block (Mobitz typeII) also initiated. We performed TOE again in the recovery room under sedative condition. But the patient showed almost same EF value (62%) as that during surgery. Bigeminy, trigeminy and incomplete AV block continued for about 19 hours after surgery. We monitored EF by TEE on the first and second postoperative day and the patient showed higher EF (73%) than that during surgery. Finally, the patient recovered these arrythmia with 3L/min of oxygen alone on the second postoperative day. On the 15th day after operation, she received another cycle of postoperative chemotherapy; however, she showed no sign of bigeminy, trigeminy, AV block or the prolongation of PR and QTc interval during and after postoperative chemotherapy.

Discussion

According to the Practice Guidelines for Preoperative Transoesophageal Echocardiography, an increased risk of haemodynamic disturbance during the perioperative period is a category-II indicatation for perioperative TOE.[1] Our patient matched these criteria.

As an alternative to TOE monitoring during surgery, we considered the use of a pulmonary artery catheter, which has been suggested for patients with significant cardiovascular disease who are at risk of haemodynamic disturbance.[2] We rejected this because 1) it is more invasive than TOE, 2) TOE can provide useful information in haemodynamically unstable patients,[3–5] and 3) direct visualization of the heart can provide clinically important new information. In addition, using the same diagnostic technique during and after surgery can improve assessment of the course the cardiovascular disease[6] (Fig. 1).

Neoadjuvant chemotherapy is increasingly being used in the treatment of patients with primary breast carcinoma.[7] We performed the combined neoadjuvant chemotherapy with low dose of ADM (50 mg/m^2) and TXT (60 mg/m^2) for four courses. We sometimes experienced low level of blood pressure, sinus bradycardia and atrioventricular block caused by the toxicity of ADM during surgery. And one possibility could be that taxanes, especially TXT enhance the cardiotoxicites of ADM.[8–11] We investigated perioperative myocardial function of twenty consecutive patients by TOE. We have included this data in Table 1. The average ejection fraction (EF) of the patients with neoadjuvant chemotherapy was 70% and this data was almost same as that of 20 patients without neoadjuvant chemotherapy (average EF = 72%, $P = 0.15$). Finally, we were able to show that patients who followed our regimen of neoadjuvant chemotherapy for

Table 1 Cardiac complications associated with neoadjuvant chemotherapy of adriamycin and taxotere

Case	Age	Cardiac complication during surgery	Prechemo-therapeutic EF by TTE (%)	Postchemo-therapeutic EF by TTE (%)	Perioperative median EF by TOE (%)
1	49	None	78	76	70
2	65	None	69	73	74
3	51	None	70	73	79
4	61	None	68	69	68
5	44	None	74	73	69
6	41	None	68	69	74
7	44	None	70	68	74
8	32	None	76	70	75
9	45	None	70	68	78
10	45	None	70	68	75
11	58	Negative T	68	64	68
12	55	None	72	78	69
13	58	None	78	74	69
14	41	None	76	70	74
15	61	Bigeminy, trigeminy, II AV block Mobitz type	74	70	60
16	59	VPC	73	69	73
17	60	None	69	79	70
18	35	None	80	75	75
19	64	VPC	68	73	71
20	44	None	78	75	74
Average	44.5		72.4	71.7	68.6

EF: ejection fraction; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography; AV-block: arterioventricular block; VPC: ventricular premature contraction

breast cancer had few cardiovascular system problems during surgery. However, further investigation of the perioperative chemotherapy-induced myocardial dysfunction by TOE is necessary.

In conclusion, TOE can be useful for less invasive perioperative haemodynamic monitoring in patients with cardiovascular disease, and should be considered if extended perioperative haemodynamic monitoring is indicated for breast cancer patients with neoadjuvant chemotherapy.

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Recent Advances in Gastric Cancer Treatment

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Key words Gastric cancer, Cancer, Registration, Guidelines, Clinical studies, Gastrectomy, Chemotherapy

Introduction

We have developed successful gastric cancer treatment modalities during recent 40 years. The results have been reported not only in surgical treatment but also in recent chemotherapies. Since, however, various regional disparities in treatment outcomes were reported in Japan, the Ministry of Health, Labour and Welfare (MHLW) expressed requirements to reformulate appropriate guidelines. The Japanese Gastric Cancer Association (JGCA) promptly published "JGCA Gastric Cancer Treatment Guidelines"[1] and "Digests of JGCA Gastric Cancer Treatment Guidelines".[2] JGCA and its forerunner The Japanese Research Society for Gastric Cancer have been publishing "Japanese Classification of Gastric Carcinoma",[3] which is considered to present the standard treatment for gastric cancer. Physicians should refer to this book, which has comprehensive coverage including clinical anatomy. With the recent emphasis on evidence-based medicine (EBM), guidelines should be described good treatment methods with evidence. However, high-quality evidence is difficult to obtain.

Morbidity and Outcomes of Gastric Cancer Treatment

In Osaka, there is an excellent regional cancer registration system which is operated by Osaka Medical Association, Osaka Prefectural Government, and Osaka Medical Center for Cancer and Cardiovascular Diseases. This system has been specially exempted from the recently enforced "Personal Information Protection Law". There is a figure called "cancer incidence" (the proportion of patients who developed cancer during a given year per 100,000 population) reported in this system. At present, the incidence of gastric cancer is 50 for males and 25 for females. Since the figure reported 20 years ago was approximately 100 for males, there has been a 50% reduction during the past 20 years (Fig. 1).

According to the report of Fujimoto, et al.[4] in 2003, 40% of all patients had localized cancer including early cancer, and 6.3% of these patients were diagnosed by mass screening. The overall 5-year survival rate was approximately 48%. Although early gastric cancer is detected more and more, there still are many advanced cancers. The overall survival rate is not satisfactory (Fig. 2).

Gastric Cancer Treatment Guidelines

After the Japanese Research Society for Gastric Cancer was reorganized to the Japanese Gastric Cancer Association in 1998, "JGCA Gastric Cancer Treatment Guidelines" was published. The JGCA published the 1st edition of the guidelines in 2001 and the 2nd edition in 2004. A book for patients titled "Digests of Gastric

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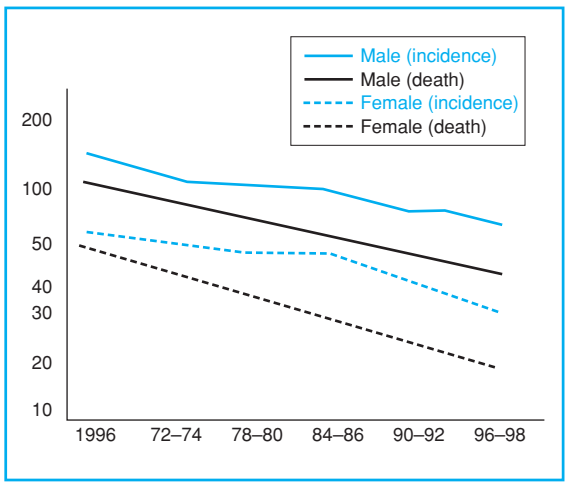


Fig. 1 Incidence and death ratio of gastric cancer in Osaka

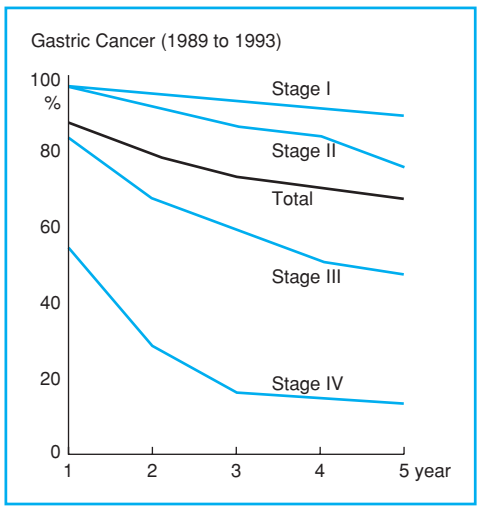


Fig. 2 Survival curves

Cancer Treatment Guidelines" was published in December 2001.

The introductory part of the guidelines states that all of guidelines are evidence based in principle. However, even the extensive description concerning surgical treatment is rarely guaranteed by the data from clinical trials. The "standard treatment in the guidelines is subtotal/total gastrectomy + D2 dissection. Surgical operations that are less extensive than the standard treatment are referred to as limited operation, while more extensive operations are referred to as extended operation.

The following sections outline ongoing clinical trials and the methods of attractive treatment.

EMR/ESD

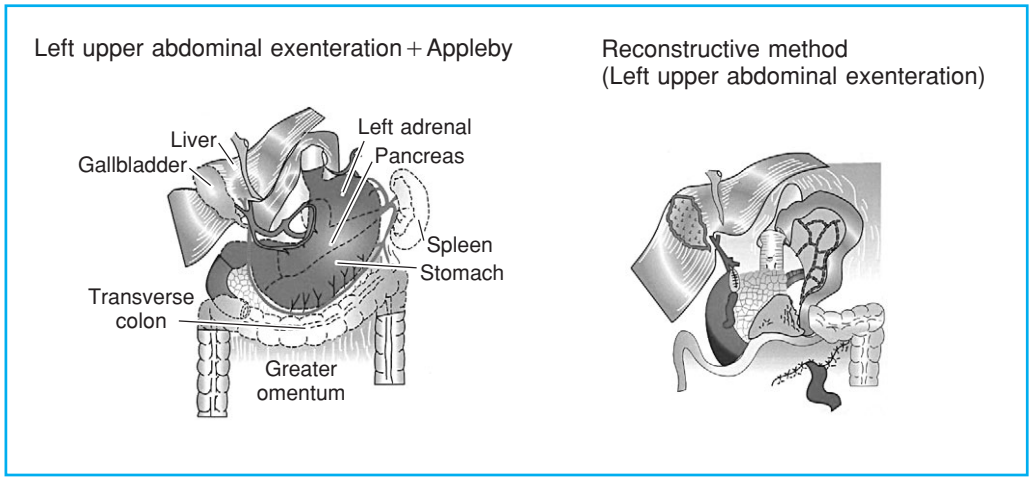
The method to resect cancer using an endoscopical technique was developed over 20 years ago. With subsequent development of instruments for this procedure, endoscopic mucosal resection (EMR) has now become a technique performed almost routinely by endoscopists. However, there has been no study proving the safety and good outcome in a large population. A surveillance program of EMR involving the cooperation of member physicians has just started.

On the other hand, endoscopic submucosal dissection (ESD) intended to remove a wider area of the mucosa has been introduced. Since the use of this procedure is in the stage of skill acquisition, it will take some time before clinical studies start.

Sentinel Lymph Nodes

The sentinel lymph node is the first lymph node to which cancer is expected to spread. There have been several attempts to identify the sentinel lymph node associated with gastric cancer. If we know which lymph node would be the first station of the metastasis of early cancer and if we could be sure that the absence of metastasis in the biopsy of this lymph node indicates the absence of metastasis in other sites, the need for lymph node dissection would be eliminated. Reports from overseas have demonstrated the significance of sentinel lymph nodes in malignant melanoma and breast cancer. Similar studies concerning gastric cancer are mostly conducted in Japan, and clinical trials to evaluate the effectiveness are ongoing.[5,6]

At present, clinical studies are ongoing to verify the applicability of the sentinel lymph node theory to gastric cancer. One is the study conducted by the Japanese Society for Sentinel Node Navigation Surgery. In this study, isotope and dye tracers are injected, hot nodes or blue-stained nodes are excised intraoperatively, and histological examination is performed using rapid methods and permanent preparations. D2 dissection is performed later whether metastasis is detected or not. Another study is conducted



(Quoted from Extended surgery for type 4 gastric carcinoma[9])

Fig. 3 Extended organ resection (Left upper abdominal exenteration)

by the Japan Clinical Oncology Group (JCOG). A dye (indocyanine green) is injected, stained lymph nodes are excised, and histological examination is performed using rapid methods and permanent preparations. D2 dissection is performed later to verify whether or not the stained lymph nodes are the ones where metastasis takes place. Both studies are intended to confirm the absence or low occurrence of false negative results.

Clinical Trials of Extended Surgery

Clinical trial on the meaning of D3 dissection

Ohashi et al. reported that a few patients with paraaortic node metastasis who underwent curative gastrectomy including para-aortic node dissection could survive over five years.[7] This extended nodes dissection became popular about 15 years ago. Since the technique is a little bit complicated and it takes additional time, we felt a need to evaluate this technique and the outcome.

In 1995, JCOG started a clinical study to examine the value of this extended surgery. The phase III study is to compare the extended lymph node dissection (D2 plus para-aortic node dissection) to standard dissection (D2) for advanced gastric cancer in terms of the adverse events and survival rates.

During the registration period of approximately 5 years, 520 cases were enrolled from 24 facilities. The study is now in the followup period, and results will become visible in several years.

Extended surgery for schirrhous gastric cancer

The treatment results for schirrhous gastric cancer are notoriously poor. The 5-year survival rate after curative surgical is reported to be approximately 15%. A report from western Europe claims that schirrhous gastric cancer is not an indication for surgical operation.[8] A characteristic feature of schirrhous gastric cancer is retroperitoneal recurrence, in which cancer cells invade the retro-peritoneum and, spreading downwards, cause stenosis of the intestines and the ureters.

A procedure of extended surgery for schirrhous gastric cancer resecting whole stomach and adjacent organs to prevent retroperitoneal recurrence was introduced approximately 20 years ago. The extended operation, Left Upper Abdominal Exenteration, includes en bloc removal of the whole stomach, transverse colon, transverse mesocolon, body and tail of pancreas, and spleen. This method provided good results in patients up to stage III, but the results in stage IV disease were not better than those of conventional treatment. Although anticancer chemotherapy was used simultaneously, this study failed to show the effectiveness of chemotherapy on the survival rate.[9] A randomized phase III study has yet to be planned (Fig. 3).

Table 1 Phase III trials comparing best supportive care and chemotherapy

Authors		No. of Pts.	RR (%)	MST (m)	
Murad	MTX/5-FU/ADM	30	50	9	$P=0.01$
	BSC	10		3	
Pryhonen	MTX/5-FU/EPI	21	29	12.3	$P=0.0006$
	BSC	20		3.1	
Glimelius	ETP/LV/5-FU	10	30	10	$P<0.02$
	BSC	8		4	

BSC: best supportive care

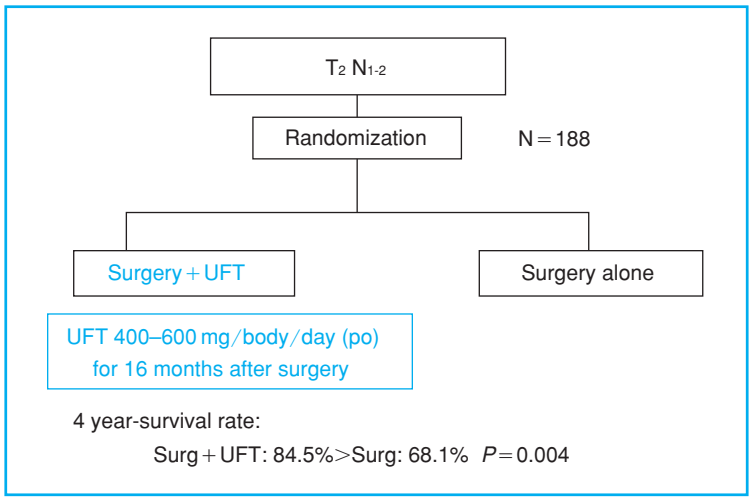


Fig. 4 N-SAS study

Chemotherapy

Only reports from overseas have demonstrated the effectiveness of chemotherapy on survival period of patients. The most basic chemotherapeutic agent is believed currently 5-FU. The next step is to identify the chemotherapeutic modality that is more effective than 5-FU (Table 1).

5-FU vs. CPT-11 + CDDP vs. TS-1

At present, JCOG is conducting a phase III study designed to prove that CPT-11+CDDP or TS-1 is more effective than 5-FU. Patient registration has just been completed, and at least 3 years will be needed before results can be obtained after the followup period. In future, we should look for a therapeutic method that is more effective than these options, using whichever is better as the reference therapy.

Postoperative UFT therapy

Various postoperative chemotherapies have been carried out, but few were found to be effective. A recent study proved the effectiveness of postoperative UFT therapy as compared with no chemotherapy. However, the subjects of this study were limited to patients with $T_2N_{1\text{-}2}$ disease, rather than the more common T_3 disease. The result of this study shines as the first successful evidence that postoperative chemotherapy can be effective for patients with $T_2N_{1\text{-}2}$ disease (Fig. 4).[10]

Postoperative TS-1 therapy

A study designed to prove the effectiveness of postoperative oral administration of TS-1 started 3 years ago. The registration of more than 1,000 patients has been completed, and the study is now in the follow-up period. While expectations

are high for the effectiveness of TS-1, the actual results are not obtained yet. Another phase III study using TS-1 as the reference treatment has already begun, but such an attempt is premature.

Conclusion

Following the issuance of the guidelines for gastric cancer treatment, there has been much discussion concerning the level of evidence qualifying the guidelines. Clinical trials will be providing evidences to the future guidelines. Clinical trials are not conducted in a special case, but supported by the participation of many facilities and many patients. Participating in a clinical trial which has promising better effectiveness is a far better option than continuing convenient treatment without evidence.

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Risk Management in Hospitals

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Introduction

News relating to medical errors frequently appears in newspapers and on TV. Medical accidents happen in various ways and are an unwelcome event not only for the general public, but also for health providers. There is a pressing need for strengthening risk management in hospitals to prevent these accidents. Risk management in hospitals should be based firstly on the collection and analysis of information concerning medical accidents. The second step should be to develop specific prevention system against accidents based on the analysis outcome, and the outcome should be fed back to the clinical field. Thus, the system is expected to shape a better framework for medical provision by improving the awareness of health providers toward medical accidents.

Definition of Medical Accident

There is currently no commonly acceptable definition of the term "medical accident." The Ministry of Health, Labour and Welfare of Japan defined this term in the "Guidelines for Medical Safety in National Hospitals and Sanatoriums" in 2003, stating that: "Medical accidents contain all kinds of events causing injury or death of a person that may occur at any point during the entire process of health care provision, including cases such as where the victim is a health care worker and a person who has a fall in a corridor of a medical institution." However, this description does not provide a clear definition of medical accidents, as it only means "all kinds of events causing injury or death of a person," without clarifying what is specifically meant to be an accident. Under this interpretation, even predictable complications could be classified as a medical accident. This could result in postoperative complications being claimed to be medical accident.

The term "medical accident" is often misunderstood as malpractice. The term "malpractice" should be used carefully, because it implies negligence on the part of medical institutions and health care workers. Medical accidents should be divided into two types; "no-fault medical accidents" and "at-fault medical accidents."

Fault or negligence mentioned in the context of malpractice means that a health care provider fails to exercise duty of care, which results in the injury of a patient or delay in their health recovery. Evidence of fault or negligence is sometimes difficult to evaluate at the time of the accident and this requires full inspection. The medical standard for the duty of care that should be exercised by the health care provider varies according to the medical standard at the time when the accident happens, and it is important to note that the standard judgment of fault may change according to the times.

The Scale of Medical Institutions and the Frequency of Malpractice

Let us consider the relationship between the occurrence of malpractice and the scale of hospitals. We assume an extreme case in which a single physician performs all medical services in a hospital and this physician makes an error, such

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as in drug administration, at the frequency of once every 100 years. In this hypothetical case, the possible frequency of malpractice by the physician would be one or none during his or her lifetime. On another assumption, if 100 health care workers are involved in medical practice such as drug prescription and drug administration and each of them makes an error at the same frequency of once every 100 years as above, this hospital would experience an error once a year. Therefore, the larger the number of health care workers in a hospital, the higher the occurrence of malpractice in the hospital.

If we want to eliminate malpractice in a hospital with 1,000 health care workers, the frequency of an error made by each worker must be 1,000 times lower than once every 100 years, i.e., once every 100,000 years. To attain this frequency, total and fundamental improvement of the awareness of the health care workers toward medical errors is required. Compared with the safety awareness level in airlines, railways, and construction sites, the level of safety awareness among individual health workers is still far from sufficient.

Nationwide Efforts to Prevent Medical Accidents in Japan

Nationwide efforts are being undertaken to prevent medical accidents by sharing related information among hospitals in Japan. One is a system of mandatory reports to the Japan Council for Quality Health Care, which started in October 2004. In this system, hospitals are required to submit reports to the Council about cases which are considered useful as an educational example, whether at fault or not, and whether the incident produced serious results or not. And the first report was released in April 2005. In national university hospitals efforts have also been made in performing mutual checking to ensure safety, and releasing information on medical accidents. In this way, efforts to promote the public disclosure of information concerning medical accidents are being made to prevent the occurrence and repetition of medical accidents.

Liability and Prevention of Malpractice

Health care providers involved in malpractice are asked to take certain responsibilities and are subject to certain penalties. These include civil liabilities which may include demands for damages and demands for apology, criminal liabilities which may include accusations of professional negligence causing injury and death, administrative penalties that may require suspension of license and practice, and social and moral penalties in which they may be reported in and criticized by the media.

Medical negligence which is totally inexcusable, and may cause most serious results would be mismatched blood transfusion, wrong medication, foreign objects left in the body, and wrong-site surgery. These four types of malpractice must not be committed at all. However, the unfortunate situation is that these cases occupy the highest percentage of reported cases.

The issues related to risk management in hospitals are diverse, ranging from individual to organizational levels. From the standpoint of prevention of malpractice, the most important is "to ensure thorough checking just before each medical act." Even given the existence of a complicated system and numerous health care workers involved in medical practice, it is essential for each worker to ask and confirm for himself/herself whether or not it is correct procedure before starting a medical act.

Conclusion

It is essential to recognize that "to err is human," and abandon the idea that you alone will never commit an error. This kind of recognition by health care workers is a basic element in the effort to substantially promote and improve medical safety and risk management in hospitals.