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Study Report on Economic Evaluation of Capital Equipment

a summary of the report requested by

the American Medical Devices and Diagnostics Manufacturers' Association (AMDD)

About this report

This study report is a summary of the economic evaluation of medical technologies requested by the American Medical Devices and Diagnostics Manufacturers' Association (AMDD). The organization and researchers of the study are described below:

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Dr. Fukuda resigned from University of Tokyo in October 2011. Thereafter, Dr. Igarashi has succeeded as the main researcher for the project. Contents contained in this study report are solely for research purposes, and they are not intended to influence reimbursement discussions. Within the study report, CT colonography refers to technology not yet covered by reimbursement. However, CT colonography is reimbursed as of April 2012.

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I. Economic evaluation of capital equipment

I-1. Overview of health economic evaluation

When healthcare is practiced, clinical efficacy and safety are clearly important. In addition to such clinical evidence, economic verification called “economic evidence” has recently become necessary, especially in Europe and the U.S. Because taxes or insurance premiums are used as a source of revenue for the public medical insurance systems introduced in many countries including Japan, such sources of revenue are limited and efficient provision of healthcare is vital. Health economic evaluation aims at providing healthcare efficiently by evaluating the cost-effectiveness of various medical technologies.

One of the typical methods for health economic evaluation is cost-effectiveness analysis. The basic method of cost-effectiveness analysis is explained with the following example:

Given that there are two treatment methods for a certain disease: existing Treatment A and new Treatment B. Treatment A costs JPY10,000 per patient and cures the disease with a probability of 50%. Treatment B costs JPY14,000 per patient and cures the disease with a probability of 60%.

This means that Treatment A cures 50 of 100 patients with JPY1,000,000, while Treatment B cures 60 of 100 patients with JPY1,400,000. Which is more effective, Treatment A or B? The simplest method is to calculate cost divided by effectiveness for each treatment method. Treatment A cures 50 patients with JPY1,000,000. This equals JPY20,000 (JPY1,000,000/50 patients) to cure one patient. On the other hand, Treatment B costs JPY23,000 (JPY1,400,000/60 patients) per patient. Therefore, Treatment A is less expensive than Treatment B to cure one patient.

With these results, can it be concluded that the conventional Treatment A should be used rather than the new Treatment B from the perspective of efficiency? Treatment A is less expensive than Treatment B to cure one patient. However, many people would have a sense of resistance to the decision that Treatment A is more economical only for this reason, especially when actual clinical situations are taken into account, because Treatment B is more effective than Treatment A. In order to evaluate cost-effectiveness accurately, it is necessary to compare “how much cost increases” and “how much effectiveness is improved” between a new technology (Treatment B) and a conventional one (Treatment A), rather than just dividing the cost of the new technology by effectiveness.

In actual analyses, the incremental cost-effectiveness ratio (ICER) based on this concept is

calculated. When ICER is calculated, the incremental cost is divided by the incremental effectiveness for a new treatment method compared to a traditional method, rather than dividing the cost of the new treatment method by effectiveness. This calculation provides the necessary cost to increase one unit of effectiveness (outcome). In the example mentioned above, ICER is (JPY1,400,000 – JPY1,000,000)/(60 patients – 50 patients) = JPY40,000 per increase of one person cured. This leads to the interpretation that a cost of JPY40,000 is required to cure one more patient. Efficiency is considered to be better, or cost-efficiency is greater as this value is smaller. A decision must be made, however, on how small the value should be to prove the value of replacing the treatment method.

In cost-effectiveness analysis, outcomes that correspond to the disease are often used. For example, extended life years are often used for life-threatening diseases such as cancer and cardiac disease. It is also possible to use intermediate indices such as blood pressure for hypertension and HbA1c for diabetes for evaluation. Meanwhile, an analysis using the index of quality adjusted life years (QALY) that combines extended life years and health status (especially health-related quality of life [HRQOL]), which is particularly called cost utility analysis, has recently become popular mainly in European countries and the U.S. QALY is calculated by weighing the number of life years with the value of HRQOL which is expressed in this case on a scale of 0 (death) to 1 (perfectly healthy). Generally, the HRQOL score of an ill person is between 0 and 1. One life year in a completely healthy way is 1 QALY. If the state of a certain disease is expressed as 0.7, one life year in this state will be 0.7 QALY. The advantage of using QALY is that it can be used for therapeutic or preventive intervention of various diseases, allowing diseases that do not influence the vital prognosis but would reduce QOL during the period of disease to be evaluated.

I-2. Issues related to insurance reimbursement of capital equipment

Several issues have been raised for the medical reimbursement associated with clinical practice using capital equipment. The most important problem is that there is a time lag in the introduction of technologies from overseas to Japan. It is generally recognized that unlike medical materials, diagnoses and procedures using capital equipment are not reimbursed as the price of the device, but included in the reimbursement applied to tests and procedures using the device. Because the reimbursement is integrated, it is difficult to reflect increased usefulness of tests or procedures due to the improvement of devices in the reimbursement promptly. In the case of new technologies, the new insurance application classification (C2) in which such technologies are not included in the existing reimbursement but calculated under a new item is available, but this has been applied to only a small number of cases. Moreover, the criteria for application of the classification and method of evaluation are not always well defined. Therefore, companies face uncertainty in making investment decisions

for new medical devices.

The government also recommends innovation in healthcare-related technologies. The “Draft for Comprehensive Reform of Social Security and Tax” (June 30, 2011) by the government suggests the necessity of “further consideration for the evaluation of innovation from the perspective of health economics in the determining reimbursement” as well as the establishment of an infrastructure for accelerated clinical trials and approval to promote medical innovation.

Prior to this publication, the Ministry of Economy, Trade and Industry compiled a report entitled “To Promote Economic and Social Evaluation of Medical Devices” in 2008 to organize the basic concept for evaluation in addition to the importance of the evaluation of medical innovation.

When new medical technologies are evaluated, the evaluation of efficacy and safety is critical. It is also important to evaluate the health economics as mentioned above because healthcare is offered primarily under the public medical insurance system in Japan.

I-3. Considerations for the economic evaluation of capital equipment

Health economic evaluation can be applied to treatment and prevention using various medical technologies or drugs. Drugs are commonly evaluated in health economic evaluation studies. When the economy of medical devices is evaluated, several issues need be considered. The first issue to be considered is that the intended use of medical devices is not limited to one purpose. While the intended use of drugs is often limited according to their indications, medical devices, especially large ones, are often applied to various purposes. CT and MRI, for example, are used for the testing of various diseases and conditions. As efficacy and safety evidence is necessary for each method of use, it is necessary to evaluate the economic evidence for each method of use. If the same medical device is applied to different diseases, the efficiency may differ. It is difficult to evaluate the efficiency of multi-purpose medical devices uniformly, and cost-effectiveness should be evaluated for each usage.

The second issue is utilization rate of devices. Substantial capital investment is necessary, especially for capital equipment. Therefore, the cost differs according to how much the device is used (for example, how many times the device is used in a day). The facility cost can be calculated from service life with depreciation expense, etc. and electricity and other utility costs for operation can also be estimated to some extent. Cost per use is different, however, according to how many times the device is used in a year, especially if the fixed cost is large. The cost is generally calculated by setting a standard rate of utilization, but this is also based on assumptions. In health economic evaluation, not the initial cost reflecting utilization at medical institutions, but the reimbursement

rate is often used from the position of medical cost payers. In this instance, reimbursement rates are used instead of the actual cost. In this regard, consideration is necessary because reimbursement does not always reflect the actual cost appropriately.

The third issue is improvement of devices. Especially in the case of capital equipment, computer software or other tools that control the device play an important role, and are frequently updated. Improvement of devices often increases efficiency of diagnosis or treatment, but how to consider them in cost calculation remains an issue. If major update of the device leads to significant clinical improvements, separate evaluation from the conventional technology may be possible. As for minor improvements on a frequent basis, it is practically difficult to evaluate all of such improvements.

II. Examples of health economic evaluation

In this study report, specific examples were evaluated as the economic evaluation of medical technologies using capital equipment. The technologies used as examples were those based on capital equipment that have some evidence in clinical application in Japan and are currently not reimbursed. Clinical evidence was required because it was necessary to collect as much data as possible to set parameters based on the assumption of the actual use in Japan when economic evaluation was conducted. The reason why technologies that are currently not reimbursed were used as examples was to help consider how health economic evaluation should be conducted if it is applied to the decision on reimbursement or price setting in the future.

The following two examples were evaluated: 1) health economic evaluation of the introduction of CT colonography (CTC) to colorectal cancer screening, and 2) economic evaluation of MR-guided focused ultrasound surgery (FUS) for uterine fibroids. CTC is a technology using CT testing between fecal occult blood test and optical colonoscopy in colorectal cancer screening. FUS is a clinically applied technology as a treatment method for uterine fibroid that can preserve the uterus without surgery.

Ⅱ-1. Economic evaluation of the introduction of CT colonography (CTC) to colorectal cancer screening

Ⅱ-1-1. Epidemiology of colorectal cancer in Japan

The number of patients with colorectal cancer was 107,815 (2006), and the number of deaths was 42,800 (2009). Colorectal cancer was the second and third common cancer for all ages in men and women, repectively.[1)] Morbidity (2005) was84.4/100,000 persons, and mortality (2009) was 34.0/100,000 persons (Fig. 1).[2)]

Morbidity and mortality have increased almost constantly since the statistics were first calculated in 1975 and 1958, respectively. Especially for mortality, as of 2009, colorectal cancer was the 3rd and 1st leading cause of cancer death by site in men (37.4/100,000 persons) and women (30.8/100,000 persons), respectively (Fig. 2).[1-2)]

Ⅱ-1-2. Current situation and issues of colorectal cancer screening in Japan

1) Current situation of colorectal cancer screening

Currently, cancer screening methods only for the following 5 sites have already established scientific evidence. These 5 sites are the stomach, uterine cervix, breasts, lungs and colons [3)] The Basic Plan to Promote Cancer Control Programs based on the Cancer Control Act enacted in 2006 set a goal of achieving the 50% uptake rate in each cancer screening in order to enable early detection of cancer.[4)] Early detection in an asymptomatic state is especially important for patients with colorectal cancer to have a favorable prognosis, because the overall cure rate of colorectal cancer is about 70% and nearly 100% is cured if it is detected at an early stage. As a means of early detection, colorectal cancer screening by fecal occult blood test (FOBT) and optical colonoscopy (OC) is considered to be effective. Improvement of the colorectal cancer screening uptake rate may be linked directly to the improvement of morbidity and mortality.

However, 6,693,859 out of 40,132,369 eligible persons were screened for colorectal cancer according to the report in 2010,[5)] indicating that the colorectal cancer screening uptake rate was about 16.7%. Moreover, only 291,726 out of 461,396 FOBT-positive persons took OC, [5)] although it is desirable for persons with FOBT-positive to take OC. In other words, about 40% of FOBT-positive persons who need OC do not take OC. Cancer patients in this non-OC group miss an opportunity for early detection by OC, and their colorectal cancer may be diagnosed after the cancer become more serious.

The major reasons why people avert screening are “bothersome,” “busy,” and “no nearby screening institution.” There is also insufficient understanding about the test (for example, “reluctance to feel pain during the test,” “unfamiliarity with the test”). As a result, only 13,597 out of 64,466 estimated cancer patients (about 21%) were actually diagnosed with colorectal cancer and cancer was overlooked in nearly 80% of patients in the eligible population for colorectal cancer screening in 2010 as shown in Fig. 4, under the assumption that FOBT and OC screening uptake rates are 50% and 100%, respectively, and that uptake rates of the tests are unaffected whether the patient has colorectal cancer or not.

2) Future policies and expected issues

In the project for the promotion of cancer screening in Fiscal 2011, a program to provide free coupons for colorectal cancer screening to people aged 40, 45, 50, 55 or 60 years was approved to raise the colorectal cancer screening uptake rate, which is currently about 16.7%, to 50%.[6)]

If this goal of the program is achieved, the number of detected patients with colorectal cancer will increase by 50,869 (= 64,466 – 13,597) persons from the current level (2010).[5)] However, early diagnosis will not be achieved because 23,706 (= 64,466 – 40,760) persons, which account for about 40% of 64,466 persons, will not take OC, despite positive FOBT, if the OC screening uptake rate is not improved from the current level (63.2%). In this case, the goal of increasing the number of early detected patients by colorectal cancer screening will not be achieved sufficiently, although the numerical goal of improving the colorectal cancer screening uptake rate will be achieved. It is necessary to improve not only the colorectal cancer screening uptake rate but also the OC screening uptake rate in the FOBT-positive group, in order to increase the number of early detected patients.

3) CT colonography (CTC)

CTC is a noninvasive testing method that diagnoses colorectal cancer by dilating the colons with gas and taking a three-dimensional image of the colon using an advanced multi-slice CT scanner.[6)] CTC has less burden on patients such as pain and examination time compared to the conventional colonoscopy. Therefore, it has become popular as a new colorectal cancer screening method in Europe and the U.S. In Japan, it has been used mainly as a preoperative diagnostic method for colorectal cancer. CTC is also attracting attention as a screening method in anticipation of decreasing mortality of colorectal cancer and improving the screening uptake rate of colonoscopy in the colorectal cancer screening. The National Cancer Center has started CTC-based colorectal cancer screening since November 2010,[6)] and expansion of CTC-based colorectal cancer screening is expected in Japan in the future.

Ⅱ-1-3. Estimation of cost-effectiveness for the introduction of CTC to colorectal cancer screening

1) Literature review

In principle, estimation of cost-effectiveness is evaluated with the incremental cost-effectiveness ratio (ICER) by comparing the cases where CTC is introduced and not introduced to colorectal cancer screening. Perspectives of analysis are healthcare payer's perspective and societal perspective. While the costs for screening and treatment of related diseases are considered from both healthcare payer's perspective and societal perspective, the loss of productivity due to the disease is only included from societal perspective in general.

Studies on the evaluation of cost-effectiveness for the introduction of CTC to colorectal cancer screening have already been conducted in the U.K.[8-9)] Lee *et al.*[8)] evaluated cost-effectiveness when CTC is introduced as the primary screening. Sweet *et al.*[9)] evaluated the impact on UK NHS budget, resources and outcomes when CTC is introduced to the current colorectal cancer screening either as a primary screening or as a secondary screening(following a positive FOBT). In 2011, colorectal cancer screening in the U.K. consisted of FOBT every two years followed by OC in persons with positive FOBT. Both studies performed analysis from the perspective of the National Health Service (NHS) in the U.K. and only the direct medical cost was included.

Sweet *et al.*[9)] suggested that the addition of CTC to the existing programme as a secondary screening to triage FOBT positive patients was less costly compared to using OC to follow-up FOBT positive patients but would increase the number of deaths from colorectal cancer by 2 persons per 100,000 persons/10 years. This issue should be discussed carefully in this study while taking into account Japanese situation. In contrast, using CTC as a 5 yearly primary screening was more expensive than biennial FOBT screening but resulted in improved outcomes (fewer deaths).

In this study, the cost-effectiveness of the introduction of CTC to colorectal cancer screening in Japan was evaluated in reference to the previous studies.[8-9)] ICER for additional colorectal cancer detected, that for additional colorectal cancer averted, and that for life year gained were calculated from healthcare payer's perspective to evaluate the change in the screening effectiveness of the introduction of CTC in a single year and effectiveness over multiple years including long-term prognosis.

2) How to introduce CTC to colorectal cancer screening

The following three colorectal cancer screening strategies were established for the analysis in this study. These strategies are illustrated in Table 2 and Fig 5. In the explanation below, the numbers in parentheses indicate the screening uptake rate of each testing. The screening uptake rate of each test (FOBT, CTC, and OC) was based on the data in 2010.[5)] The FOBT screening uptake rate was 16.7%, and the OC screening uptake rate in FOBT-positive persons was 63.2%. Since no data were available for the CTC screening uptake rate, we assumed that half of the patients who hesitated to take OC would take CTC screening and all of those who were CTC-positive would take OC.

<Strategy 1> —CTC not introduced—

The general colorectal cancer screening protocol conducted in Japan in 2011 was followed. In this protocol, FOBT is performed in persons who are eligible for colorectal cancer screening and who visit a medical institution for screening (16.7%), and then OC is performed in FOBT-positive persons who are willing to take OC (63.2%). CTC is not introduced.

<Strategy 2> —CTC introduced maximally—

FOBT is performed in persons who are eligible for colorectal cancer screening and who visit a medical institution for screening (16.7%). CTC is performed in FOBT-positive persons who are willing to take CTC (81.6%). OC is performed in all CTC-positive persons (100%). 63.2% of patients who were FOBT-positive are thought to be willing to take OC. We assume that all of them are also willing to take CTC. In addition, among others (100-63.2=36.8%), we assume that half of them can take CTC. Therefore, overall uptake rate of CTC is calculated to be 63.2% + 0.5x36.8%=63.2%+18.4%=81.6%.

<Strategy 3> —CTC introduced only in persons who are willing to take CTC—

FOBT is performed in persons who are eligible for colorectal cancer screening and who visit a medical institution for screening (16.7%). OC is performed in FOBT-positive persons who are willing to take OC (63.2%). In this strategy, unlike strategy 2, candidates of CTC are not all patients who were FOBT-positive but only those who were FOBT-positive and hesitated to take OC. Half of them are assumed to take CTC. Therefore, CTC uptake rate was calculated to be 0.5x(100-63.2%)=18.4%., and OC is performed in all CTC-positive persons (100%).

Ⅱ-1-4. Method

1) Target population

In the analysis of screening effectiveness in a single year, persons eligible for colorectal cancer screening in the Reports on Community Healthcare and Elderly Healthcare Service in Fiscal 2009[5)] were used as a cohort.

In the analysis of effectiveness of the introduction of CTC over multiple years, persons aged 40 to 65 years were analyzed.

2) Model

A decision tree model (Fig. 6) was constructed based on the data from the Reports on Community Healthcare and Elderly Healthcare Service in Fiscal 2009 [5)] to analyze the screening effectiveness of the introduction of CTC in a single year.

Moreover, a Markov model (Fig. 7) for colorectal cancer was constructed in reference to the previous studies[8-10)] and was adjusted using the available epidemiological data in Japan to estimate effectiveness of the introduction of CTC over multiple years.

3) Transition probability

The transition probability (Table 3) among each stage was adjusted based on epidemiological data [1-2, 11)] in Japan in reference to the previous study. [10)]

4) Sensitivity and specificity of the tests

The sensitivity and specificity of each test used in the colorectal cancer screening were set to the values as presented in Table 4 based on domestic and overseas papers [12-19)] as well as discussions with clinical experts.

5) Perspective

Analysis was performed on healthcare payer's perspective and included costs of screening, polypectomy and cancer treatment. FOBT costs were excluded for this study, since they would be the same among all 3 strategies.

6) Cost

The costs were set as presented in Table 5. [20)] The costs of CTC and optical colonoscopy were based on the cost of cancer screening at the National Cancer Center. The costs of each stage of the Dukes classification were roughly estimated with cooperation from clinicians because there are various treatment methods and the cost depends largely on the condition of patients.

7) Outcome measures

Outcome measures were the number of detected colorectal cancers for the single-year analysis, and the decrease in the number of deaths from colorectal cancer and the increase of expected life years

(person-year) for the multiple-year analysis.

8) Time horizon (duration of analysis)

The effectiveness of the introduction of CTC over multiple years was estimated over a time horizon of 20 years in the basic analysis, and also 10 years and a lifetime (until age 100) in the sensitivity analysis.

9) Discount rate

The annual discount rate was set as 3% for both cost and effectiveness, and sensitivity analysis was performed in the range of 0% to 5%.

10) Sensitivity analysis

In both analyses of screening effectiveness in a single year and effectiveness over multiple years, one-way sensitivity analysis was performed for parameters that may have large effects on the results.

Ⅱ-1-5. Results

1) Screening effectiveness and economy of the introduction of CTC in a single year

The introduction of Strategy 2 was estimated to increase the number of persons whose colorectal cancer was detected by screening by 2,299 (= 16,511 – 14,212) persons in a year compared to Strategy 1. On the other hand, the cost of screening increased by JPY5,061,880,000 (= JPY11,094,480,000 – JPY6,032,600,000) in a year. Therefore, the ICER was JPY5,061,860,000 /2,299 additional colorectal cancer detected = JPY2,202,000 per additional colorectal cancer detected.

Meanwhile, introduction of Strategy 3 increased the number of persons whose colorectal cancer was detected by screening by 3,720 (= 17,932 –14,212) persons compared to Strategy 1. On the other hand, the cost of screening increased by JPY2,499,460,000 (= JPY8,532,060,000 – JPY6,032,600,000) in a year. Therefore, the ICER was JPY2,499,460,000 /3,708 additional colorectal cancer detected = JPY672,000 per additional colorectal cancer detected.

In the above analysis, true morbidity in the risk population of colorectal cancer screening was estimated to be 0.00636 (636 persons have colorectal cancer per 100,000 persons in the risk population) based on the data from the Reports on Community Healthcare and Elderly Healthcare Service in Fiscal 2009. [5] The sensitivity and specificity of FOBT were set as 0.528 and 0.946, respectively, and those of CTC were set as 0.900 and 0.860, respectively, and those of OC were set

as 1.00 and 1.00, respectively. Because these values have large effects on analytical results, one-way sensitivity analysis was performed for the sensitivity and specificity as well as the screening uptake rate of each test. Results are presented in Table 7.

2) Effectiveness and economy of the introduction of CTC over multiple years

When Strategies 1 to 3 were introduced as a method of colorectal cancer screening for a long period, as the result of estimation, the number of deaths from colorectal cancer per 100,000 persons and expected life year (person-year) were estimated to shift as presented in Table 8, and the total cost was estimated to shift as presented in Table 9.

The results of each strategy were compared when the time horizon was 20 years.

When people aged 40 to 65 years were eligible for colorectal cancer screening, Strategy 2 decreased the number of cancer deaths by 23 (= 1,078 – 1,055) persons per 100,000 persons, increased the expected life year by 116 (= 1,435,146 – 1,435,030) person-years per 100,000 persons, and required an additional cost of JPY910,110,000 per 100,000 persons compared to Strategy 1. In this case, the ICER was JPY910,110,000/23 additional colorectal cancer death averted = JPY39,660,000 per additional colorectal cancer death averted and JPY910,110,000/116 life years gained = JPY7,804,000 per life year gained.

Strategy 3 decreased the number of cancer deaths by 37 (= 1,078 – 1,041) persons per 100,000 persons, increased the expected life year by 186 (= 1,435,216 – 1,435,030) person-years per 100,000 persons, and required an additional cost of JPY90,340,000 per 100,000 persons compared to Strategy 1. In this case, the ICER was JPY90,340,000/37 additional colorectal cancer death averted = JPY2,465,000 per additional colorectal cancer death averted and JPY90,340,000/186 life years gained = JPY484,000 per life year gained.

One-way sensitivity analysis was performed for sensitivity, specificity, and the examination cost of FOBT, CTC, and OC, and annual treatment cost of each stage of the Dukes classification. Moreover, one-way sensitivity analysis was performed for the discount rate within the range of 0% to 5% because the duration of the analysis was long in this study.

The results of the sensitivity analysis expressed with the ICER per additional colorectal cancer death averted are presented in Table 11, and those per life year gained in Table 12.

Ⅱ-1-6. Discussion

1) Appropriateness of the model

The Markov model used in this study was constructed in reference to the previous studies [8-10] and was adjusted for transition probability in reference to available epidemiological data related to colorectal cancer in Japan such as the five-year survival rate, cumulative morbidity, cumulative mortality, morbidity, and mortality of each stage of the Dukes classification. [1-2, 11] For example, the annual mortality of each Dukes' stage was applied to Japan using the domestic data of five-year survival rate, and the morbidity of colorectal cancer at each age was adjusted by comparing to the domestic data of cumulative morbidity and mortality. An estimation was made by using values reported in the previous studies [8-10] because there were no data about the transition among each stage such as transition probability from a stage of the Dukes classification to another one. Comparison between the cumulative morbidity calculated by the model constructed in this study and actual data in Japan is illustrated in Fig. 11.

Recurrence of colorectal cancer was not considered as a stage in the Markov model constructed in this study. The major reason for this was that epidemiological data about recurrence of colorectal cancer in Japan were not sufficient. In addition, metastatic cancer to other organs such as the liver and lungs observed in Dukes' C or D colorectal cancer was not considered as a stage in the model, too. Because these stages were not included in the model, recurrent cancer and metastatic cancer to other organs were not incorporated into the model in terms of cost. Recurrent cancer and metastatic cancer to other organs were considered to be incorporated into the model in terms of mortality and expected life years, however, which correspond to effectiveness, because the five-year survival rate used for adjustment of transition probability included deaths from recurrent cancer and metastatic cancer to other organs. The change in the number of patients in each stage of the Dukes classification after introduction of CTC was checked. As illustrated in Figures 12 and 13, the number of patients with Dukes' C or D colorectal cancer was considered to decrease after the introduction of CTC. This means that the total cost for Dukes' C or D is expected to decrease after the introduction of CTC. In the real-world situation, treatment costs of colorectal cancer should include the costs of metastasis, whereas they are not included in this study. Then, treatment costs for colorectal cancer are underestimated, especially for the later stages. The amount of cost-saving introduced by CTC implementation is also underestimated. If we include the costs of metastasis, ICER will be improved.

2) Sensitivity and specificity of each test

In this study, the following three tests were used in the colorectal cancer screening: fecal occult blood test (FOBT), CT colonography (CTC) and optical colonoscopy (OC).

When several papers [12-18] were reviewed, many studies about the sensitivity and specificity of

FOBT had various limitations such as the insufficient size of the population, apparent bias in the population, and insufficient description of the method. After discussion with clinical experts, domestic data [11] were handled as provisional values in the basic analysis, and their uncertainty was considered by sensitivity analysis.

Based on this discussion, sensitivity of FOBT was set as 0.528 in the analysis of screening effectiveness in a single year. The use of a uniform value may be inadequate because the frequency or possibility of bleeding is considered to be different according to the Dukes' stage. This value was the smallest, however, among the three FOBT sensitivity values (Dukes' A = 0.528, Dukes' B = 0.700, Dukes' C & D = 0.783) to colorectal cancer, and it is thus considered to work adversely on the introduction of CTC in the analysis.

Although the sensitivity and specificity of CTC depend largely on the skills of the interpreting physicians, it was decided to use the results of a clinical study [19] by assuming that inter-physician variation was equalized. The overall sensitivity and specificity of actually performed CTC are likely to be lower than those published in the report, [19] however, considering the fact that the number of clinicians who are familiar with interpretation of CTC is limited in Japan. A sensitivity analysis was performed for this issue to consider the uncertainty.

Both the sensitivity and specificity of OC used in the definite diagnosis were set as 1.00. The effects of any change in the sensitivity of OC were considered in the sensitivity analysis presented in Tables 11 and 12. If specificity is not 1.00, some people are diagnosed to be positive in the definite diagnosis and treated for colorectal cancer even though they do not actually have colorectal cancer. When screening effectiveness in a single year was estimated, the unit was defined as "cost per newly detected patient with colorectal cancer." Therefore, definite diagnosis of a false positive result was also considered and a sensitivity analysis was performed also for the specificity of OC. This issue was not considered in the Markov model and sensitivity analysis was not performed, since there were no sufficient domestic epidemiological data about persons with false-positive results in the definite diagnosis.

3) Shift of the number of patients in the Markov stages and setting the cost for the stages

A shift in the number of patients in each stage of Dukes' classification in the analysis of the effectiveness of the introduction of CTC introduction over multiple years is illustrated in Figs. 12 to 17. A comparison of the annual number of patients between Strategy 1 and Strategy 2 or 3 is presented in Table 13.

As shown in Table 13, the new cost was generated and the total cost increased when the number of patients increased. On the other hand, part of the cost became unnecessary and the total cost decreased when the number of patients decreased.

It was difficult to calculate the treatment cost uniformly because the treatment cost for each stage depends largely on the condition of the individual patients. Therefore, the cost was estimated roughly with cooperation from clinical experts in consideration of the increase or decrease in the number of patients shown in Table 13. As a result, the treatment cost for low-risk and high-risk polyps with increased number of patients was set at a larger value so that the increment of total cost became overestimated, while treatment cost for Dukes' B, C, and D with decreased number of patients was set at a smaller value so that the reduction of cost became underestimated. This cost setting was considered to work adversely on the introduction of CTC and did not impair the robustness of this study.

4) Results of sensitivity analysis

In the sensitivity analysis for the analysis of screening effectiveness in a single year, there was a common trend that the ICER increased with decreased sensitivity and specificity, and the ICER decreased with increased sensitivity and specificity. It was also revealed that the ICER fluctuated largely depending on the value of true morbidity.

In the basic analysis of this study, true morbidity was set as 0.00636, which means that 636 persons have colorectal cancer in 100,000 persons who are eligible for colorectal cancer screening. This value was calculated based on the data from the Reports on Community Healthcare and Elderly Healthcare Service in Fiscal 2009 [5)] under the assumption that there is no difference in FOBT and OC screening uptake rates between people who actually have and who do not have colorectal cancer.

This value of true morbidity has not been reported as a statistical number. In 2006, the crude morbidity of all cancers was 543/100,000 persons at all ages. [1)] The crude morbidity in people aged 40 years or older who are eligible for colorectal cancer screening is 997/100,000 persons. [1)] Considering these numbers, the true morbidity of colorectal cancer of 636/100,000 persons is considered to be an overestimation. In other words, the assumption made in the calculation of the true morbidity that there is no difference in FOBT and OC screening uptake rates between people who actually have and who do not have colorectal cancer may be incorrect. There is likely to be a bias that stimulates screening with subjective symptoms so that people who actually have the disease were encouraged to take screening.

In the analysis of the effectiveness of the introduction of CTC over multiple years, there was also a common trend that the ICER increased with decreased sensitivity and specificity, and the ICER decreased with increased sensitivity and specificity as in the single-year case.

However, sensitivity of FOBT to polyps shifted in an opposite way to other parameters. The ICER decreased (i.e., better cost-effectiveness) when sensitivity decreased from 0.200 to 0.100, and the ICER increased (i.e., worse cost-effectiveness) when sensitivity increased to 0.300.

This is possibly because if the sensitivity of FOBT to polyps decreases, the number of patients who progress to Dukes' A or severer colorectal cancer increases and the number of detected patients with colorectal cancer increases. The sensitivity of each strategy in each stage (Dukes' A or severer) is presented in Table 14.

If the percentage of people who progress to Dukes' A is increased by the reduction of sensitivity to polyps, the absolute percentage of patients who progress to Dukes' B or a severer disease is larger with Strategy 1 than Strategy 2 or 3 because the difference in sensitivity for Dukes' A is larger than that for polyps. The same applies to the percentage of people who progress to Dukes' C or D. As a result, the number of patients in Dukes' C or D may decrease largely after the introduction of CTC compared to the basic analysis, resulting in smaller ICER (better cost-effectiveness).

5) Outcome measures

The number of patients who are diagnosed with colorectal cancer by colorectal cancer screening was used as the outcome in the analysis of screening effectiveness of the introduction of CTC in a single year, and the number of deaths from colorectal cancer and expected life years in the analysis of the effectiveness of the introduction of CTC over multiple years. It is impossible to evaluate the effect on the quality of life (QOL), however, although it is possible to evaluate the effect (mortality) on the vital prognosis of the disease when the number of deaths from cancer and expected life years are used as the outcome measures. The effect on QOL is important for cancer, and studies on the QOL of patients with cancer have recently been conducted. Quality adjusted life years (QALY) are sometimes used as an outcome measure in economic evaluations. This approach allows analysis that considers not only survival but also QOL during survival. This method was not used in this study, however, because QOL data were not sufficient for diseases or stages analyzed in the study. Further data collection is needed in the future.

Ⅱ-1-7. Conclusion

The screening effectiveness of the introduction of CTC in a single year compared to Strategy 1,

which is the current colorectal cancer screening protocol, was JPY2,202,000 and JPY672,000 per additional colorectal cancer detected for Strategies 2 and 3, respectively. The additional costs associated with introduction were about JPY5 and JPY2.5 billion a year for Strategies 2 and 3, respectively.

In the analysis of effectiveness of the introduction of CTC over multiple years when the time horizon was 20 years, the ICER was JPY39,660,000 per additional colorectal cancer death averted and JPY7,800,000 per life year gained for Strategy 2. The ICER was JPY2,470,000 per additional colorectal cancer death averted and JPY480,000 per life year gained for Strategy 3.

These ICER values will be further improved with a longer time horizon (i.e., a lifetime) than the basic analysis. Not only short-term but also long-term effects should be included in the consideration when CTC is introduced to colorectal cancer screening.

In this study, the model was constructed so that it works adversely on the introduction of CTC for the part where data were ambiguous, because epidemiological data for colorectal cancer were not sufficient. It is desirable to perform a reanalysis with more sufficient data for the sensitivity and specificity of FOBT and breakdown of medical cost in each stage of the Dukes classification.

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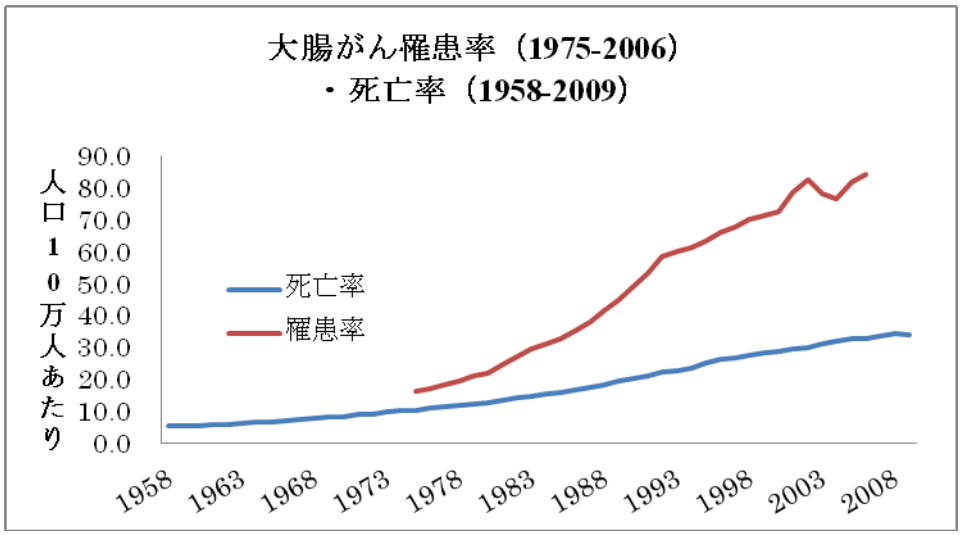
Fig. 1 Morbidity and mortality of colorectal cancer (per 100,000 persons)

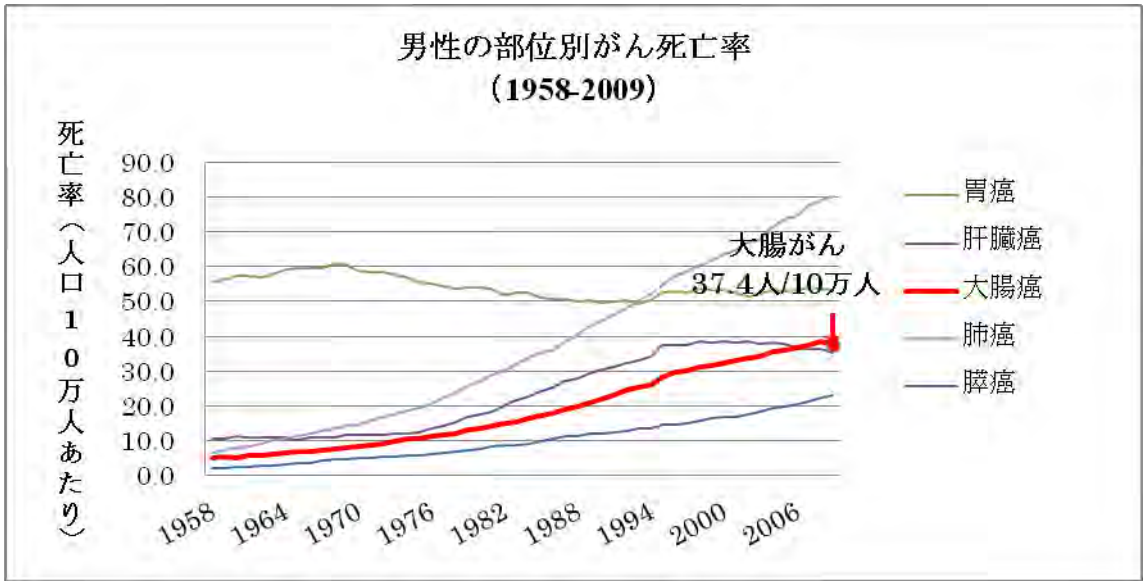


Morbidity (1975 to 2006) and mortality (1958 to 2009) of colorectal cancer

Per 100,000 persons

Mortality Morbidity

Fig. 2 Cancer mortality by site in men



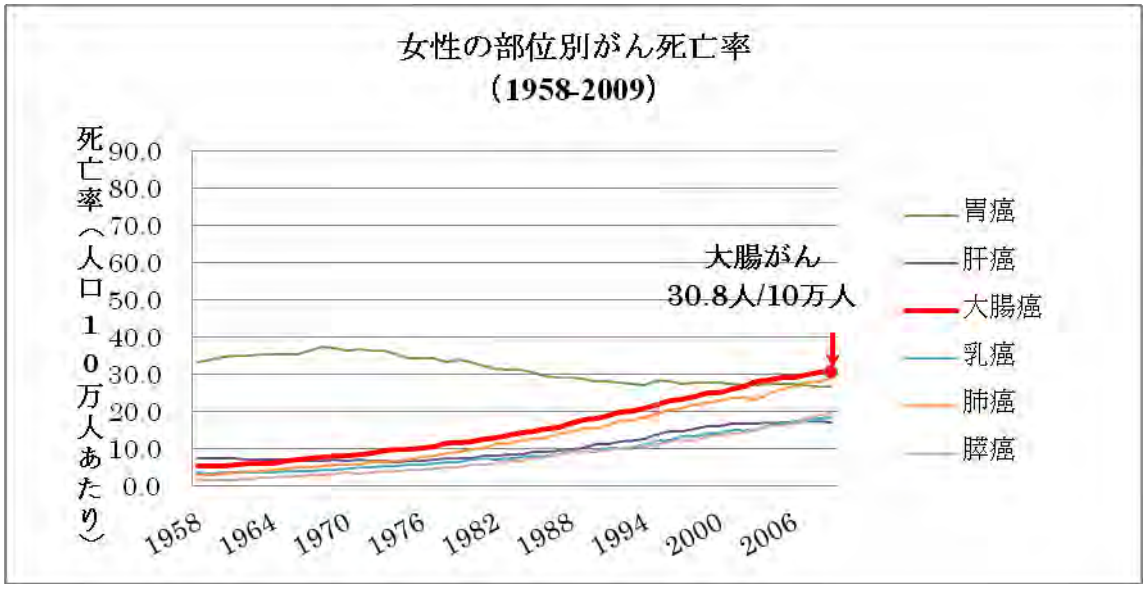
Cancer mortality by site in men (1958 to 2009)

Mortality (per 100,000 persons)

Colorectal cancer 37.4/100,000 persons

Gastric cancer Liver cancer Colorectal cancer Lung cancer Pancreatic cancer

Fig.3 Cancer mortality by site in women



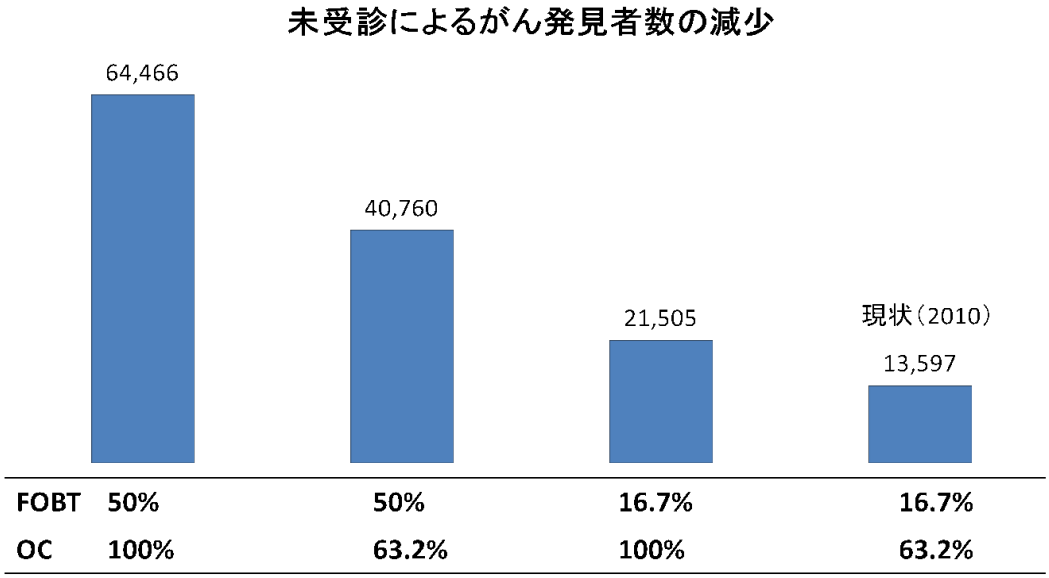
Cancer mortality by site in women (1958 to 2009)

Mortality (per 100,000 persons)

Colorectal cancer 30.8/100,000 persons

Gastric cancer Liver cancer Colorectal cancer Breast cancer Lung cancer Pancreatic cancer

Fig. 4 Decrease in the number of detected cancers due to nonattendance at screening



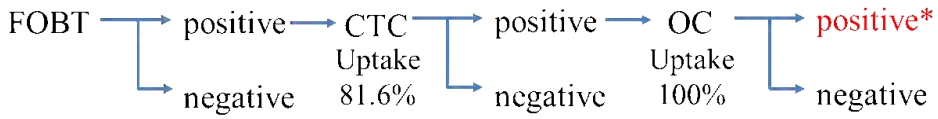
Decrease in the number of detected cancers due to nonattendance at screening

Current (2010)

Fig. 5 Colorectal cancer screening protocol

Strategy 1: existing colorectal cancer screening protocol

Strategy 2: protocol with completely introduced CT testing



Strategy 3: protocol with partly introduced CT testing

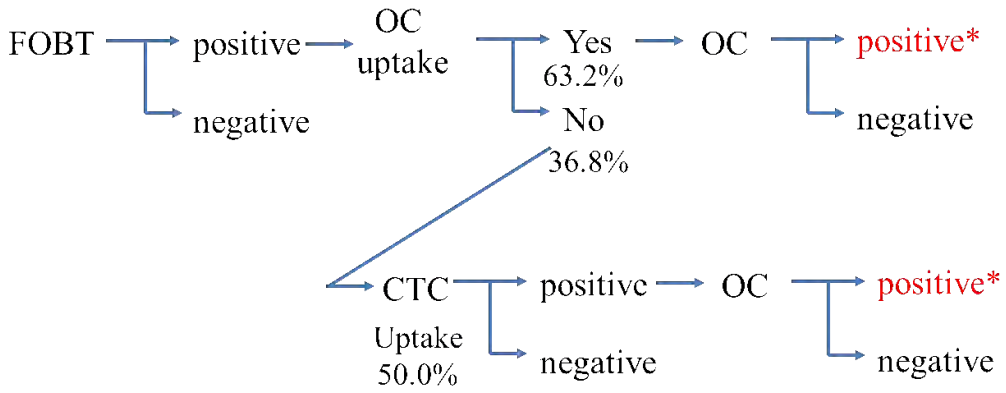


Fig. 6 Decision tree model used for analysis of screening effectiveness of the introduction of CTC in a single year

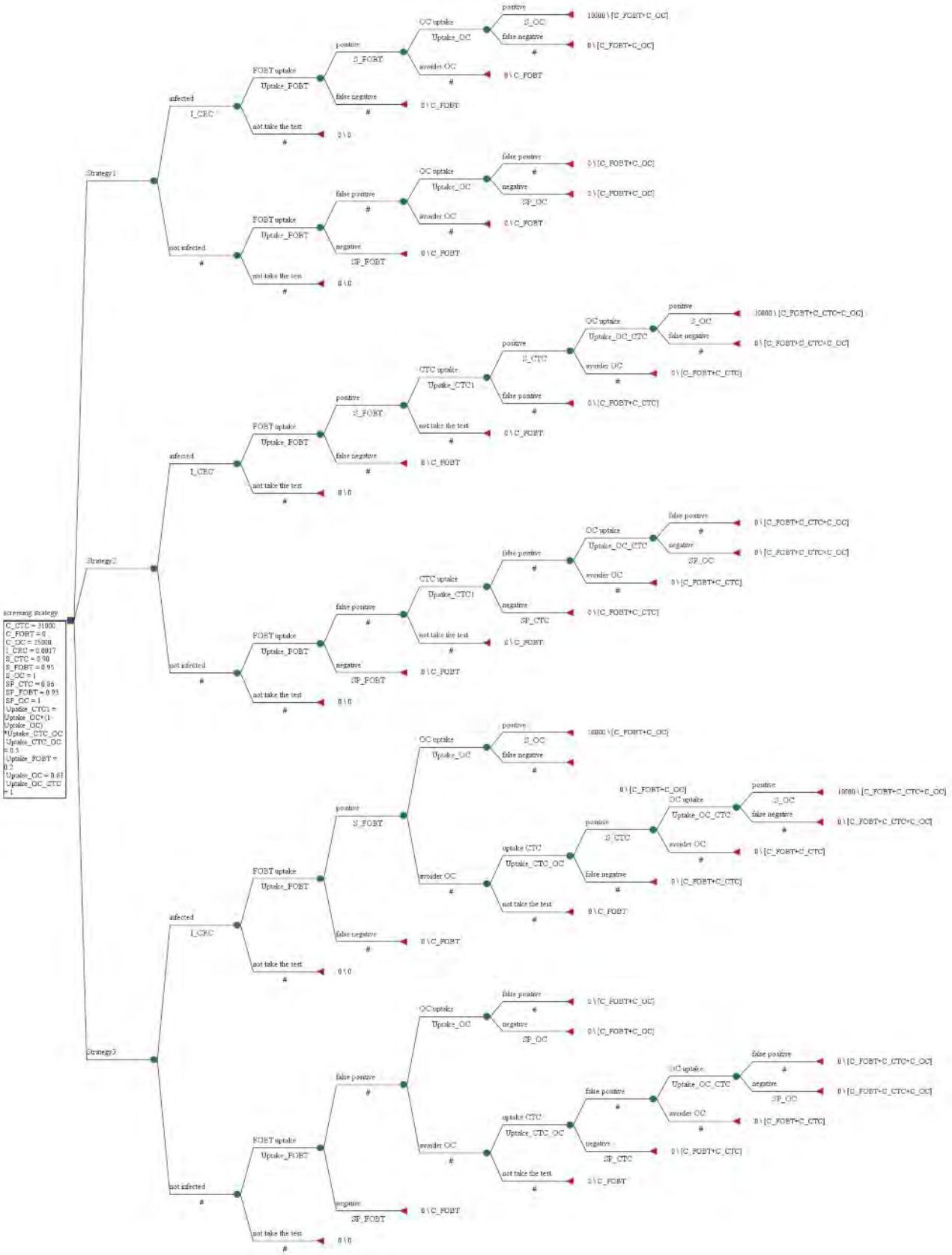
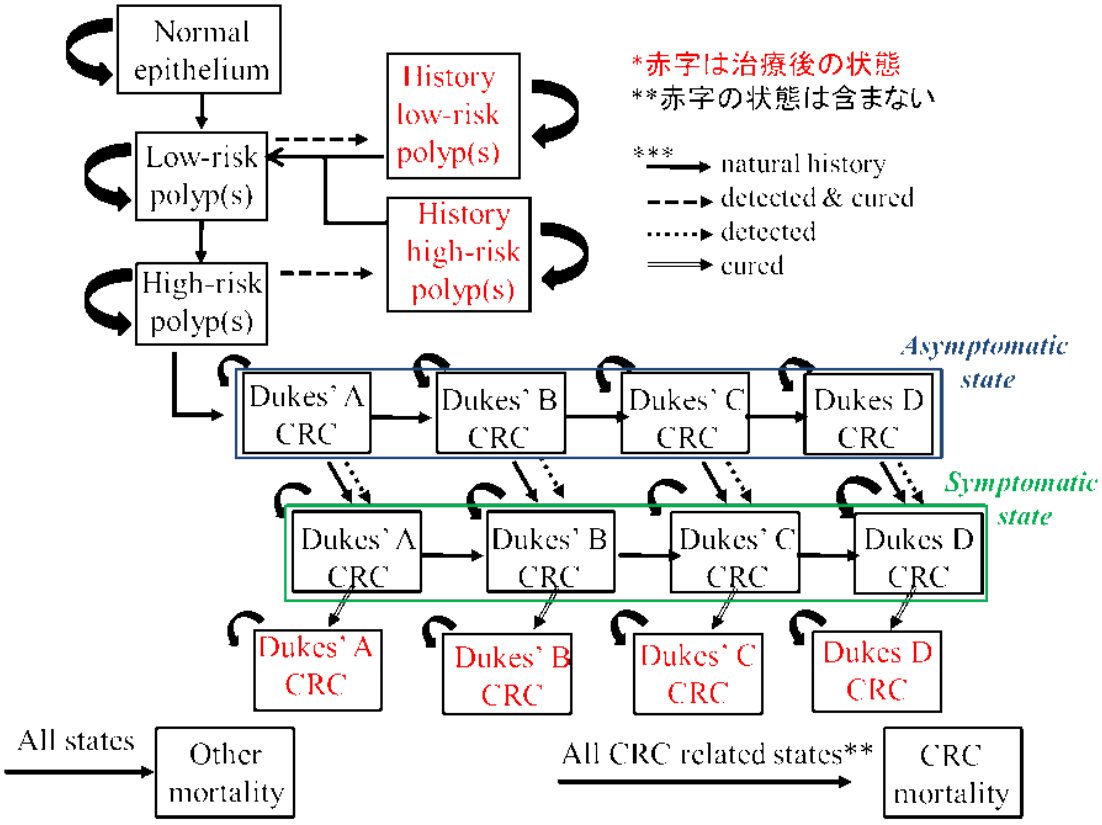


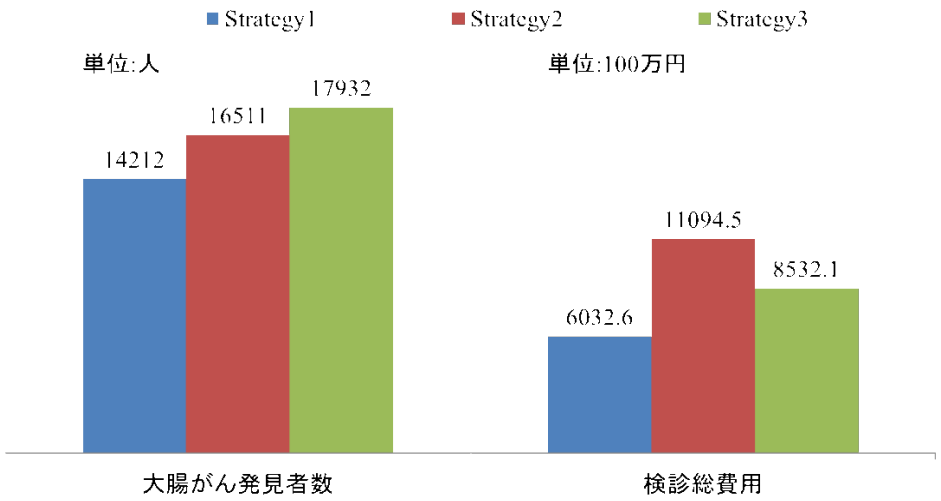
Fig. 7 Pathological model of colorectal cancer



*Red letters indicate states after treatment.

*States in red letters are not included.

Fig. 8 Number of detected patients with colorectal cancer and total cost with each strategy



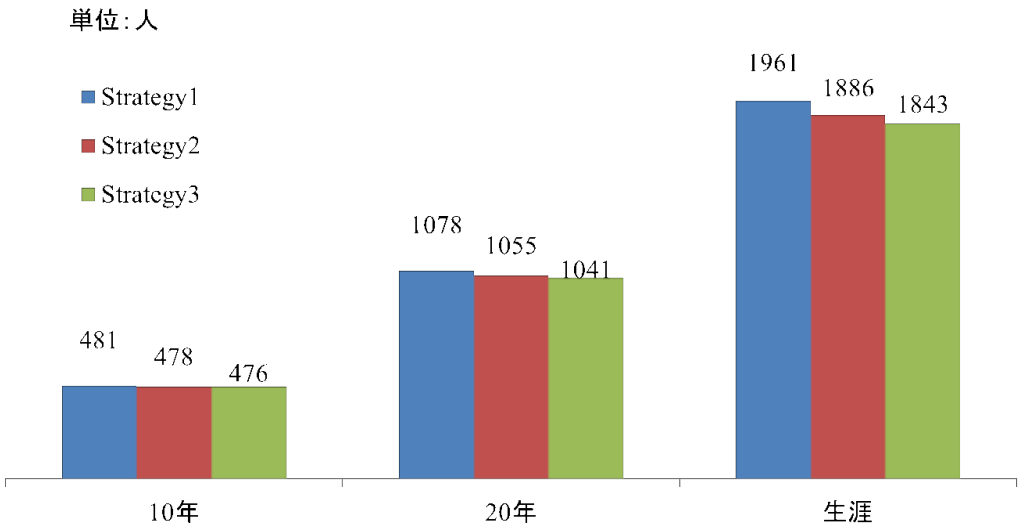
Unit: persons

Unit: JPY1,000,000

Number of detected patients with colorectal cancer

Total cost of screening

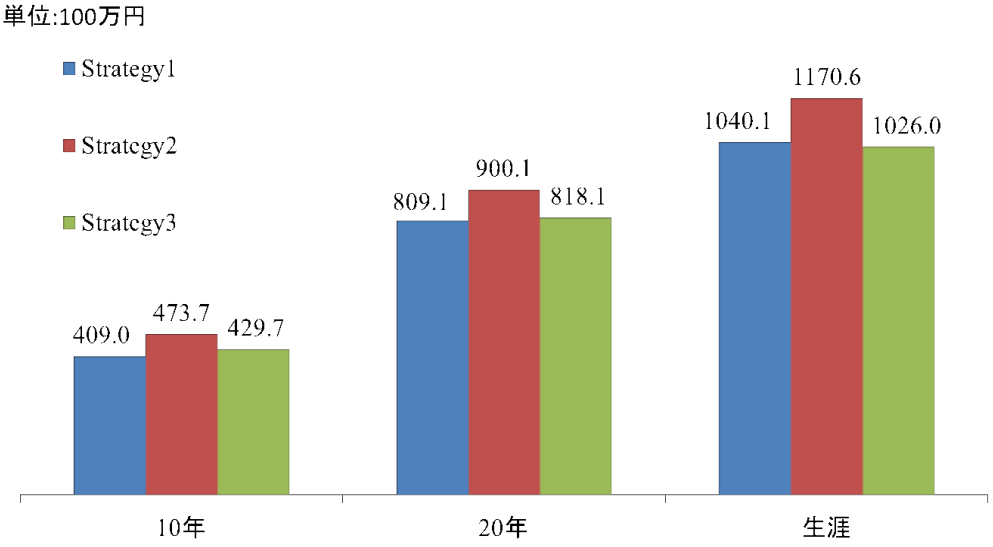
Fig. 9 Shift in the number of deaths from colorectal cancer with each strategy (per 100,000 persons)



Unit: persons

10 years 20 years Lifetime

Fig. 10 Shift in the total cost related to colorectal cancer with each strategy (per 100,000 persons)



Unit: JPY1,000,000

10 years 20 years Lifetime

Fig. 11 Comparison between the model and actual data (cumulative morbidity)

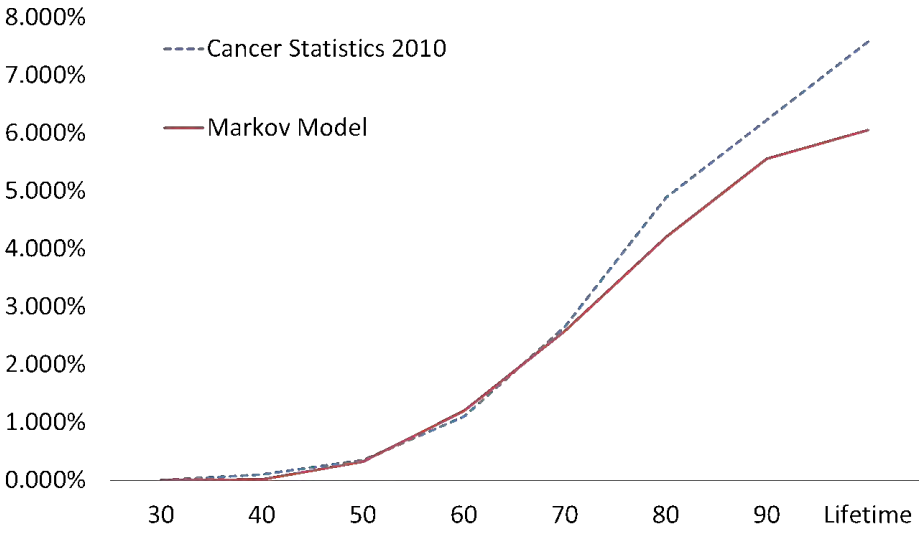
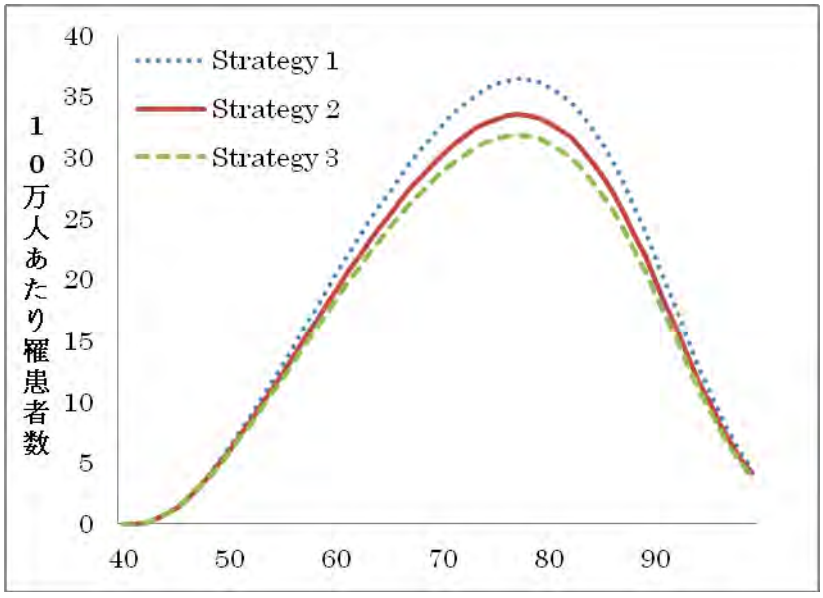
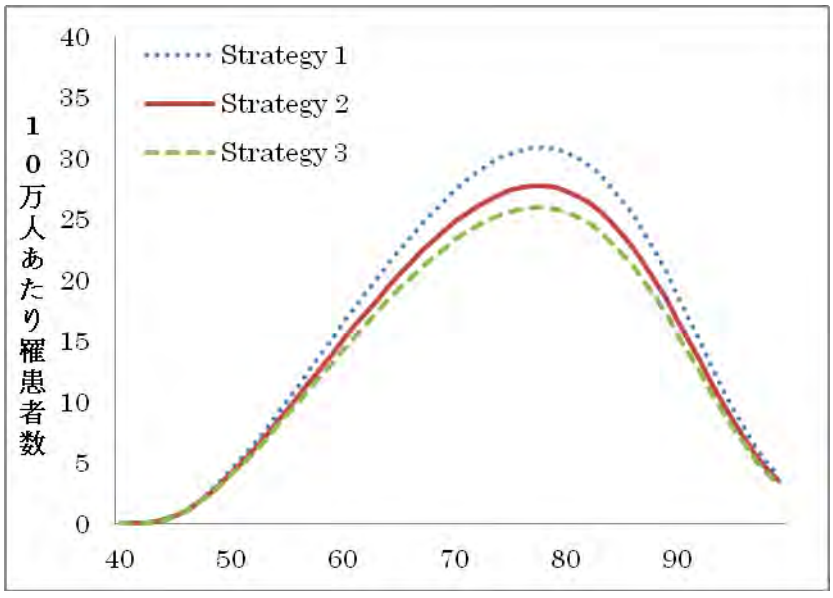


Fig. 12 Shift in the annual number of patients in Dukes' stage C with each strategy



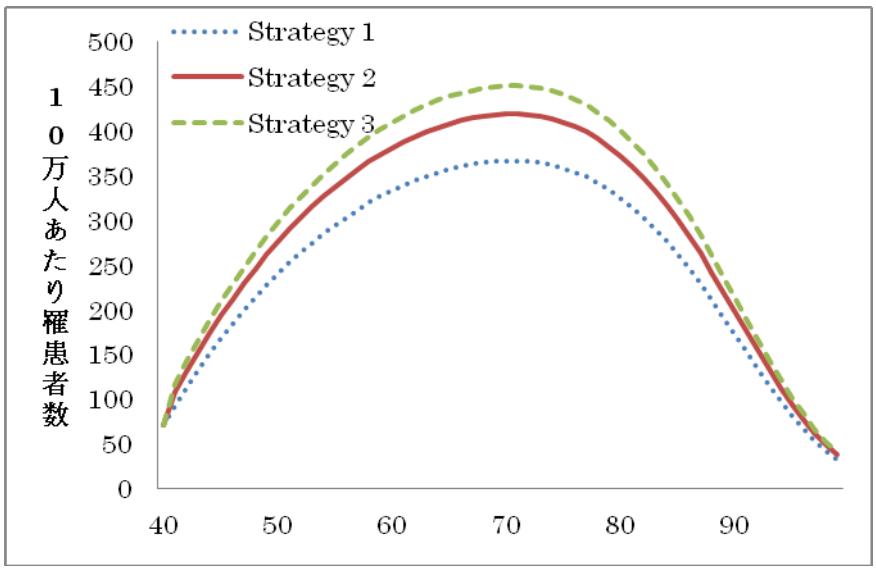
Number of patients per 100,000 persons

Fig. 13 Shift in the annual number of patients in Dukes' stage D with each strategy



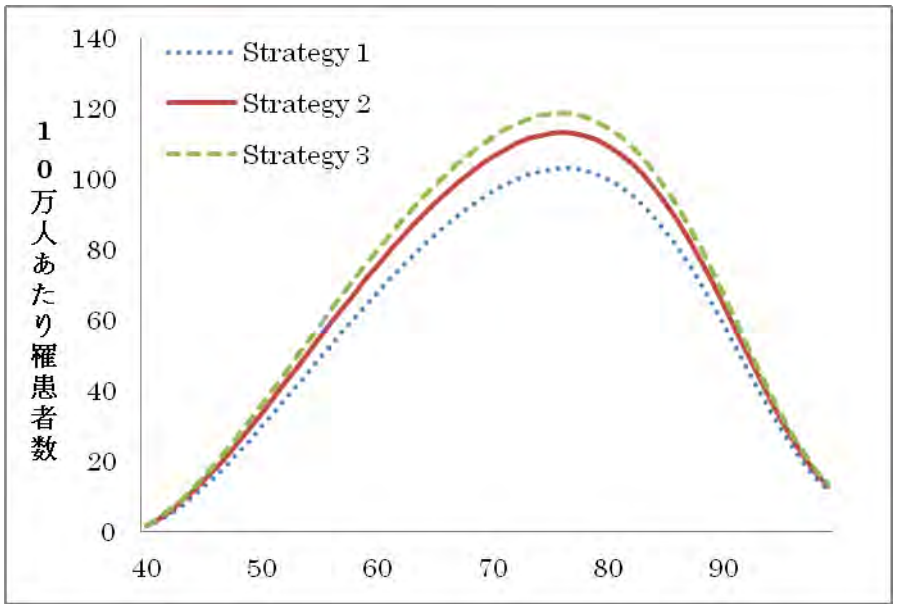
Number of patients per 100,000 persons

Fig. 14 Shift in the annual number of patients with low-risk polyp(s) with each strategy



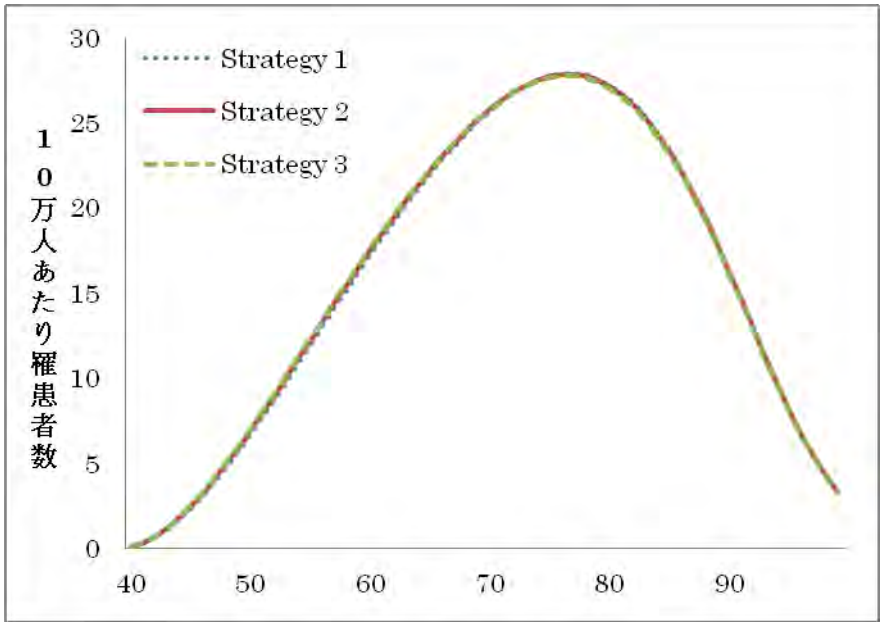
Number of patients per 100,000 persons

Fig. 15 Shift in the annual number of patients with high-risk polyp(s) with each strategy



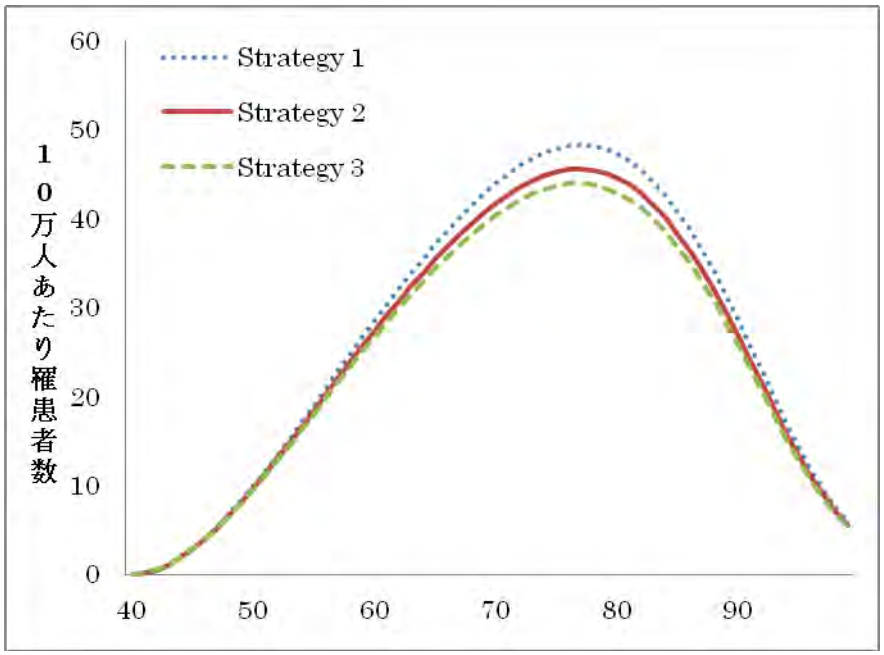
Number of patients per 100,000 persons

Fig. 16 Shift in the annual number of patients in Dukes' stage A with each strategy



Number of patients per 100,000 persons

Fig. 17 Shift in the annual number of patients in Dukes' stage B with each strategy



Number of patients per 100,000 persons

Table 1 Summary of existing studies

	Lee D *et al.* (2010)	Sweet A *et al.* (2011)
Target population and intervention	The following four methods were compared as the primary screening in a cohort aged 60 to 69 years in the U.K. to evaluate the impact of the introduction of CTC: 1. FOBT every 2 years 2. FSIG every 10 years 3. OC every 10 years 4. CTC every 10 years	The following 3 methods were compared in a population cohort aged 50 years or older as of 2006 in the U.K. to evaluate the impact of the introduction of CTC: 1. Conventional method (FOBT every other years → OC) 2. CTC introduced to the conventional method (FOBT → CTC → OC) 3. CTC every 5 years (CTC → OC)
Position of analysis	Medical cost payer (NHS)	Medical cost payer (NHS)
Time horizon	Lifetime	10 years
Cost	Direct cost only	Direct cost only
Estimation of the shift in health status	Using Markov model	Using Markov model
Primary outcomes	Death and QALY were used as primary outcomes.	The number of detected or diagnosed patients with colorectal cancer and number of deaths were used as primary outcomes.
Results	CTC every 10 years was superior to and more dominant than the existing method of FOBT every 2 years in terms of cost saving and health benefits (survival, QALY)	There was no large difference in the number of detected or diagnosed patients with colorectal cancer among each method. Method 2 resulted in cost reduction of 77,628 pounds per 100,000 persons/10 years compared to Method 1. Method 3 resulted in cost increase of 3,347,972 pounds per 100,000 persons/10 years compared to Method

		2.
Necessary verification	Total cost when CTC is introduced Excess or deficiency in terms of medical resources	Verification for not only screening and diagnosis processes but also long-term prognosis The increased number of deaths from colorectal cancer with Method 2 by 2 persons per 100,000 persons/10 years compared to Method 1

Table 2 Tests in each colorectal cancer screening protocol

	FOBT	CTC	OC
Strategy 1	◎	—	○
Strategy 2	◎	○	○
Strategy 3	◎	△	○

◎: Performed in persons who are willing to take the test without preconditions

○: Performed in persons who are willing to take the test among those with positive results in the previous test

△: Performed in persons who are willing to take the test among those who do not take OC right away

Table 3 Transition probability in the Markov model

	Transition probability	
	Preceding study[9)]	After adjustment
Progression probability		
From normal epithelium to low-risk polyp(s)	0.012	
From low-risk polyp(s) to high-risk polyp(s)	0.024	
From high-risk polyp(s) to asymptomatic Dukes' A	0.034	
From asymptomatic Dukes' A to Dukes' B	0.583	
From asymptomatic Dukes' B to Dukes' C	0.656	
From asymptomatic Dukes' C to Dukes' D	0.865	
Probability of death from colorectal cancer		
Dukes' A	0	0.0239
Dukes' B	0.01	0.0457
Dukes' C	0.602	0.0805
Dukes' D	0.3867	0.342
Probability of developing subjective symptoms		
Dukes' A presentation	0.065	
Dukes' B presentation	0.26	

Dukes' C presentation	0.46
Dukes' D presentation	0.92
Probability of progressing to colorectal cancer after polypectomy	
After polypectomy of low-risk polyp(s) (first year)	0.18
After polypectomy of low-risk polyp(s) (two year)	0.05
After polypectomy of high-risk polyp(s) (first year)	0.25
After polypectomy of high-risk polyp(s) (two year)	0.06

Table 4 Sensitivity and specificity of each test

	Sensitivity				Specificity
	polyps	Dukes' A	Dukes' B	Dukes' C & D	Common to all sites
FOBT	0.200	0.528	0.700	0.783	0.946
CTC	0.900	0.900	0.900	0.900	0.860
OC	1.000	1.000	1.000	1.000	1.000

Note) Because definite diagnosis is performed by optical colonoscopy, it was assumed that both the sensitivity and specificity of the optical colonoscopy is 1.000.

Table 5 Cost of each test, annual treatment cost in each stage of the Dukes classification

Test/treatment	Cost (JPY)
CTC	31,000
OC	25,000
Polypectomy (≤2cm in diameter)	78,000
Polypectomy (≥2 cm in diameter)	98,000
Malignant tumor resection (colon)	840,400
Malignant tumor resection (rectum)	1,130,900
Postoperative chemotherapy (6 months)	400,000
Chemotherapy (Dukes' D, annual)	4,000,000
follow up (Dukes' A & B)	35,570
follow up (Dukes' C & D)	44,972
Annual cost by stage	
low-risk and high-risk polyps	78,000
Dukes' A (first year after start of treatment)	98,000
Dukes' A (2 to 5 years after treatment)	35,570
Dukes' B (first year after start of treatment)	941,745
Dukes' B (2 to 5 years after treatment)	35,570
Dukes' C (first year after start of treatment)	1,341,745
Dukes' C (2 to 5 years after treatment)	44,792
Dukes' D (1 to 5 years after treatment)	4,044,792

Table 6 Screening results of colorectal cancer screening in a single year

	Number of CTC cases	**Number of OC cases**	**Number of detected patients with colorectal cancer (persons)**	**Total cost (JPY10,000)**	**Increased number of detected patients (vs. S-1*)**	**Increased total cost (JPY10,000) (vs. S-1*)**	**ICER** ** **(vs. S-1*)**
Strategy 1	0	241,304	14,212	603,260	—	—	—
Strategy 2	311,476	57,549	16,511	1,109,448	2,299	506,188	220.2
Strategy 3	70,172	254,269	17,932	853,206	3,720	249,946	67.2

* S-1 is the abbreviation of Strategy 1.

** The unit of ICER is JPY10,000/additional CRC detection (cost per additional colorectal cancer detected)

Table 7 Results of sensitivity analysis (unit: JPY10,000 per additional CRC detection)

		ICER (S-1 vs. S-2)			ICER (S-1 vs. S-3)		
	Variable	Worst	Base	Best	Worst	Base	Best
True morbidity	PIR (0.00318-0.00636)	413.9 (0.00318)	220.2 (0.00636)	— —	128.8 (0.00318)	67.2 (0.00636)	— —
Screening uptake rate	FOBT (0.167-0.50)	—	220.2 (0.167)	—	—	67.2 (0.167)	—
	CTC (0.250-0.750)	865.2 (0.250)	220.2 (0.500)	151.7 (0.750)	—	67.2 (0.500)	—
	OC (0.316-0.948)	dominated*[6] (0.948)	220.2 (0.632)	95.5 (0.316)	—	67.2 (0.632)	—
Sensitivity	FOBT (0.264-0.792)	412.7 (0.264)	220.2 (0.528)	155.7 (0.792)	128.4 (0.264)	67.2 (0.528)	46.8 (0.792)
	CTC (0.450-1.00)	dominated (0.450)	220.2 (0.900)	123.5 (1.00)	131.9 (0.450)	67.2 (0.900)	60.7 (1.00)
	OC (0.500-1.00)	439.9 (0.500)	220.2 (1.00)	—	134.4 (0.500)	67.2 (1.00)	—
Specificity	FOBT	1908.2	220.2	27.2	603.7	67.2	5.94

	(0.473-1.00)	(0.473)	(0.946)	(1.00)	(0.473)	(0.946)	(1.00)
	CTC	356.8	220.2	175.4	86.3	67.2	61.0
	(0.430-1.00)	(0.430)	(0.860)	(1.00)	(0.430)	(0.860)	(1.00)
	OC	—	220.2	—	—	67.2	—
	(0.500-1.00)		(1.00)			(1.00)	

* "Base" means basic analyses without any change in variables. "Worst" means cases with the worst cost-effectiveness (largest ICER). "Best" means cases with the best cost-effectiveness (smallest ICER).

* Values in parentheses under variables indicate the range that was changed in the sensitivity analysis. Values in parentheses under ICERs indicate the value of variables corresponding to the ICER.

* "—" indicates the same values as those of the basic analysis.

* "Dominated" means cases where the effectiveness (the number of detected patients with colorectal cancer in this case) was decreased by the introduction of CTC.

Table 8 Number of deaths from colorectal cancer per 100,000 persons and expected life years (person-year) (aged 40 to 65 years)

	Strategy 1		Strategy 2		Strategy 3	
Time horizon	Number of deaths	Expected life years (person-year)	Number of deaths	Expected life years (person-year)	Number of deaths	Expected life years (person-year)
10 years	481	857,453	478	857,459	476	857,463
20 years	1,078	1,435,030	1,055	1,435,146	1,041	1,435,216
Lifetime*	1,961	2,303,265	1,886	2,304,064	1,843	2,304,534

* Analysis with a time horizon of a lifetime was performed at up to age 100.

Table 9 Total cost related to colorectal cancer per 100,000 persons (unit: JPY)

	Strategy 1	Strategy 2		Strategy 3	
Time horizon	Total cost	Total cost	Increment (vs. S-1)	Total cost	Increment (vs. S-1)
10 years	JPY4,089,530,000	JPY4,736,960,000	JPY647,430,000	JPY4,297,100,000	JPY207,570,000
20 years	JPY8,090,880,000	JPY9,000,990,000	JPY910,110,000	JPY8,181,220,000	JPY90,340,000
Lifetime*	JPY10,401,050,000	JPY11,705,800,000	JPY1,304,750,000	JPY10,260,260,000	JPY−140,790,000

Table 10 Cost per additional colorectal cancer death averted and cost per life year gained (ICER)

Time horizon	Strategy 2 vs. Strategy 1		Strategy 3 vs. Strategy 1	
	Per colorectal cancer death averted	Per life year gained	Per colorectal cancer death averted	Per life year gained
10 years	JPY204,185,000	JPY103,797,000	JPY40,700,000	JPY20,640,000
20 years	JPY39,660,000	JPY7,804,000	JPY2,465,000	JPY484,000
Lifetime*	JPY17,570,000	JPY1,632,000	dominant	dominant

Table 11 Results of sensitivity analysis (cost per colorectal cancer death averted) Unit (JPY10,000)

		ICER (S-1 vs. S-2)			ICER (S-1 vs. S-3)		
	Variable	Worst	Base	Best	Worst	Base	Best
Discount rate	(0%-5%)	4,579.6 (5%)	3,966.0 (3%)	2,478.8 (0%)	392.0 (5%)	246.5 (3%)	81.8 (0%)
Screening uptake rate	FOBT (0.167-0.500)	8,884.2 (0.500)	3,966.0 (0.167)	—	1,332.6 (0.500)	246.5 (0.167)	—
	CTC (0.250-0.750)	19,378.2 (0.250)	3,966.0 (0.500)	2,358.3 (0.750)	275.3 (0.250)	246.5 (0.500)	220.5 (0.750)
	OC (0.316-0.948)	dominated (0.948)	3,966.0 (0.632)	2,866.1 (0.316)	126.4 (0.948)	246.5 (0.632)	144.4 (0.316)
Sensitivity	FOBT_P (0.100-0.300)	10,219.6 (0.300)	3,966.0 (0.200)	591.9 (0.100)	765.8 (0.300)	246.5 (0.200)	dominant (0.100)
	FOBT_A (0.264-0.792)	8,576.2 (0.264)	3,966.0 (0.528)	2,936.3 (0.792)	3,229.6 (0.264)	246.5 (0.528)	78.1 (0.792)
	FOBT_B (0.350-1.00)	9,150.5 (0.350)	3,966.0 (0.700)	3,713.2 (1.00)	346.1 (0.350)	246.5 (0.700)	246.3 (1.00)
	FOBT_CD (0.392-1.00)	8,817.9 (0.392)	3,966.0 (0.783)	3,901.2 (1.00)	283.4 (0.392)	246.5 (0.783)	218.0 (1.00)
	CTC (0.450-1.00)	dominated (0.450)	3,966.0 (0.900)	2,067.1 (1.00)	743.3 (0.450)	246.5 (0.900)	198.3 (1.00)
	OC (0.500-1.00)	17,721.7 (0.500)	3,966.0 (1.00)	—	1,060.6 (0.500)	246.5 (1.00)	—

Specificity	FOBT (0.473-1.00)	10,087.0 (0.473)	3,966.0 (0.946)	3,727.7 (1.00)	641.2 (0.473)	246.5 (0.946)	202.6 (0.100)
	CTC (0.430-1.00)	9,001.2 (0.430)	3,966.0 (0.860)	3,933.1 (1.00)	260.0 (0.430)	246.5	241.9 (1.00)
Testing cost	CTC (JPY23,250-38,750)	5,094.1 (38,750)	3,966.0 (31,000)	2,906.8 (23,250)	405.9 (38,750)	246.5 (31,000)	86.7 (23,250)
	OC (JPY18,750-31,250)	4,037.1 (31,250)	3,966.0 (25,000)	3,309.5 (18,750)	357.2 (31,250)	246.5 (25,000)	112.1 (18,750)
Annual treatment cost by Dukes' stage	low-risk & high-risk polyp (JPY58,500-97,500)	4,051.9 (97,500)	3,966.0 (78,000)	3,827.6 (58,500)	348.1 (97,500)	246.5 (78,000)	dominant (58,500)
	Dukes' A (JPY73,500-122,500)	3,966.2 (122,500)	3,966.0 (98,000)	1,377.8 (73,500)	247.7 (122,500)	246.5 (98,000)	dominant (73,500)
	Dukes' B (JPY706,000-1,177,000)	3,978.0 (706,000)	3,966.0 (942,000)	3,951.6 (1,177,000)	288.9 (706,000)	246.5 (942,000)	232.9 (1,177,000)
	Dukes' C (JPY1,006,000 −1,677,000)	4,406.4 (1,006,000)	3,966.0 (1,342,000)	3,447.2 (1,677,000)	302.5 (1,006,000)	246.5 (1,342,000)	221.9 (1,677,000)
	Dukes' D (JPY3,000,000−5,000,000)	4,131.8 (3,000,000)	3,966.0 (4,000,000)	3,713.3 (5,000,000)	562.8 (3,000,000)	246.5 (4,000,000)	dominant (5,000,000)

* "Base" means basic analyses without any change in variables. "Worst" means cases with the worst cost-effectiveness (largest ICER). "Best" means cases with the best cost-effectiveness (smallest ICER).

* Values in parentheses under variables indicate the range that was changed in the sensitivity analysis. Values in parentheses under ICERs indicate the value of variables corresponding to the ICER.

* "—" indicates the same values as those of the basic analysis.

* "Dominant" means cases where effectiveness was improved (the number of cancer deaths decreased in this case) and cost decreased compared to the control.

* "Dominated" means cases where effectiveness (the number of detected patients with colorectal cancer in this case) was decreased by the introduction of CTC.

Table 12 Results of sensitivity analysis (cost per life year gained)　Unit (10,000)

		ICER (S-1 vs. S-2)			ICER (S-1 vs. S-3)		
	Variable	Worst	Base	Best	Worst	Base	Best
Discount rate	(0%-5%)	916.0 (5%)	780.4 (3%)	604.1 (0%)	78.9 (5%)	48.4 (3%)	9.6 (0%)
Screening uptake rate	FOBT (0.167-0.50)	1,692.0 (0.500)	780.4 (0.167)	—	248.1 (0.500)	48.4 (0.167)	—
	CTC (0.250-0.750)	3,780.8 (0.250)	780.4 (0.500)	462.2 (0.750)	54.1 (0.250)	48.4 (0.500)	44.9 (0.750)
	OC (0.316-0.948)	dominated (0.948)	780.4 (0.632)	505.7 (0.316)	126.4 (0.948)	48.4 (0.500)	25.6 (0.316)
Sensitivity	FOBT_P (0.100-0.300)	1,986.0 (0.300)	780.4 (0.500)	28.1 (0.100)	152.2 (0.300)	48.4 (0.500)	dominant (0.100)
	FOBT_A (0.264-0.792)	1,851.4 (0.264)	780.4 (0.528)	586.0 (0.792)	660.0 (0.264)	48.4 (0.528)	14.8 (0.792)
	FOBT_B (0.350-1.00)	1,818.2 (0.350)	780.4 (0.700)	762.0 (1.00)	72.3 (0.350)	48.4 (0.700)	48.3 (1.00)
	FOBT_CD (0.392-1.00)	1,782.4 (0.392)	780.4 (0.786)	43.2 (1.00)	82.3 (0.392)	48.4 (0.786)	44.8 (1.00)
	CTC (0.450-1.00)	dominated (0.450)	780.4 (0.900)	297.1 (1.00)	179.0 (0.450)	48.4 (0.900)	39.0 (1.00)
	OC (0.500-1.00)	3,559.0 (0.500)	780.4 (1.00)	—	209.6 (0.500)	48.4 (1.00)	—
Specificity	FOBT (0.473-1.00)	1,983.8 (0.473)	780.4 (0.946)	753.2 (1.00)	125.8 (0.473)	48.4 (0.946)	40.1 (1.00)
	CTC (0.430-1.00)	1,770.3 (0.430)	780.4 (0.860)	773.5 (1.00)	51.0 (0.43)	48.4 (0.86)	47.5 (1.00)
Testing cost	CTC (JPY23,250-38,750)	1,002.4 (38,750)	780.4 (31,000)	559.9 (23,250)	79.7 (38,750)	48.4 (31,000)	17.0 (23,250)
	OC (JPY18,750-31,250)	794.4 (31,250)	780.4 (25,000)	762.4 (18,750)	70.2 (31,250)	48.4 (25,000)	24.4 (18,750)
Annual treatment cost by Dukes'	low-risk & high-risk polyp (JPY58,500-97,500)	798.3 (97,500)	780.4 (78,000)	760.3 (58,500)	66.0 (97,500)	48.4 (78,000)	dominant (58,500)
	Dukes' A	784.1	780.4	621.1	48.6	48.4	dominant

stage	(JPY73,500-122,500)	(122,500)	(98,000)	(73,500)	(122,500)	(98,000)	(73,500)
	Dukes' B (JPY706,000-1,177,000)	782.8 (706,000)	780.4 (942,000)	777.6 (1,177,000)	56.7 (706,000)	48.4 (942,000)	45.7 (1,177,000)
	Dukes' C (JPY1,006,000−1,677,000)	794.9 (1,006,000)	780.4 (1,342,000)	773.3 (1,677,000)	59.0 (1,006,000)	48.4 (1,342,000)	41.1 (1,677,000)
	Dukes' D (JPY3,000,000−5,000,000)	813.1 (3,000,000)	780.4 (4,000,000)	730.7 (5,000,000)	562.8 (3,000,000)	48.4 (4,000,000)	dominant (5,000,000)

* "Base" means basic analyses without any change in variables. "Worst" means cases with the worst cost-effectiveness (largest ICER). "Best" means cases with the best cost-effectiveness (smallest ICER).

* Values in parentheses under variables indicate the range that was changed in the sensitivity analysis. Values in parentheses under ICERs indicate the value of variables corresponding to the ICER.

* "—" indicates the same values as those of the basic analysis.

* "Dominant" means cases where effectiveness was improved (the number of cancer deaths decreased in this case) and cost decreased compared to the control.

* "Dominated" means cases where effectiveness (the number of detected patients with colorectal cancer in this case) was decreased by the introduction of CTC.

Table 13 Increase or decrease in the number of patients in each pathological state after the introduction of CTC

Pathological state	Strategy 2	Strategy 3
Low-risk polyp(s)	Increase	Increase
High-risk polyp(s)	Increase	Increase
Dukes' A	Increase then decrease	Increase then decrease
Dukes' B	Decrease	Decrease
Dukes' C	Decrease	Decrease
Dukes' D	Decrease	Decrease

Table 14 Sensitivity of each strategy to the population

	Strategy 1	Strategy 2	vs. Strategy 1	Strategy 3	vs. Strategy 1
Polyp (FOBT sensitivity: 0.100)	0.0106*	0.0372	+0.0266	0.0382	+0.0277
Polyp (FOBT sensitivity: 0.300)	0.0317	0.1115	+0.0798	0.1146	+0.0830
Dukes' A	0.0557	0.1962	+0.1404	0.2017	+0.1460
Dukes' B	0.0739	0.2601	+0.1862	0.2675	+0.1936
Dukes' C & D	0.0826	0.2909	+0.2083	0.2992	+0.2165

*FOBT screening uptake rate × sensitivity of FOBT × OC screening uptake rate × sensitivity of OC if Strategy 1 is performed in a population of 100,000 persons.

If 1,000 of 100,000 persons have a polyp(s), an average of 1,000 × 0.0106 = 10.6 persons are diagnosed to have a polyp(s) from Table 14.

Ⅱ-2. Economic evaluation of MR-guided focused ultrasound surgery (FUS) for uterine fibroids

Ⅱ-2-1. Introduction

Uterine fibroid is a benign tumor that is common in women aged in their 30s or 40s. About 20% to 30% of adult women are estimated to have this disease. Asymptomatic uterine fibroid is often untreated, but when the myoma enlarges, symptoms such as dysmenorrhea and anemia develop and treatment becomes necessary. Treatment methods include drug therapy using hormone agents and surgery. A typical surgical therapy is a total hysterectomy. A total hysterectomy is performed by laparotomy or laparoscopy. This method does not involve the risk of recurrence because the uterus is totally removed. However, patients become infertile and cannot bear a child after surgery because the uterus is removed. As uterine fibroids are especially common in women before childbirth, treatment methods that can preserve fertility are attracting attention. One of such methods is myomectomy. Because this method removes only the myoma, fertility is retained. Surgery is performed by either laparotomy or laparoscopy, and whether surgery is indicated for the myoma is determined based on its type, size, and location. In addition, hospitalization is required because this is a surgical method, and there are also physical burdens and bleeding risks. Meanwhile, MR-guided focused ultrasound surgery (hereinafter referred to as FUS) that treats uterine fibroid without surgery is also attracting attention recently[1)]. FUS induces necrosis of the myoma by delivering focused ultrasound and increasing the temperature to 60 to 90°C. Ultrasound is delivered after the precise position is defined by MRI, because it is necessary to identify the position to focus the ultrasound precisely. It is an up-and-coming treatment method with less physical burden and without the need for hospitalization or anesthesia. On the other hand, this technology requires a large amount of individual payments by patients, as it is not covered by the Japanese medical insurance system. Essentially, technologies that provide clinically remarkable results should be covered by a public medical insurance system. FUS is still at the stage of evaluation, however, partly because the number of patients who have taken FUS is small. Treatment requires special instruments that cost a lot of money. It is important to assess the economy of the method as a part of evaluation.

Another treatment method is uterine artery embolization (hereinafter referred to as UAE). This method reduces the size of the myoma by embolizing the artery that supplies the uterine fibroid with nutrients. As with FUS, UAE is not covered by the public medical insurance system in Japan.

In this study, the economy of FUS for uterine fibroids was evaluated from the position of public medical cost payers. Myomectomy, which preserves fertility as with FUS and has already been covered by insurance, was used as the control.

Ⅱ-2-2. Method

In this study, evaluation was performed using the following method to assess the economy of FUS compared to myomectomy.

Women with uterine fibroids for which FUS is adopted were assumed as patients in this study. The treatment option was whether FUS or myomectomy would be performed. It was assumed that a total hysterectomy would be performed when the disease recurs, because there are risks of unrelieved symptoms or recurrence in both cases. The course of treatment was described using a decision tree model, and the expected values of cost and outcome when either FUS or myomectomy were selected were calculated (Fig.1). The transition probability in the decision tree model was based on data on treatment results in Japan[2)] and overseas literature[3,4)]. The probability of relieving symptoms was set at 0.92 and 0.90 for FUS and myomectomy, respectively (Table.1). There was a risk of recurrence in both cases. The recurrence rate within 6 months was defined as 0.06 and 0.05 for FUS and myomectomy, respectively. Although there have been no reports of serious adverse events for FUS, myomectomy has risks of adhesion of intraperitoneal organs, injury of the intestinal tract, and sometimes death. The risk of death was defined as 0.002, and the probability of serious adverse events other than death was defined as 0.02.

In the cost calculation, only the medical cost was calculated from the position of medical cost payers under the public medical insurance system (Table.2). The cost was based on the medical remuneration point chart in Fiscal 2010. In the case of myomectomy, it was assumed that a ten-day hospitalization and cost of JPY598,180 were necessary. Although FUS is currently not covered by insurance, its cost was included by assuming insurance coverage. In the base case, a cost of JPY600,000 was assumed in reference to the price at institutions that adopt this technology. In the case of a total hysterectomy, it was assumed that ten-day hospitalization and a cost of JPY625,340 were necessary. Although the cost to treat adverse events associated with myomectomy is different depending on the event, a uniform cost of JPY100,000 was assumed in the base case and sensitivity analysis was performed.

Quality adjusted life years (hereafter referred to as QALY) were used as the outcome measure. Recently, QALY is often used for economic evaluation of medical technologies or drugs. As this value incorporates both survival and QOL, it is used for discussion about distribution of medical resources to various medical technologies or drugs. In this study, an evaluated value of QOL for the state of uterine fibroids was obtained from the literature[3)] and used in the calculation. The evaluated value of QOL was 0.67 for uterine fibroids and 0.76 when symptoms were relieved by

treatment(Table.3).

Because occurrence within one year was modeled for the course of treatment, the cost was not discounted. The expected survival when the patient survived after one year was calculated by hypothesizing twenty years after discount.

A one-way sensitivity analysis was performed by assuming the case where the cost of FUS was changed.

Ⅱ-2-3. Results

In the base case, the expected value of the cost was JPY684,546 and JPY690,673 for FUS and myomectomy, respectively, indicating that the cost was JPY6,127 lower in FUS (Table.4). The expected value of outcome was 20.754 QALY and 20.721 QALY for FUS and myomectomy, respectively, indicating that the outcome was 0.042 QALY higher in FUS. FUS was considered to be dominant because of the lower expected cost and higher expected effectiveness.

The results of the sensitivity analysis showed that additional cost was generated when the cost of FUS and some other factors changed compared to myomectomy, but this was considered to be within the economically acceptable range (Fig.2).

Ⅱ-2-4. Discussion

In the analysis of the base case, FUS reduced the cost and increased expected QALY compared to myomectomy. In the sensitivity analysis, it was suggested that there were effects of the change in the cost.

Studies on economic evaluation of FUS for uterine fibroids have been conducted in several foreign countries. O'Sullivan *et al.* (2009) evaluated total hysterectomy, myomectomy, FUS, and UAE compared to drug therapy. Drug therapy was the most inexpensive, followed by total hysterectomy, FUS, UAE, and myomectomy. FUS required US$41,400 per increase of 1 QALY compared to total hysterectomy, which was more dominant than myomectomy. The total cost is considered to be higher for FUS or myomectomy that may require treatment when the disease recurs, while it is enough to consider the one-time treatment cost for a total hysterectomy because the disease does not recur. This study also included the labor loss due to treatment in the evaluation from the position of society. This part was larger for a total hysterectomy or myomectomy that require hospitalization than for FUS. In the first place, the problem remains as to whether a total hysterectomy should have

been included in the option, because fertility was not taken into account.

Zowell *et al.* (2008)[4] performed economic evaluation by comparing FUS to other treatment methods (total hysterectomy, myomectomy, and UAE) from the position of the NHS in the U.K. In the base case, FUS reduced more cost, acquired higher QALY and was more dominant than the combination of other treatment methods based on the rate of implementation. This result did not change if the rate of implementation of other treatment methods changed. However, the total cost increased when hospitalization cost due to other treatment methods became cheaper or when the cost of FUS increased.

In the U.K., NICE (National Institute for Health and Clinical Excellence) evaluated individual medical technologies. The guidance for FUS issued in November 2011 suggested that short-term evaluation of efficacy and safety was appropriate, but long-term efficacy and fertility should be studied further[5]. The guidance also described the necessity of explaining about the possibility of recurrence or adverse events to patients and the procedure should be performed by physicians who have received special education. The guidance did not refer to the economy.

Similar to the above overseas study results, the present study showed that FUS was more dominant (cost decreased and effectiveness increased) than myomectomy. Unlike myomectomy, the cost of FUS is lower because hospitalization is unnecessary and serious adverse events do not occur. The necessary cost when the disease recurs is expected to be equivalent because the possibility of recurrence is almost the same. Therefore, the difference in the initial cost of implementation is considered to be influential. Based on the present study, it was considered that FUS is more economical than myomectomy in patients for whom FUS is indicated.

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1.

Table 1 Transition probability

	Myomectomy	FUS
Symptom relief	0.90	0.92
Recurrence within 6 months	0.05	0.06
Serious adverse events	0.02	0.00
Death	0.002	0.00

Table 2 Cost

Myomectomy	JPY
Charge for hospitalization	222,260
Charge for surgery	188,500
Charge for anesthesia	114,300
Charge for blood transfusion	15,000
Other	58,120
	598,180
FUS	600,000
When adverse events occur	100,000

Table 3 Evaluated value of QOL

	Evaluated value
Uterine fibroids (symptomatic)	0.67
Symptom relief	0.76

Table 4 Results (base case)

	Myomectomy	FUS	Increment
Expected cost (JPY)	690,673	684,546	-6,127
Expected effectiveness (QALY)	20.712	20.754	0.042

Fig. 1 Decision tree model for FUS and myomectomy

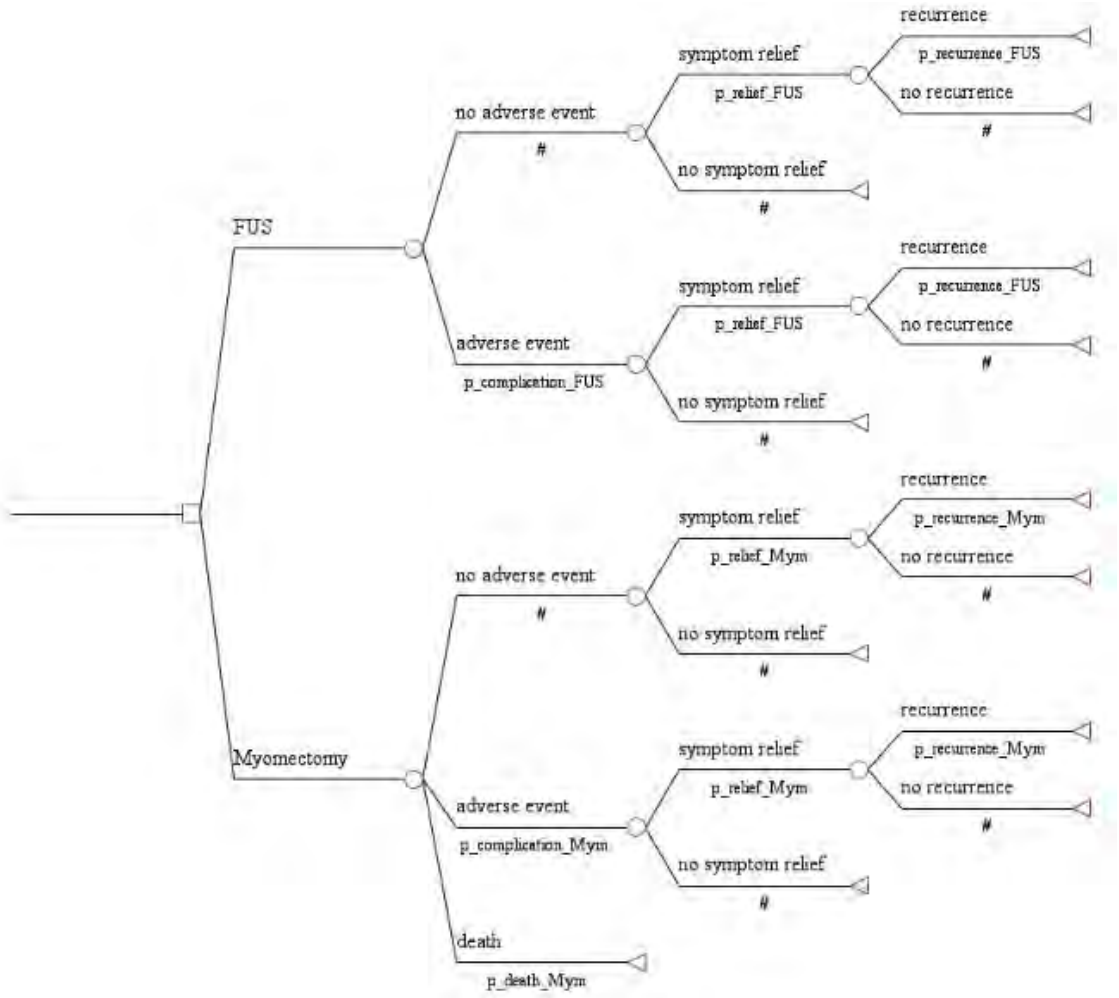
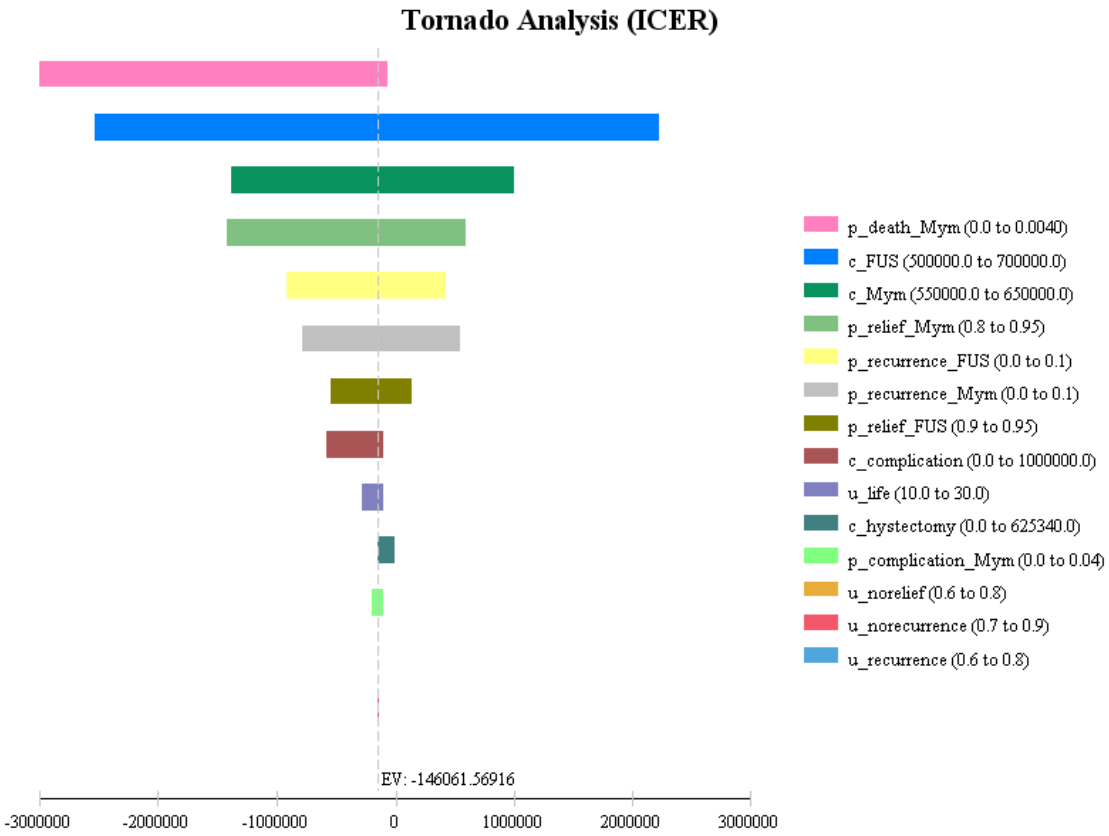


Fig. 2 Result of one way sensitivity analysis



Ⅲ. Outlook of economic evaluation of capital equipment

Installation of capital equipment requires large initial investment. In order to make appropriate evaluation, it is necessary to undertake evaluation based on various intended use. It should be noted, however, that it is difficult to evaluate all expected intended use in a single analysis. One method of evaluating medical devices is based on the value of medical practice using such devices. This study report attempts to describe the economic evaluation for the following two subjects: 1) CT-based colorectal cancer screening and 2) MR-guided focused ultrasound surgery (FUS) for uterine fibroids. A model was constructed for each of the two approaches compared to other technologies to assess cost-effectiveness. Several issues were revealed during this process.

The first issue is the limitation of data. When economic evaluation is performed, it is first necessary to assess efficacy and safety. Although the efficacy and safety of drugs are evaluated by clinical trial in general, the number of appropriately controlled clinical studies is limited for technologies using capital equipment. In the present instance, estimation of the efficacy and safety was based on overseas clinical studies and data of use from limited institutions in Japan. Ideally, there should be Japanese clinical studies that evaluate the efficacy and safety of a technology directly compared to the control technology in the economic evaluation. Because such technologies are not readily available, the evaluation had to be undertaken with limited situations.

The second issue is price setting. All of the technologies assessed in the present study are currently paid by patients themselves because they are not covered by either public screening systems nor medical reimbursement (note: CTC is reimbursed as of April 2012). All analyses were performed from the position of medical cost payers by assuming coverage by a public medical system. In these analyses, the prices of these technologies were based on the individual payments of patients under the current system. Because the amount paid by the patients themselves is different depending on the institution, the prices were set based on examples at representative institutions. Moreover, the current price for the technologies may not be the same as the reimbursement, even if it would be introduced in the future. Considering the current structure where the price of a new medical technology is often not the same as the reimbursement desired by medical institutions or related academic societies, it is necessary to further discuss how to set the prices of new medical technologies.

The third issue is how to utilize the results of economic evaluation. In some foreign countries, the results of economic evaluation are used for the choice of medical practice provided under a public medical security system. In Japan, such discussion has just begun and vigorous debate about how to

apply these results should be encouraged. A method that can evaluate the value of medical devices appropriately is necessary towards that end. As mentioned earlier, some medical devices are used for multiple purposes, and it is thus necessary to assess each of the intended use. Further studies are necessary as to what kind of technologies using medical devices should be included in the economic evaluation and how the cost for installation or improvement of accompanying computer software should be handled.

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