Cost–utility analysis of an advanced pressure ulcer management protocol followed by trained wound, ostomy, and continence nurses

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ABSTRACT

The high prevalence of severe pressure ulcers (PUs) is an important issue that requires to be highlighted in Japan. In a previous study, we devised an advanced PU management protocol to enable early detection of and intervention for deep tissue injury and critical colonization. This protocol was effective for preventing more severe PUs. The present study aimed to compare the cost-effectiveness of the care provided using an advanced PU management protocol, from a medical provider's perspective, implemented by trained wound, ostomy, and continence nurses (WOCNs), with that of conventional care provided by a control group of WOCNs. A Markov model was constructed for a 1-year time horizon to determine the incremental cost-effectiveness ratio of advanced PU management compared with conventional care. The number of quality-adjusted life-years gained, and the cost in Japanese yen (¥) ($US1 = ¥120; 2015) was used as the outcome. Model inputs for clinical probabilities and related costs were based on our previous clinical trial results. Univariate sensitivity analyses were performed. Furthermore, a Bayesian multivariate probability sensitivity analysis was performed using Monte Carlo simulations with advanced PU management. Two different models were created for initial cohort distribution. For both models, the expected effectiveness for the intervention group using advanced PU management techniques was high, with a low expected cost value. The sensitivity analyses suggested that the results were robust. Intervention by WOCNs using advanced PU management techniques was more effective and cost-effective than conventional care.

The prevalence of pressure ulcers (PUs) in Japan has been reported to be 2.0%,[1] which is lower than the prevalence of 12.3% reported by the International Pressure Ulcer Prevalence Survey.[2] However, severe PUs defined as full-thickness skin loss account for 43.0% of the PUs that develop in Japanese patients,[1] which is much higher than the 14% reported by another survey.[3] Thus, although preventive measures are well-applied in Japan, the high prevalence of severe PUs is an important issue that requires to be highlighted, particularly because patients with severe PUs often either require long-term hospitalization or have comorbidities, such as infection.[4,5] Thus, these extended hospitalizations are associated with higher costs, which represent a significant unnecessary cost to the health and social care system.[6,7] Recently, pathological examinations have focused on deep tissue injury (DTI) caused by PU deterioration. Furthermore, the concept of critical colonization, in which wound healing may be delayed in the absence of the typical clinical features of infection, is being increasingly recognized.

In a previous study,[8] we devised an advanced PU management protocol to enable early detection of and intervention for DTI and critical colonization. Furthermore, we demonstrated the effectiveness of such a protocol implemented by wound, ostomy, and continence nurses (WOCNs). An advanced PU management protocol based on a review of the literature and opinions from experts was devised to prevent deterioration and facilitate healing. In the past, DTI and critical colonization could be assessed only grossly,[9] and intervention was thereby delayed, which resulted in severe PUs and delayed healing.[10] On the basis of objective indices provided by ultrasonography and a noncontact thermometer, care can be provided in a timely

manner, which may prevent severe PUs and accelerate healing. This protocol included six steps: (1) ultrasonography to assess deep tissue; (2) use of a noncontact thermometer to detect critical colonization;[11] (3) conservative sharp debridement; (4) dressing selection; (5) negative-pressure wound therapy; and (6) vibration therapy as an adjunct treatment to improve tissue microcirculation.[8]

This advanced PU management protocol is effective in terms of preventing more severe PUs; however, there has not been an economic evaluation. Therefore, the present study evaluated the economic efficiency of introducing this protocol in clinical practice. The present study aimed to compare the cost-effectiveness from the medical provider perspective of care provided by trained WOCNs who followed an advanced PU management protocol with that of a control group of WOCNs who provided conventional care.

METHODS

A decision analytics model with a cohort model of 75-year-old patient was constructed for a 1-year time horizon to compare the incremental cost-effectiveness ratio (ICER) of advanced PU management with that of conventional care. Model inputs were taken from the data of a previous study,[8] which was a multicenter, 3-week, prospective survey, clustered, nonrandomized, controlled trial conducted between July and December 2009 across Japan.[8] The present study used the pooled data of both the intervention group and control group from the original trial.

The study protocol and documents were submitted to and approved by the Research Ethics Committee of the University of Tokyo, Graduate School of Medicine (#2,436) and of each participating institution.

Model and time horizon

A Markov model (Figure 1) was constructed (TreeAge Pro 2015 Software INC., Williamstown, MA) on the basis of the wound-healing process; the model was used to compare the cost-effectiveness of advanced PU management with that of conventional care. The health statuses used in the model were d1/2, D3/4/5, DU, and healed according to the depth, exudate, size, infection/inflammation, granulation tissue, necrotic tissue, and pocketing (DESIGN-R) score.[12–14] The DESIGN-R validated PU status assessment tool included assessment of the depth, exudate, size, infection/inflammation, granulation tissue, necrotic tissue, and pocketing. The total score was calculated from six items, excluding the depth, and ranged from 0 to 66 points, with higher scores representing more severe PUs. The inter-rater reliability and predictive validity for wound healing of this scale have been established previously.[12–14]

Patients could experience continuous progression of PU states defined by the depth scores of d1/2 (d1, persistent redness; d2, lesion extends into dermis), D3/4/5 (D3, lesion extends into the subcutaneous tissue; D4, lesion extends to muscle, tendon, and bone; D5, lesion extends into the articular or body cavity or is impossible to measure the depth), and DU (unstageable for necrotic tissue) over 3-week cycles for up to 17 stages. A 1-year time horizon means that essentially most of the PUs were considered to have healed. Generally, a 2-week period is recommended for evaluation;[15] however, one Markov cycle length corresponded to 3 weeks because the original study focused on DTI and critical colonization.[8] Thus, DTI required a 3-week period for evaluation because DTI does not involve disruption of the skin integrity initially.[16]

Mortality and recurrent PU after healing were not incorporated into the model because the duration of analysis was only 1 year.

Costs

The cost items were calculated by microcosting. Treatment costs and labor costs for health professionals were determined as direct-cost items. Costs of intervention, such as ultrasonography, noncontact thermometer, and vibration, were calculated according to the frequency of use. Capital costs for apparatuses used in advanced PU management were calculated on the basis of straight-line depreciation over a 5-year service life from the purchase unit price. The cost of ultrasound as precision equipment was calculated to depreciate over a 4-year service life. Costs of treatment materials, such as tape and gauze, were calculated according to amount used and market product price. For ointment and dressing costs, the National Health Insurance reimbursement list and drug price were used. Labor costs were calculated by the fiscal year 2013 Basic Survey on Wage Structure mean wages[17] for each job category to calculate wages per hour on the basis of actual recording of time spent on treatment. Considering that pressure redistribution mattresses were selected for treatment purposes, calculations of the costs of use of pressure redistribution mattresses were included.

For the purpose of this study, the analysis was performed from the viewpoint of the medical provider, so direct nonhealth care costs paid by the patient were not calculated. In addition, overhead costs, such as medical facility costs (land, buildings), whether or not the intervention was performed, shared services (administrative departments, other), preparation of medical facility, and fuel, were not included. For currency conversion purposes, it was assumed that ¥10,000 was equivalent to $US83.3 ($US1 = ¥120; 2015).

The average treatment costs and standard deviations for 3 weeks for each health state are shown in Table 1. Discounting was not applied considering the 1-year time horizon for this model.

Probabilities

Probabilities from the original study were used in the model to direct the probability of different health states at each division node (Table 1). A researcher and a plastic surgeon determined the health states on the basis of photographs taken during the initial intervention and after 3 weeks, without evaluating the exudate amount, wound size, and pocketing (undermining). For the researcher and a plastic surgeon who were both blinded to the two protocol groups, the intraclass correlation coefficient was 0.85.

Two models were created, and simulations were performed with 100% distribution on d1/2 for the first cohort in Model 1 and 100% distribution on D3/4/5 in Model 2. By analyzing Models 1 and 2, it was possible to simulate changes in the severity of PUs over 1 year. In particular, it

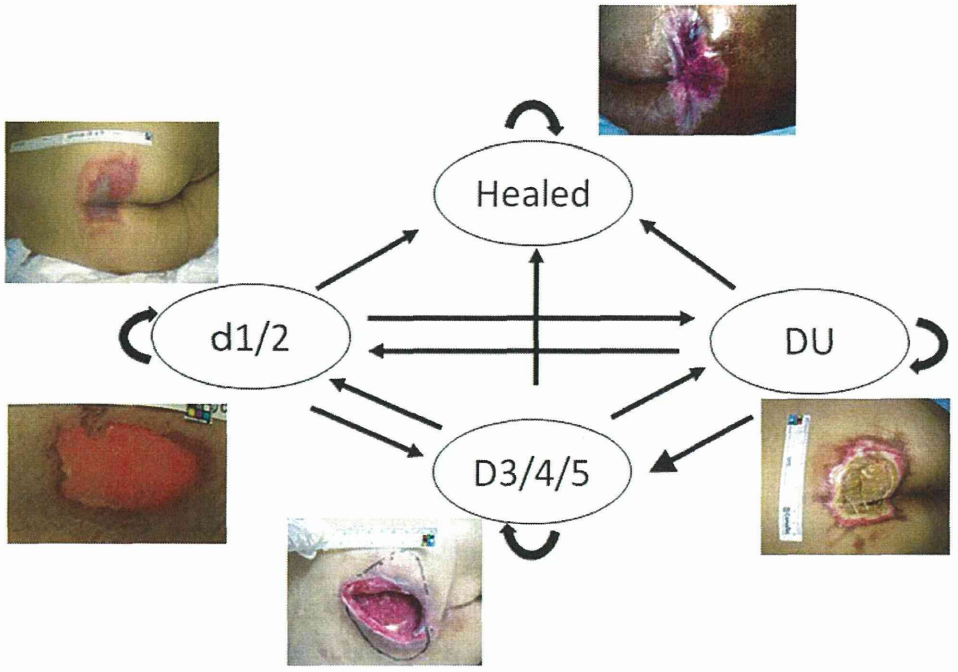

Figure 1. Morkov Model depicting the management of PU. Note: The health states used in the model were d1/2, D3/4/5, DU, and healed and were based on the DESIGN-R scores. Patients could experience continuous progression of PU states d1/2, D3/4/5, and DU over 3-week cycles for up to 17 stages. D3/4/5 were based on the depth scores (d, D score) of the DESIGN-R tool. DU, (unstageable). PU, pressure ulcer.

was possible to clarify the effectiveness of advanced PU management techniques for severe PUs using Model 2.

Utilities

The utilities for various health states with this model were obtained from the literature: grade 1/2 was 0.68, grade 3/4 was 0.36, and healing PU was 0.8.[18] Primary data were not available in the literature for the utility score of DU; this model used the 0.36 score from the previous report,[14] which was based on the healing speed being comparable with that of D3/4/5 (Table 1). We estimated the standard deviation of each utility by varying the base utility case estimates over a range of ±50%.

Sensitivity analyses

The univariate sensitivity analyses were performed by varying the base case estimates by ±20.0% and assessing the impact on the model results. Ranges for costs were derived from the 95% confidence intervals of the original data and are summarized in Table 1.

A Bayesian multivariate probability sensitivity analysis was performed using Monte Carlo simulations with advanced PU management. Probability sensitivity analysis applied a distribution for each variable to characterize the impact of uncertainty on all parameters simultaneously. Beta distributions were used for variables with values ranging between 0.0 and 1.0 (i.e., probabilities), and gamma distributions were used for two parameters (utilities and costs), considering the means. The result of this analysis enabled a cost-effectiveness acceptability curve to be constructed, showing the probability of advanced PU management to be cost-effective at varying levels of willingness to pay for additional quality-adjusted life-years (QALY).

RESULTS

Cost–utility analysis

The results of the cost–utility analysis using the Markov model are shown in Table 2. Two different models were created for initial cohort distribution, and for both models, the expected effectiveness for the intervention group using advanced PU management techniques was high, with a low expected cost value, which meant that advanced PU management was dominant. In particular, in Model 2 in which severity was D3/4/5, the expected cost value for the intervention group for 1 year was ¥130,567, whereas it was approximately twice as high for the control group at ¥256,068. The QALY value was 0.07 QALY higher for the intervention group, which showed a greater effectiveness for the severe PU model.

The results of distribution simulations for Models 1 and 2 are shown in Table 3. In Model 1, 99.7% of the d1/2 intervention group had healed after 1 year, and only 0.23% of PUs had worsened from d1/2 to D3/4/5 and not healed

Table 1. The details of the data associated with treatment of PUs based on original study

Markov state	Base value probabilities		Sensitivity range
Intervention group			
d1/2 → Healed	0.67		0.54–0.80
d1/2 → D3/4/5	0.00		0.00–0.02
d1/2 → DU	0.05		0.04–0.06
D3/4/5 → Healed	0.13		0.10–0.15
D3/4/5 → d1/2	0.10		0.08–0.12
D3/4/5 → DU	0.08		0.06–0.09
DU → Healed	0.00		0.00–0.02
DU → d1/2	0.11		0.08–0.13
DU → D3/4/5	0.56		0.44–0.67
Control group			
d1/2 → Healed	0.60		0.48–0.72
d1/2 → D3/4/5	0.01		0.01–0.02
d1/2 → DU	0.14		0.11–0.17
D3/4/5 → Healed	0.09		0.07–0.11
D3/4/5 → d1/2	0.00		0.00–0.02
D3/4/5 → DU	0.16		0.13–0.19
DU → Healed	0.05		0.04–0.05
DU → d1/2	0.07		0.05–0.08
DU → D3/4/5	0.34		0.27–0.41
	Utilities	(SD)	Range
Intervention/control group			
d1/2	0.68	(0.34)	0.54–0.82
D3/4/5	0.36	(0.18)	0.29–0.43
DU	0.36	(0.18)	0.29–0.43
Healed	0.80	(0.40)	0.64–0.96
	Cost	(SD)	95%CI
Intervention group			
d1/2	16,218	(17,562)	10,746–21,691
D3/4/5	22,754	(12,855)	18,587–26,921
DU	50,111	(35,545)	32,435–67,787
Healed	0	0	0–0
Control group			
d1/2	13,742	(13,124)	10,658–16,826
D3/4/5	35,297	(27,576)	25,519–45,075
DU	26,295	(25,037)	18,683–33,907
Healed	0	0	0–0

Notes: Cost (¥)
SD, standard deviation; CI, confidence interval.

after 1 year. In comparison, 96.5% of the PUs in the control group had healed, whereas 3.2% of PUs had not healed after 1 year.

In Model 2, which represented severe PUs at D3/4/5, 97.6% had healed after 1 year in the intervention group, whereas 2.0% of PUs remained at the severe level of D3/4/5 or DU. In contrast, in the control group, 86.0% of severe PUs had healed, whereas 13.0% remained as severe PUs after 1 year, with 8.7% classed as D3/4/5 and 4.3% as DU.

Sensitivity analysis

Results of the univariate sensitivity analysis on Model 1, which varied the utility values, costs, and values for transition probability, showed that parameters with a high effect on ICER were utility values for the state of healing from d1 in the control group, total mean costs for D3/4/5 in the control group, utility values for the state of DU from d1 in the control group, total mean costs for DU in the control group, and total mean costs for d1/2 in the control group; however, none of the parameters affected the dominant result. Similarly, in Model 2, the intervention group remained dominant even when the parameter values were changed.

Probabilistic sensitivity analysis using Monte Carlo simulation was also performed, and when ICER threshold values for 1 QALY were set at ¥0–7 million, the cost effectiveness acceptability curves for Models 1 and 2 showed that the probability of ICER falling into the threshold values was 86.0%–89.0% (Figure 2).

DISCUSSION

The originality of the present study is that it is the first to show empirical clinical evidence of the efficiency of an advanced PU management protocol for DTI and critical colonization, which are issues associated with severe PUs. Results of simulation of the process of healing PUs using models for analysis have shown high effectiveness and low cost. Evaluating this evidence against the five grades of recommendation for "grades of recommendation for the adoption and appropriate utilization of new technologies" advocated by Laupacis et al., the evidence fits the highest priority standard of "compelling evidence for adoption and appropriate utilization";[19] therefore, the evidence suggests that the PU management protocol deserves to be introduced as a top priority.

The Markov model analysis results for Model 2 showed that 97.6% of severe PUs in the intervention group healed within 1 year, whereas the rate of healing for the control group remained at 86.0%. Previous studies have reported estimated values for healing within 1 year of 78.8% for Stage III and 59.1% for Stage IV;[20] comparison with these results suggests that the effectiveness of intervention in the present study can be considered high.

Cohort distribution results for Model 1 show that the rates of progression of DU from d1/2 PUs to severe PUs in 3 weeks (1 stage after) from the start of intervention were 4.8% for the intervention group and 13.9% for the control group. This progression of DU from d1/2 may indicate DTI. After 1 year, the percentage of PUs that had not healed in the intervention group was 0.3%, whereas it was higher (3.5%) in the control group. This suggests that the introduction of advanced PU management techniques can prevent aggravation through DTI and that introduction of the technique could have considerable clinical significance.

A high expected QALY was obtained for the intervention group for both models in the Markov model results. The gap with the control group was largest in Model 2 for severe PUs, with an incremental effect of 0.07 QALY.

Table 2. The results of the cost–utility analysis using the Markov model

Model	Cost(yen)*	⊿ Cost(yen)	QALY	⊿ QALY	ICER(yen/QALY)
Model 1. d1/2					
Control	67,907	—	0.74	—	—
Intervention	35,217	−32,690	0.77	0.03	Dominant
Model 2. D3/4/5					
Control	256,068	—	0.59	—	—
Intervention	130,567	−125,501	0.66	0.07	Dominant

Note: Yen; ¥10,000 = $US83.3 (as of 2015).
ICER, incremental cost-effectiveness ratio.

Considering that the incremental effect in Model 1, which was the minor PU model, was 0.03 QALY, it can be argued that the impact of intervention through advanced PU management techniques is particularly observable for severe PUs, for which improvement in patient quality of life (QOL) through intervention is marked. Previous studies[18] evaluating new techniques related to PUs by analyzing cost effectiveness have reported an incremental effect of 0.01–0.03 QALY for new techniques. Although the intervention technique in the present study was different, it seems that the incremental effect of 0.07 QALY in the present study is high as an intervention effect for PUs. Effects of PUs on health-related QOL have been reported for problems, such as pain and distress in changing body position, change in body image, loss of privacy through treatment, and isolation from family and friends.[21–24] These negative effects have been reported to particularly escalate as the severity of the ulcer increases.[24] Through prevention of severe PUs and promotion of healing of severe PUs, intervention through advanced PU management techniques can make a substantial contribution to the improvement of health-related QOL of patients.

In model analysis, sensitivity analysis was performed for the parameters, but none of the results had an effect on dominance, which suggested that the results were robust even if some of the parameters were uncertain. The present study focused on differential effects between the intervention and control groups, so estimations of overhead costs, such as basic hospital inpatient costs and the time required for preventive care (for example, changing body position), were not included. For this reason, the results do not reflect the full costs required for all aspects of PU treatment, and this should be considered in any comparison with other research results.

The utility value used in the present study was extrapolated from previous studies, and the results were measured by medical staff on a rating scale. It has been reported that, generally, utility values obtained from proxy assessment tend to be lower than those obtained by patient assessments.[25] However, because the focus of the present study was on the difference in the effects between the intervention and control groups, it is unlikely that any uncertainty in parameters because of assessments being made by medical staff had much effect. Sensitivity analysis of the utility value was performed by changing the value ±20.0%; however, there was yet no change in the dominant result. Therefore, the results appeared to be robust.

In terms of transition probability, one-way sensitivity analysis with changing of the value ±20.0% was performed; however, there was no change in the dominant result. In the cost-effectiveness acceptability curve obtained through probabilistic sensitivity analysis, ICER stayed within threshold levels for the intervention group in Models 1 to 2 at a

Table 3. The results of 1-year distribution simulations for Models 1 and 2 unit : %

	Health states after 1 year	Intervention group	Control group
Model 1	Healed	99.7	96.5
	Severe PU (D3/4/5,DU)	0.23	3.2
Model 2	Healed	97.6	86.0
	Severe PU (D3/4/5,DU)	2.0	13.0

Notes: D3/4/5, based on the depth score (D score) of the DESIGN-R tool; DU, (unsteageable)

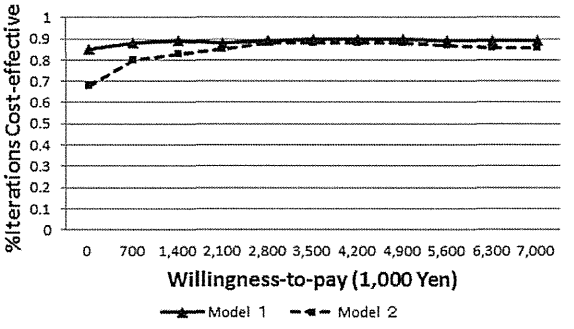

Figure 2. The cost effectiveness acceptability curve. Note: ICER stayed within threshold levels for the intervention group in Models 1 to 2 at a rate of ≥80.0 percent. ICER, incremental cost-effectiveness ratio.

rate of ≥80.0%, which stochastically supported the high efficiency of advanced PU management techniques.[26]

Estimations were made for the economic effect of the introduction of advanced PU management techniques to a 500-bed (N) general hospital. The case hypothesized for these estimations was severe PUs and was based on the assumption of a mean bed occupancy rate of 81.0%[27] and PU prevalence rate (Pr) of 2.0%,[1] of which 43.0% were severe PUs (Ra) at ≥Stage III.[1] The mean hospital stay was assumed to be 30.6 days.[27] On the basis of these assumptions, the number of patients with severe PUs per year could be estimated as follows: $N \times 0.81 \times Pr \times Ra \times 365/30.6 = 41.5$ persons per year. Based on the figure of ¥125,501 in Model 2, that is, the difference between PU treatment costs of the intervention group and control group, estimations of the amount for the sum of 41.5 persons show a cost difference of approximately ¥5.2 million per year.

The total number of hospital beds in Japan in 2013 was 1,573,772.[27] On the basis of this fact, the effect on medical costs across Japan was estimated using the formula above. In this case, the number of patients with PUs would be 130,767, and assuming intervention through the introduction of advanced PU management techniques for these patients, it is estimated that approximately ¥16.4 billion could be saved per year, which would be extremely efficient in national health care cost budget cuts.

In the present study, death and recurrence were not established as situation parameters. It is extremely rare for PUs to be a direct cause of death, and the mean age of the patients in the model was 75 years, an age at which the rate of natural death for men is 0.030 and for women is 0.013[28]; thus, the effect on results over the analysis period of 1 year was considered to be extremely small. Similarly, regarding recurrence of PUs, both the intervention group and control groups in the study received conservative treatment, so there were no factors contributing to different rates of recurrence between the two groups, and this effect was not studied because the period of analysis was 1 year.

The utility values used in the model analysis were based on values used in previous studies, and utility values used in research conducted outside Japan were used. There is a possibility that health preferences of Japanese people differ, but data from surveys of PU patients in Japan do not exist, so there is a limitation in the data that can be extrapolated.

CONCLUSIONS

The aim of the present study was to examine the effectiveness of an advanced PU management technique protocol by evaluating its efficiency and the possibility for clinical introduction through implementation of a cost–utility analysis in which QALY and medical costs were estimated. Analysis performed using Markov models over a 1-year time horizon resulted in clarification of the following points:

1. Intervention by WOCNs using advanced PU management techniques was more effective and cost less than existing management care, which indicated high efficiency.
2. Results of cost-effectiveness acceptability curves produced through probabilistic sensitivity analysis supported the high efficiency of the technique, with an ICER probability within 86.0%–89.0% of threshold values for the intervention group.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

REFERENCES

1. Takeda T, Shido K, Abe M, Tanaka K, Noguchi M, Hashimoto I, et al. Surveillance Committee Report 2013. *Jpn J Press Ulcers* 2015; 17: 58–68. Japanese.
2. VanGilder C, Arnlung S, Harrison P, Meyer S. Results of the 2008-2009 International Pressure Ulcer Prevalence (TM) survey and a 3-year, acute care, unit-specific analysis. *Ostomy Wound Manage* 2009; 55: 39–45.
3. VanGilder C, MacFarlane GD, Harrison P, Lachenbruch C, Meyer S. The demographics of suspected deep tissue injury in the United States: an analysis of the International Pressure Ulcer Prevalence Survey 2006-2009. *Adv Skin Wound Care* 2010; 23: 254–61.
4. Han H, Lewis VL Jr, Wiedrich TA, Patel PK. The value of Jamshidi core needle bone biopsy in predicting postoperative osteomyelitis in grade IV pressure ulcer patients. *Plast Reconstr Surg* 2002; 110: 118–22.
5. Scott JR, Gibran NS, Engrav LH, Mack CD, Rivara FP. Incidence and characteristics of hospitalized patients with pressure ulcers: State of Washington, 1987 to 2000. *Plast Reconstr Surg* 2006; 117: 630–4.
6. Bennett G, Dealey C, Posnett J. The cost of pressure ulcers in the UK. *Age Ageing* 2004; 33: 230–5.
7. Brem H, Maggi J, Nierman D, Rolnitzky L, Bell D, Rennert R, et al. High cost of stage IV pressure ulcers. *Am J Surg* 2010; 200: 473–7.
8. Kaitani T, Nakagami G, Sugama J, Tachi M, Matsuyama Y, Miyachi Y, et al. Evaluation of an advanced pressure ulcer management protocol followed by trained wound, ostomy, and continence nurses: a non-randomized controlled trial. *Chronic Wound Care Manage Res* 2015; 2: 39–51.
9. Black J, Baharestani MM, Cuddigan J, Dorner B, Edsberg L, Langemo D, et al. National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. *Adv Skin Wound Care* 2007; 20: 269–74.
10. Edwards R, Harding KG. Bacteria and wound healing. *Curr Opin Infect Dis* 2004; 17: 91–6.
11. Nakagami G, Sanada H, Iizaka S, Kadono T, Higashino T, Koyanagi H, et al. Predicting delayed pressure ulcer healing using thermography: a prospective cohort study. *J Wound Care* 2010; 19: 465–6, 468, 470.
12. Matsui Y, Furue M, Sanada H, Tachibana T, Nakayama T, Sugama J, et al. Development of the DESIGN-R with an observational study: an absolute evaluation tool for monitoring pressure ulcer wound healing. *Wound Repair Regen* 2011; 19: 309–15.
13. Sanada H, Moriguchi T, Miyachi Y, Ohura T, Nakajo T, Tokunaga K, et al. Reliability and validity of DESIGN, a

tool that classifies pressure ulcer severity and monitors healing. *J Wound Care* 2004; 13: 13–8.
14. Sanada H, Iizaka S, Matsui Y, Furue M, Tachibana T, Nakayama T, et al. Clinical wound assessment using DESIGN-R total score can predict pressure ulcer healing: Pooled analysis from two multicenter cohort studies. *Wound Repair Regen* 2011; 19: 559–67.
15. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance; Hasler E (ed.) Prevention and treatment of pressure ulcers: quick reference guide. Perth, Australia: Cambridge Media, 2014.
16. Sato M, Sanada H, Konya C, Sugama J, Nakagami G. Prognosis of stage I pressure ulcers and related factors. *Int Wound J* 2006; 3: 355–62.
17. Japan Rōdōshō Seisaku Chōsabu. Chingin Sensas Rōdō jikan seido to rōdō hiyō no jittai: chingin, rōdō jikan seido tō sōgō chōsa: Tokyo: Rōdō Hōrei Kyōkai, 2014: 92–101. Japanese.
18. Fleurence RL. Cost-effectiveness of pressure-relieving devices for the prevention and treatment of pressure ulcers. *Int J Technol Assess Health Care* 2005; 21: 334–41.
19. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992; 146: 473–81.
20. Brandeis GH, Morris JN, Nash DJ, Lipsitz LA. The epidemiology and natural history of pressure ulcers in elderly nursing home residents. *JAMA* 1990; 264: 2905–9.
21. Gorecki C, Brown JM, Nelson EA, Briggs M, Schoonhoven L, Dealey C, et al. Impact of pressure ulcers on quality of life in older patients: a systematic review. *J Am Geriatr Soc* 2009; 57: 1175–83.
22. Gorecki C, Lamping DL, Brown JM, Madill A, Firth J, Nixon J. Development of a conceptual framework of health-related quality of life in pressure ulcers: a patient-focused approach. *Int J Nurs Stud* 2010; 47: 1525–34.
23. Franks PJ, Winterberg H, Moffatt CJ. Health-related quality of life and pressure ulceration assessment in patients treated in the community. *Wound Repair Regen* 2002; 10: 133–40.
24. Langemo DK, Melland H, Hanson D, Olson B, Hunter S. The lived experience of having a pressure ulcer: a qualitative analysis. *Adv Skin Wound Care* 2000; 13: 225–35.
25. Naglie G, Tomlinson G, Tansey C, Irvine J, Ritvo P, Black SE, et al. Utility-based quality of life measures in Alzheimer's disease. *Qual Life Res* 2006; 15: 361–43.
26. Ohkusa Y, Sugawara T. Research for Willingness to pay for one QALY gain. *J Health Care Soc* 2006; 16: 157–65. Japanese.
27. Ministry of Health Labour and Welfare Japanese Government. Annual Health Labour and Welfare Report 2013-2014. 2013. Available at http://www.mhlw.go.jp/english/wp/wp-hw8/(accessed March 24, 2015).
28. Ministry of Health Labour and Welfare Japanese Government. Abridged Life Tables for Japan 2013. 2013. Available at http://www.mhlw.go.jp/english/database/db-hw/lifetb13/dl/lifetb13-05.pdf (accessed March 24, 2015).

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Optimal use of colonoscopy and fecal immunochemical test for population-based colorectal cancer screening: a cost-effectiveness analysis using Japanese data

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Abstract

Objective: There have been few cost-effectiveness analyses of population-based colorectal cancer screening in Japan, and there is no consensus on the optimal use of total colonoscopy and the fecal immunochemical test for colorectal cancer screening with regard to cost-effectiveness and total colonoscopy workload. The present study aimed to examine the cost-effectiveness of colorectal cancer screening using Japanese data to identify the optimal use of total colonoscopy and fecal immunochemical test.

Methods: We developed a Markov model to assess the cost-effectiveness of colorectal cancer screening offered to an average-risk population aged 40 years or over. The cost, quality-adjusted life-years and number of total colonoscopy procedures required were evaluated for three screening strategies: (i) a fecal immunochemical test-based strategy; (ii) a total colonoscopy-based strategy; (iii) a strategy of adding population-wide total colonoscopy at 50 years to a fecal immunochemical test-based strategy.

Results: All three strategies dominated no screening. Among the three, Strategy 1 was dominated by Strategy 3, and the incremental cost per quality-adjusted life-years gained for Strategy 2 against Strategies 1 and 3 were JPY 293 616 and JPY 781 342, respectively. Within the Japanese threshold (JPY 5–6 million per QALY gained), Strategy 2 was the most cost-effective, followed by Strategy 3; however, Strategy 2 required more than double the number of total colonoscopy procedures than the other strategies.

Conclusions: The total colonoscopy-based strategy could be the most cost-effective for population-based colorectal cancer screening in Japan. However, it requires more total colonoscopyprocedures than the other strategies. Depending on total colonoscopy capacity, the strategy of adding total

colonoscopy for individuals at a specified age to a fecal immunochemical test-based screening may be an optimal solution.

Key words: colorectal cancer screening, cost-effectiveness analysis, fecal immunochemical test, total colonoscopy

Introduction

Colorectal cancer (CRC) has markedly increased and is now the second most commonly diagnosed cancer and the third leading cause of cancer-related mortality in Japan (1). For the secondary prevention of CRC, a Japanese population-based CRC screening system has used the 2-day fecal immunochemical test (FIT) as a primary screening procedure on the basis of the evidence regarding its effectiveness for CRC screening (2). The effectiveness of the fecal occult blood test (FOBT) for reducing CRC-associated mortality has been clearly shown in several randomized controlled trials (3–7), whereas other case–control or cohort studies have shown the effectiveness of FIT for CRC screening and the superior sensitivity of FIT for CRC compared with that of FOBT (8–14). Japanese population-based CRC screening is offered to the entire population aged 40 years and over, and total colonoscopy (TCS) is performed for those with a positive FIT result. Recently, however, it has been reported that TCS-based CRC screening, in which TCS is performed as a primary screening procedure, is effective for reducing CRC incidence and mortality, based on long-term follow-up data in cohort studies (15,16). In this context, an analysis of the optimal combination of TCS and FIT for population-based CRC screening is required because there is yet no consensus regarding the issue.

Cost-effectiveness analysis is an essential part of the evaluation of screening strategies. Several cost-effectiveness analyses of CRC screening have been reported from the USA and several other countries (17–24). In Japan, however, there have been only limited analyses (25,26). Recently, by analyzing the TCS screening database of our institution's cancer screening division and the Japanese nationwide survey data of CRC screening, we reported that not only FIT but also TCS might be cost-effective for primary screening (27). However, the study retrospectively evaluated only the cost of identifying a CRC patient; further study using a Markov model analysis is necessary to evaluate the true cost-effectiveness of Japanese CRC screening.

In the present study, we aimed to identify the optimal combination of TCS and FIT for population-based CRC screening in the Japanese setting from the perspective of cost-effectiveness. To evaluate cost-effectiveness, we performed a Markov model analysis using Japanese clinical and cost data. To determine the optimal screening strategy, we also considered the number of TCS procedures required.

Patients and methods

Decision analytic model

We developed a state-transition Markov model that simulated the natural history of CRC development, and the actual cost-effectiveness was analyzed by Monte Carlo simulation using Tree Age Pro 2014 (TreeAge Software Inc., Williamstown, MA, USA) (28). In a Markov model, clinical situations are described in terms of discrete health states, 'Markov states,' that individuals can be in; an individual is always in one of these states, and all events of interest are modeled as transitions from one state to another. In this study, the natural history of CRC development was simulated as a transition from normal epithelium to low-risk adenomatous polyps sized 1–4 and 5–9 mm, to high-risk polyps, to CRC (from Dukes' A to Dukes' D), and ultimately to death from CRC, with reference to previous studies (17–24). Therefore, the Markov states were set as shown in Fig. 1. In addition, the detection status of colorectal polyps and CRC ('detected' or 'undetected') was considered, with CRC screening affecting the transition from 'undetected' to 'detected.' CRC was defined, according to the international classification, as a malignant epithelial tumor originating in the large bowel with invasion beyond the muscularis mucosae (29). High-risk polyps included intramucosal cancers and adenomas with a diameter ≥10 mm, with high-grade dysplasia, or with villous histology (≥25%) (30). The study setting was Japan and the initial population comprised 100 000 individuals aged 40 years who were at an average risk of CRC. The screening and analysis continued through the lifetime of the cohort. The time frame of the analysis was divided into 1 year, during which individuals were in the same health state before having the opportunity to transition to another state. The transition was governed by transition probability values mostly estimated from Japanese literature as described later. Japanese data for age-specific CRC incidence rates was the basis for determining the number of individuals in the population would develop CRC without any screening or intervention (1).

The validity of the model was assessed by comparing the lifetime cumulative risks for CRC incidence and mortality for the 40-year-old Japanese population estimated from the model of this study with those estimated from Japan's Cancer Registry and Statistics (http://gdb.ganjoho.jp/graph_db/gdb1?smTypes=67, Cancer Information Service, National Cancer Center, Japan) (1). When estimating these risks using the model, CRC screening with FIT (primary screening) and TCS (for those with a positive FIT) were considered with uptake rates set at 37 and 55% for FIT and TCS, respectively, based on the data of current Japanese uptake rates (31,32).

CRC screening strategies

To evaluate the optimal use of TCS and FIT for CRC screening, a total of three CRC screening strategies with TCS and/or FIT, including a

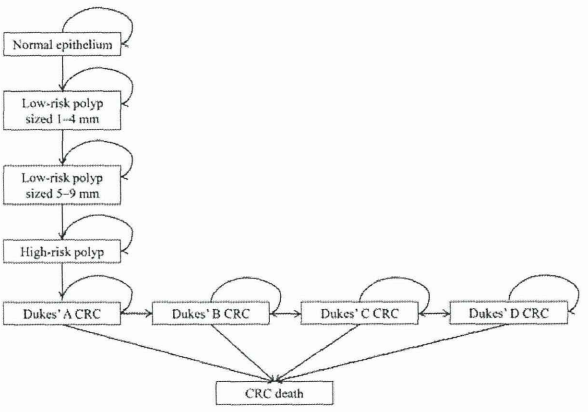

Figure 1. The natural history model of colorectal cancer. CRC, colorectal cancer.

FIT-based strategy which mostly corresponded to the current strategy of Japanese population-based CRC screening and other two strategies which used TCS more actively than the current strategy, were examined in this study (Fig. 2).

Strategy 1: a FIT-based screening strategy
The population is offered FIT at the age of 40 years. When the test is negative, it is repeated annually. Individuals with a positive FIT result are invited for TCS examination; any polyps found are removed and surveillance TCS is repeated every 3 years until no more polyps are found. When the results on TCS are normal, FIT is resumed 5 years after the TCS (Fig. 2a).

Strategy 2: a TCS-based screening strategy
The population is offered TCS as primary screening at the age of 40 years. When the test is negative, TCS is repeated 10 years later. If polyps are found, they are removed and surveillance TCS is repeated every 3 years until no more polyps are found. When the TCS results are normal, TCS is resumed 10 years later (Fig. 2b).

Strategy 3: a strategy of adding population-wide TCS for 50-year-old individuals to a FIT-based screening
This screening strategy is the same as Strategy 1 for individuals aged 40–49 years. The difference is that at the age of 50 years the whole population undergoes TCS, apart from those who underwent TCS in their 40s. After TCS, the screening continues according to the TCS results as with Strategy 1 (Fig. 2c).

Model parameters

Model parameters, including transition probabilities, test characteristics and cost, are summarized in Table 1. Most data were based on Japanese data (1,33–38), except for some data that were only available from foreign studies (20,39). The disease progression parameters from normal epithelium to colorectal polyps and cancer were calculated on the basis of the CRC incidence data from a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan project (1), and the polyp prevalence data at Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan (33). The possibility of new polyps developing after endoscopic removal of polyps was estimated with reference to the data from the Japan polyp study (34). The references for the data regarding other transition probabilities are provided in Table 1 (20,38,39).

With regard to the parameters of test characteristics, the sensitivities and specificities of FIT for colorectal polyps and cancer were set on the basis of data from detailed previous studies by Morikawa et al. (35,36). The sensitivities and specificities of TCS for colorectal polyps and cancer were set according to the data from the Japan polyp study (34). The possibility of complication (perforation and bleeding) following TCS were estimated from the nationwide report from the Japan Gastroenterological Endoscopy Society (37).

The cost included the screening-related cost and CRC treatment-related cost. The screening-related cost was set on the basis of Japanese national reimbursement tables. The CRC treatment-related cost was calculated from the cost of the treatment procedure, hospitalization, adjuvant chemotherapy and follow-up care on the basis of Japanese national reimbursement tables and expert discussion.

The uptake rate of each test (FIT and TCS) was also built into this analysis. The CRC screening uptake rate in Japan has been increasing, but the current rate (~30–40%) is lower than the Japanese government's target values (50%) and the cut-off value for the desirable level of the uptake rate (65%) provided in the European guidelines (31,40). These guidelines based their evidence on performance indicators for FIT on data with a FIT uptake rate of 61.5% (41). From this, it ideally appears that an uptake rate of at least 60% is required for population-based CRC screening. Thus, in the present study, all uptake rates were first set at 60% in the base case analysis and then changed in the sensitivity analyses.

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from a healthcare payer's perspective. The effectiveness of screening was measured in terms of the quality-adjusted life-years (QALYs) gained. Costs and QALYs were discounted at an annual rate of 3% (42). Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Among the remaining strategies, the incremental cost-effectiveness ratio (ICER) was evaluated. ICER was determined for a strategy by comparing the additional cost and effectiveness of the strategy with those of a less costly and less effective strategy; ICER was calculated as the difference in costs divided by the difference in effectiveness.

To compare the demand for endoscopic resources between different screening strategies, the number of TCS procedures performed in each strategy was also calculated.

Sensitivity analyses

In addition to the base case analysis, scenario analyses were performed with regard to the uptake rates (10% and 100%), the initial age of screening (50 years), and the age for population-wide TCS in Strategy 3 (40–60 years). A probabilistic sensitivity analysis was performed for the parameters of transition probabilities, costs, test characteristics, uptake rates and quality of life scales. In a probabilistic sensitivity analysis, these multiple parameters were varied simultaneously. We used β distributions for the parameters for which we could acquire raw data (the denominator and numerator of parameters), including the sensitivities of FIT and TCS, the probability of perforation after TCS, and that of new polyps developing after polyp resection, and gamma distributions for the other variables with a range of ±25%. A cost-effectiveness acceptability curve was drawn to show the correlation between the probability of being chosen as the most cost-effective scenario for each strategy and the willingness-to-pay (WTP) values for one additional QALY gained. The WTP value is the maximum cost that an individual is willing to pay to gain one additional QALY, and the value varies according to country; the Japanese threshold is reported to be JPY 5–6 million per QALY gained (43).

Results

Validity of the model

The cumulative risks for CRC incidence and mortality for the Japanese 40-year-old population estimated from the Cancer Registry and Statistics and those estimated from the model are shown in Fig. 3. The risks estimated from the model generally matched those from the Cancer Registry and Statistics, particularly ≤65 years of age. After the age of 65 years, the risks estimated from the model were slightly lower than those estimated from the Cancer Registry and Statistics.

Base case analysis

The outcomes for the three screening strategies and for no screening in the base case analysis are summarized in Table 2. Without any

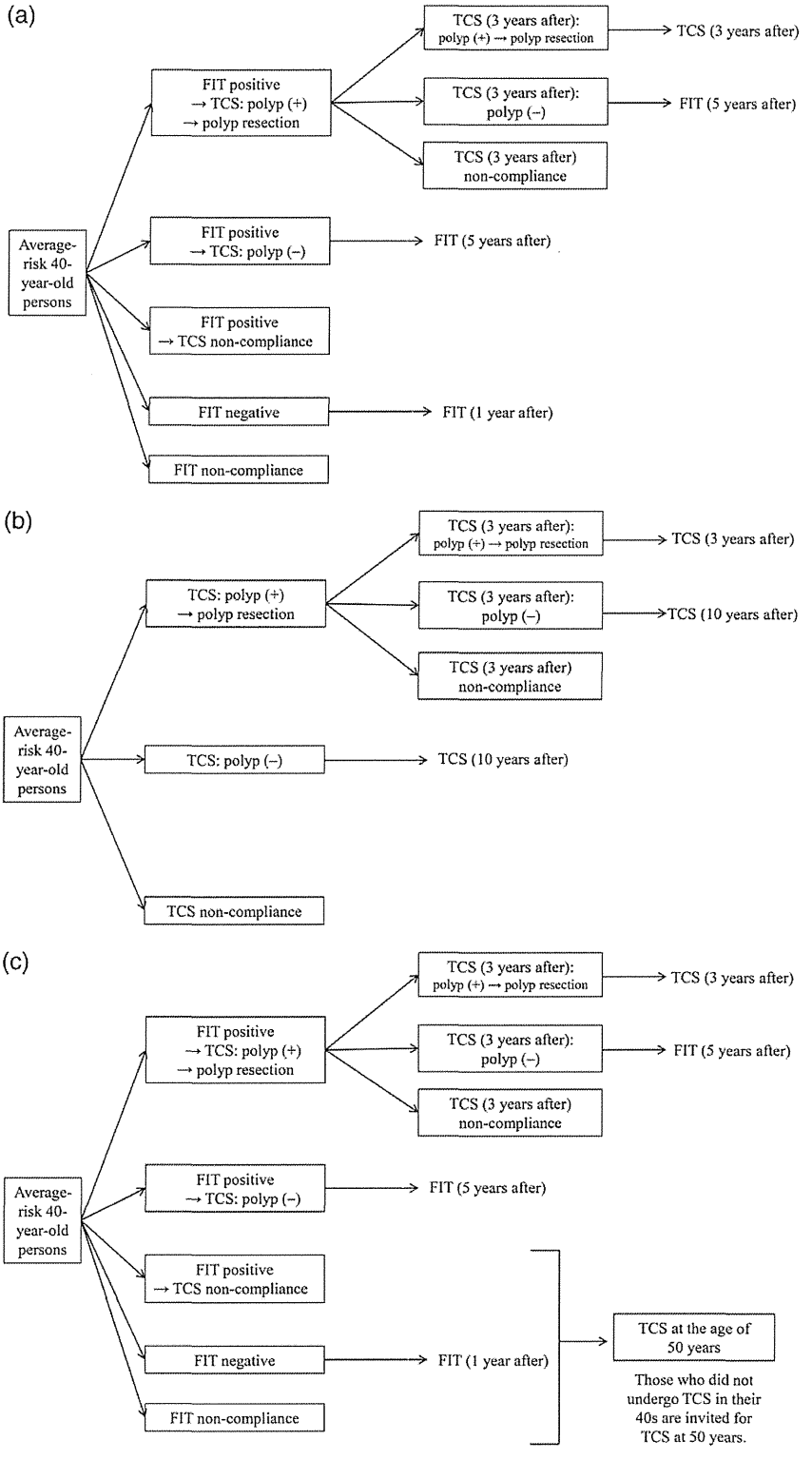

Figure 2. Three screening strategies analyzed in this study. (a) Strategy 1: A fecal immunochemical test-based screening strategy. FIT, fecal immunochemical test; TCS, total colonoscopy. (b) Strategy 2: A total colonoscopy-based screening strategy. (c) Strategy 3: A strategy of adding population-wide total colonoscopy for 50-year-old individuals to a fecal immunochemical test-based screening. During the first 10 years (40–49 years), individuals follow Strategy 1. All of those who did not undergo total colonoscopy during the first 10 years undergo total colonoscopy at the age of 50 years.

Table 1. Model parameters in the cost-effectiveness analysis

Model parameters	Baseline value	References
Transition probabilities (per year)		
Probability of progression to CRC		
From normal epithelium to 1–4 mm sized low-risk polyp	3.4–6.6% (different by age)	33
From 1–4 mm low-risk polyp to 5–9 mm low-risk polyp	1.4–5.6% (different by age)	33
From 5–9 mm low-risk polyp to high-risk polyp	1.3–5.6% (different by age)	33
From high-risk polyp to Dukes' A CRC	3.4%	20, 39
From Dukes' A CRC to Dukes' B CRC	58.3%	20, 39
From Dukes' B CRC to Dukes' C CRC	65.6%	20, 39
From Dukes' C CRC to Dukes' D CRC	86.5%	20, 39
Probability of death from CRC		
Dukes' A	1.7%	38
Dukes' B	3.2%	38
Dukes' C	7.2%	38
Dukes' D	28.4%	38
Probability of symptomatic presentation of CRC		
Dukes' A	6.5%	20, 39
Dukes' B	26.0%	20, 39
Dukes' C	46.0%	20, 39
Dukes' D	92.0%	20, 39
Probability of developing polyps following endoscopic polyp resection		
Developing low-risk polyp (1–4 mm) after endoscopic polyp resection	10.0%	34
Developing low-risk polyp (5–9 mm) after endoscopic polyp resection	5.3%	34
Developing high-risk polyp after endoscopic polyp resection	0.7%	34
Probability of recurrence after treatment of colorectal cancer		
Dukes' A	0.8%	38
Dukes' B	2.8%	38
Dukes' C	7.1%	38
Test characteristics		
FIT		
Sensitivity for 1–4 mm low-risk polyp	6.3%	35, 36
Sensitivity for 5–9 mm low-risk polyp	7.9%	35, 36
Sensitivity for high-risk polyp	26.5%	35, 36
Sensitivity for Dukes' A CRC	52.8%	35, 36
Sensitivity for Dukes' B CRC	70.0%	35, 36
Sensitivity for Dukes' C and D CRC	78.3%	35, 36
Specificity for colorectal polyp and CRC	94.6%	35, 36
TCS		
Sensitivity for 1–4 mm low-risk polyp	74.1%	34
Sensitivity for 5–9 mm low-risk polyp	86.5%	34
Sensitivity for high-risk polyp	97.6%	34
Sensitivity for CRC (Dukes' A–D)	99.9%	34
Specificity for colorectal polyp and CRC	100.0%	34
Probability of perforation after TCS without endoscopic polyp resection	0.01%	37
Probability of perforation after TCS with endoscopic polyp resection	0.06%	37
Probability of death following perforation	6.7%	37
Probability of bleeding after TCS with endoscopic polyp resection	0.5%	37
Cost (JPY)		Japanese national reimbursement tables
FIT	1600	
TCS	15 500	
Endoscopic resection of low-risk polyp	50 000	
Endoscopic resection of high-risk polyp	157 114	
Annual cost of CRC management by Dukes classification		
Dukes' A (1 year)	1 319 816	
Dukes' A (2–5 years)	35 570	
Dukes' B (1 year)	1 399 034	
Dukes' B (2–5 years)	35 570	
Dukes' C (1 year)	2 340 416	
Dukes' C (2–5 years)	44 972	
Dukes' D (1 year)	2 687 125	
Dukes' D (2–5 years)	2 544 972	

CRC, colorectal cancer; FIT, fecal immunochemical test; TCS, total colonoscopy.

screening, there would be 9541 CRC cases among the cohort of 100 000 individuals, and the calculated QALYs and total cost per person were 22.8 and JPY 156 125, respectively. Compared with no screening, all three screening strategies (Strategies 1, 2 and 3) experienced fewer CRC cases, gained more QALYs, and were less costly; i.e. all three strategies dominated no screening.

Among the three strategies, simple dominance of Strategy 3 over Strategy 1 was observed: Strategy 3 resulted in more QALYs and less cost than Strategy 1. Compared with Strategies 1 and 3, Strategy 2 yielded more QALYs, but involved greater cost. The ICERs per QALY gained for Strategy 2 against Strategies 1 and 3 were JPY 293 616 and JPY 781 342, respectively.

With regard to the number of TCS procedures, Strategy 2 required the most procedures (294 322 procedures per 100 000 population), followed by Strategy 3 (126 171 procedures per 100 000), and Strategy 1 (100 740 procedures per 100 000).

Scenario analyses

When the uptake rates decreased to 10%, Strategy 2 showed simple dominance over no screening and the other two screening strategies, whereas the ICER per QALY gained for no screening against Strategy 3 was JPY 218 464 (Table 3). When the uptake rates increased to 100%, all three screening strategies showed simple dominance over no screening, and the ICERs per QALY gained for Strategy 2 against Strategies 1 and 3 were JPY 126 810 and JPY 19 475, respectively (Table 3).

When the initial age of screening changed to 50 years, all three screening strategies dominated no screening, and the ICERs were JPY 87 804 and JPY 125 953 per QALY gained for Strategy 2 against Strategies 1 and 3 (Table 3).

The results for QALYs, costs and required number of TCS procedures when the age for population-wide TCS in Strategy 3 was changed between 40 and 60 years are shown in Table 4. Compared with the base case scenario of Strategy 3 with TCS at 50 years, the strategy with population-wide TCS at the age of 40 years resulted in fewer QALYs and higher cost. In contrast, when the population-wide TCS was performed at 55 years, more QALYs were gained with lower cost than when the TCS was performed at 50 years. The ICER per QALY gained for the strategy with TCS at 55 years against the strategy with TCS at 60 years was JPY 206 113. Against the strategy with TCS at 55 years, the ICER per QALY gained for the strategy with TCS at 45 years was JPY 782 013. The strategy with TCS at 45 years yielded more QALYs and was less costly than Strategy 2, and the ICER per QALY gained for this strategy against Strategy 1 was JPY 151 856. The required number of TCS procedures decreased as the age for population-wide TCS increased.

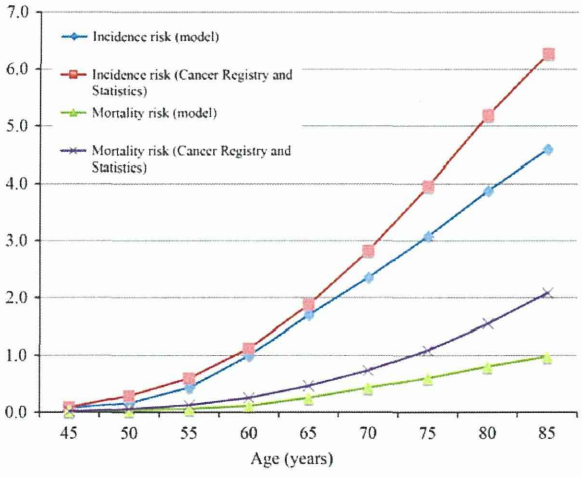

Figure 3. Comparison between cumulative risks for colorectal cancer incidence and mortality estimated from the study model and those estimated from the Cancer Registry and Statistics.

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis performed for no screening and the three strategies (Strategies 1, 2 and 3) and the cost-effectiveness acceptability curve showed a correlation between the probability of being chosen as the most cost-effective scenario for each strategy and the WTP values (Fig. 4). In the figure, the horizontal axis represents the WTP value for one additional QALY, with a range of JPY 0–10 000 000, and the vertical axis represents the probability of being chosen as the most cost-effective scenario for each strategy. When the WTP value was set at JPY 5 000 000, the probability of being chosen as the most cost-effective scenario was 2.2% for no screening, 21.0% for Strategy 1, 48.7% for Strategy 2 and 28.1% for Strategy 3. When the age for population-wide TCS was changed to 45 years in Strategy 3, the probability resulted in 2.4% for no screening, 21.8% for Strategy 1, 53.2% for Strategy 2, and 22.6% for Strategy 3.

Table 2. Results of the base case analysis

	No screening	Strategy 1	Strategy 2	Strategy 3
Cost (per person, JPY)	156 125	94 733	99 930	93 523
QALYs (per person)	22.7986	23.0001	23.0178	23.0096
CRC cases (per 100 000 persons)	9541	3926	2989	3625
TCS procedures (per 100 000 persons)	—	100 740	294 322	126 171
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates	Dominates[a]
vs. Strategy 1	Dominated[b]	—	293 616	Dominates[a]
vs. Strategy 2	Dominated[b]	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated[b]	Dominated[b]	781 342	—

[a]'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).
[b]'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).
QALY, quality-adjusted life-years.

Table 3. Results of the scenario analyses on the uptake rates and initial age of screening

	No screening	Strategy 1	Strategy 2	Strategy 3
Uptake rates: 100%				
Cost (per person, JPY)	154 694	99 382	104 961	103 789
QALYs (per person)	22.8026	23.0770	23.1210	23.0608
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates[a]	Dominates[a]
vs. Strategy 1	Dominated[b]	—	126 810	Dominated[b]
vs. Strategy 2	Dominated[b]	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated[b]	Dominates[a]	19 475	—
Uptake rates: 10%				
Cost (per person, JPY)	153 653	152 928	137 289	151 710
QALYs (per person)	22.8209	22.8278	22.8753	22.8120
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates[a]	See No screening vs. 3
vs. Strategy 1	Dominated[b]	—	Dominates[a]	see Strategy 1 vs. 3
vs. Strategy 2	Dominated[b]	Dominated[b]	—	Dominated[b]
vs. Strategy 3	218 464	77 010	Dominates[a]	—
Starting age: 50 years				
Cost (per person, JPY)	154 107	99 793	104 069	99 043
QALYs (per person)	22.8194	23.0845	23.1332	23.0933
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates[a]	Dominates[a]
vs. Strategy 1	Dominated[b]	—	87 804	Dominates[a]
vs. Strategy 2	Dominated[b]	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated[b]	Dominated[b]	125 953	—

[a]'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).
[b]'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).

Table 4. Results of the scenario analyses on the age for population-wide total colonoscopy in Strategy 3

	40 years	45 years	50 years	55 years	60 years
Cost (per person, JPY)	99 602	97 679	93 523	92 049	91 142
QALYs (per person)	22.9979	23.0195	23.0096	23.0123	23.0079
TCS procedures (per 100 000 persons)	138 687	133 193	126 171	123 659	123 106
Incremental cost per QALY gained (JPY)					
vs. 40 years	—	Dominates[a]	Dominates[a]	Dominates[a]	Dominates[a]
vs. 45 years	Dominated[b]	—	see 45 years vs. 50 years	see 45 years vs. 55 years	see 45 years vs. 60 years
vs. 50 years	Dominated[b]	420 284	—	Dominates[a]	see 50 years vs. 60 years
vs. 55 years	Dominated[b]	782 013	Dominated[b]	—	see 55 years vs. 60 years
vs. 60 years	Dominated[b]	564 055	1.400 462	206 113	—

[a]'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).
[b]'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).

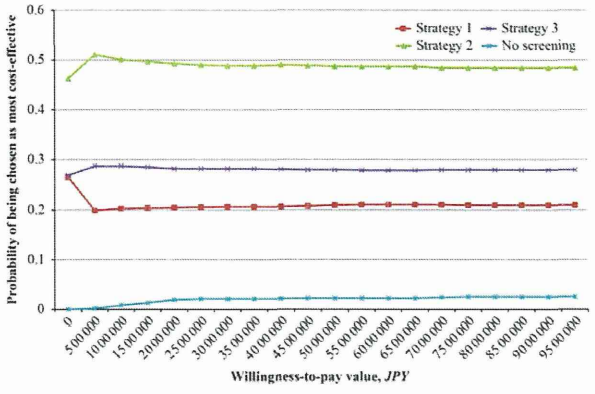

Figure 4. Probabilistic sensitivity analysis performed for the three strategies (1, 2 and 3) and no screening.

Discussion

This study examined in detail the cost-effectiveness of CRC screening with FIT and/or TCS in the Japanese settings by performing a simulation model analysis. For this analysis, we constructed a model of CRC using Japanese clinical data. The validity of the model was indicated by the finding that the cumulative risks for CRC incidence and mortality estimated from the model and the Cancer Registry and Statistics matched mostly, particularly for people ≤65 years of age. Although these risk estimates differed slightly after the age of 65 years, we believe that it does not matter in this study. On the contrary, the difference strengthens the evidence for the favorable cost-effectiveness of CRC screening indicated by the model analysis because the lower CRC incidence and mortality estimated from the model means that it may be more difficult to prove the (cost-)effectiveness of screening using the model than with real-life data.

Our results indicate that CRC screening with FIT and/or TCS was superior to no screening from the perspective of cost-effectiveness in most cases. This finding agrees with previous foreign cost-effectiveness studies on CRC screening (17–24). However, when the uptake rates decreased to 10%, the ICER per QALY gained for no screening against Strategy 3 was well below JPY 5-6 million. Considering that this amount is the upper limit of the WTP value for one additional QALY in Japan (43), it is postulated that the superiority of CRC screening to no screening in terms of cost-effectiveness will be more difficult to maintain when uptakes rates are low. To maintain the superior cost-effectiveness of CRC screening, it will be essential to achieve high screening uptake rates.

Despite a number of previous cost-effectiveness studies on CRC screening, there has been no consensus on the optimal use in terms of cost-effectiveness of FIT and TCS for population-based CRC screening (17–26). In the base case analysis of this study, the ICER per QALY gained for Strategy 2 against Strategy 1 was lower than the upper limit of the WTP value in Japan and Strategy 3 showed simple dominance over Strategy 1, which suggests that the strategies that use TCS more actively (Strategies 2 and 3) could be more cost-effective than the FIT-based screening strategy (Strategy 1). Furthermore, the sensitivity analyses showed that the strategies with greater use of TCS (Strategies 2 and 3) could be more cost-effective than the FIT-based screening strategy (Strategy 1) in most cases. This finding may largely be due to the much lower fee per TCS procedure in Japan than in other countries. Comparing cost-effectiveness between Strategies 2 and 3, the base case and sensitivity analyses showed that Strategy 2 was more cost-effective than Strategy 3 in many cases. However, the sensitivity analyses showed that the superiority of Strategy 2 against Strategy 3 with regard to cost-effectiveness was not always the case and that Strategy 3 could be more cost-effective than Strategy 2 under certain sets of model parameters and the age for population-wide TCS in Strategy 3.

If TCS is to be used more actively for population-based CRC screening, its safety and the availability of TCS resources require discussion. First, with regard to the safety of TCS, recent foreign studies have reported that the perforation rate of TCS without polypectomy was 0.01–0.03%, which is a very low rate that indicates the safety of screening TCS (44–48). Similarly, in Japan, the corresponding rate has been reported to be low, as shown in Table 1 (37). Given the safety of screening TCS, it may be possible to use it more actively than the currently performed FIT-based CRC screening. However, the risk of perforation associated with TCS cannot be completely ignored at present, particularly for the elderly population (44–48). Second, the capacity for screening TCS in Japan has not been clarified, with some surveys currently in progress, including the Japan endoscopy database project (UMIN000016093). Nevertheless, it is obvious that TCS capacity is limited in Japan and that we must arrange the CRC screening system to meet this limitation. Considering the limited TCS capacity, the TCS-based screening (Strategy 2), which requires more than double the number of TCS procedures than the other strategies in this study (Strategies 1 and 3), is likely to be the most difficult to implement.

From the cost-effectiveness aspect only, the TCS-based strategy may be the best; however, considering cost-effectiveness, safety, and the TCS capacity issue together, we postulate that the strategy of adding population-wide TCS at a specific age to the FIT-based strategy (Strategy 3) may be an optimal option for population-based CRC screening in Japan. With regard to the optimal age for population-wide TCS in Strategy 3, TCS at 45 years was the most cost-effective under the condition of the upper limit of WTP being JPY 5-6 million, according to the scenario analyses in this study. Considering that it is necessary to set the age for population-wide TCS as a range rather than one specific age to achieve a higher uptake rate, it appears that TCS within the age range 45–55 years would be acceptable from the perspective of cost-effectiveness on the basis of the study results. This would also be expected to improve the safety of the procedure because of the relatively younger age. With regard to the TCS capacity, although more TCS procedures may be required than with the FIT-based strategy, the increase is considered not to be too great; the number of TCS procedures required in Strategy 3 (TCS at 45–55 years) compared with those required in Strategy 1 was 123 659–133 193 vs. 100 740 per 100 000 individuals, whereas Strategy 2 required 294 322 TCS procedures per 100 000 individuals.

This study had several limitations. First, the natural history model of CRC in this study was based on currently available Japanese data; as a result, it was completely based on the concept of the adenoma-carcinoma sequence on which the previously reported cost-effectiveness analyses were based (17–24). However, other CRC pathways, such as the serrated pathway and the *de novo* pathway, have been reported, and it may be necessary to include these in the natural history model of CRC in future analyses, after the collection of a sufficiently large body of data on serrated polyps or *de novo* cancers (49,50). Second, the values of model parameters set in the base case analysis could vary case by case in the real world. However, sensitivity analyses, including probabilistic sensitivity analyses, were performed for the parameters. Third, indirect costs such as productivity loss cost due to CRC treatment were not considered in this study. Because limited data are available on indirect costs in Japan at present, it is currently difficult to include these costs in the cost-effective analysis. However, the cost-effective analyses in this study were performed form the healthcare payer's perspective in Japan, and thus we believe that no inclusion of indirect cost was appropriate for the analyses. For future cost-effectiveness analyses that include other perspectives, inclusion of data on the indirect costs associated with CRC in Japan would be warranted.

In conclusion, the present study examined the cost-effectiveness of population-based CRC screening in Japan. The CRC screening strategies with more active use of TCS could be more cost-effective than the FIT-based screening strategy. The TCS-based screening strategy could be the most cost-effective; however, considering the safety and limited capacity of TCS resources in addition to cost-effectiveness, the strategy of adding population-wide TCS for individuals in the age range 45–55 years to the FIT-based screening may be an optimal solution.

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Conflict of interest statement

None declared.

References

1. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H; Japan Cancer Surveillance Research Group<. Cancer incidence and

incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2014;44:388–96.
2. Saito H. Screening for colorectal cancer: current status in Japan. *Dis Colon Rectum* 2000;43:S78–84.
3. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993;328:1365–71.
4. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472–7.
5. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467–71.
6. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000; 343:1603–7.
7. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 2004;126:1674–80.
8. Hiwatashi N, Morimoto T, Fukao A, et al. An evaluation of mass screening using fecal occult blood test for colorectal cancer in Japan: a case-control study. *Jpn J Cancer Res* 1993;84:1110–2.
9. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. *Int J Cancer* 1995;61: 465–9.
10. Saito H. Screening for colorectal cancer by immunochemical fecal occult blood testing. *Jpn J Cancer Res* 1996;87:1011–24.
11. Zappa M, Castiglione G, Grazzini G, et al. Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. *Int J Cancer* 1997; 73:208–10.
12. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep* 2000;7:815–9.
13. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. *Br J Cancer* 2003;89:23–8.
14. Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S; Japan Public Health Center-based Prospective Study<. Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: a prospective cohort study in Japan. *Cancer Detect Prev* 2007;31:3–11.
15. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369: 1095–105.
16. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366: 687–96.
17. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA* 2000;284: 1954–61.
18. Sonnenberg A, Delcò F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med* 2000;133:573–84.
19. Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;137:96–104.
20. Tappenden P, Chilcott J, Eggington S, Patnick J, Sakai H, Karnon J. Option appraisal of population-based colorectal cancer screening programmes in England. *Gut* 2007;56:677–84.
21. Vijan S, Hwang I, Inadomi J, et al. The cost-effectiveness of CT colonography in screening for colorectal neoplasia. *Am J Gastroenterol* 2007;102: 380–90.
22. Tsoi KK, Ng SS, Leung MC, Sung JJ. Cost-effectiveness analysis on screening for colorectal neoplasm and management of colorectal cancer in Asia. *Aliment Pharmacol Ther* 2008;28:353–63.
23. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev* 2011;33:88–100.
24. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol* 2013;108:120–32.
25. Tsuji I, Fukao A, Shoji T, Kuwajima I, Sugawara N, Hisamichi S. Cost-effectiveness analysis of screening for colorectal cancer in Japan. *Tohoku J Exp Med* 1991;164:269–78.
26. Shimbo T, Glick HA, Eisenberg JM. Cost-effectiveness analysis of strategies for colorectal cancer screening in Japan. *Int J Technol Assess Health Care* 1994;10:359–75.
27. Sekiguchi M, Matsuda T, Tamai N, et al. Cost-effectiveness of total colonoscopy in screening of colorectal cancer in Japan. *Gastroenterol Res Pract* 2012;2012:728454.
28. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322–38.
29. Hamiliton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. *WHO Classification of Tumors of the Digestive System*. 4th ed. Lyon: IARC, 2010;134–46.
30. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. *Gastrointest Endosc Clin N Am* 2002;12:1–9. v.
31. Ministry of Health, Labor and Welfare, Japan. Comprehensive Survey of Living Conditions 2013 [in Japanese]. Health, Labor and Welfare Statistics Association, Tokyo, Japan, 2013.
32. Kitagawa S, Miyagawa K, Iriguchi Y, et al. Nationwide survey on gastrointestinal cancer screening 2012. *Journal of Gastrointestinal Cancer Screening* 2015;53:60–101.
33. Hamashima C, Sobue T, Muramatsu Y, Saito H, Moriyama N, Kakizoe T. Comparison of observed and expected numbers of detected cancers in the research center for cancer prevention and screening program. *Jpn J Clin Oncol* 2006;36:301–8.
34. Sano Y, Fujii T, Matsuda T, et al. Study design and patient recruitment for the Japan Polyp Study. *Open Access Journal of Clinical Trials* 2014;6: 37–44.
35. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005; 129:422–8.
36. Morikawa T, Kato J, Yamaji Y, et al. Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas. *Am J Gastroenterol* 2007;102:2259–64.
37. Yoshino J, Igarashi Y, Ohara H, et al. 5th report of endoscopic complications: results of the Japan Gastroenterological Endoscopy Society. *Gastroenterol Endosc* 2010;52:95–103. (in Japanese).
38. Japanese Society for Cancer of the Colon and Rectum. *JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer*. Tokyo, Japan: Kanehara & Co., Ltd., 2014. (in Japanese).
39. Sweet A, Lee D, Gairy K, Phiri D, Reason T, Lock K. The impact of CT colonography for colorectal cancer screening on the UK NHS: costs, healthcare resources and health outcomes. *Appl Health Econ Health Policy* 2011;9:51–64.
40. Segnan N, Patnick J, von Karsa L, editors. *European guidelines for quality assurance in colorectal cancer screening and diagnosis*, 1st edn. Luxemburg: Publication Office of the EU, 2010.
41. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010;59:62–8.
42. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost Effectiveness in Health and Medicine. *Pharmacoeconomics* 1997; 11:159–68.
43. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY

gained: what is the threshold of cost effectiveness? *Health Econ* 2010; 19:422–37.
44. Niv Y, Hazazi R, Levi Z, Fraser G. Screening colonoscopy for colorectal cancer in asymptomatic people: a meta-analysis. *Dig Dis Sci* 2008;53:3049–54.
45. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med* 2009; 150:849–57.
46. Bokemeyer B, Bock H, Hüppe D, et al. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. *Eur J Gastroenterol Hepatol* 2009;21:650–5.
47. Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DS. Adverse events after screening and follow-up colonoscopy. *Cancer Causes Control* 2012;23:289–96.
48. Hamdani U, Naeem R, Haider F, et al. Risk factors for colonoscopic perforation: a population-based study of 80118 cases. *World J Gastroenterol* 2013;19:3596–601.
49. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010;138:2088–100.
50. Kashida H, Kudo SE. Early colorectal cancer: concept, diagnosis, and management. *Int J Clin Oncol* 2006;11:1–8.

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Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer

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ABSTRACT

Objectives: The combination use of gefitinib and epidermal growth factor receptor (EGFR) testing is a standard first-line therapy for patients with non-small cell lung cancer (NSCLC). Here, we examined the cost-effectiveness of this approach in Japan.
Materials and methods: Our analysis compared the 'EGFR testing strategy', in which EGFR mutation testing was performed before treatment and patients with EGFR mutations received gefitinib while those without mutations received standard chemotherapy, to the 'no-testing strategy,' in which genetic testing was not conducted and all patients were treated with standard chemotherapy. A three-state Markov model was constructed to predict expected costs and outcomes for each strategy. We included only direct medical costs from the healthcare payer's perspective. Outcomes in the model were based on those reported in the Iressa Pan-Asia Study (IPASS). The incremental cost-effectiveness ratio (ICER) was calculated using quality-adjusted life-years (QALYs) gained. Sensitivity and scenario analyses were conducted.
Results: The incremental cost and effectiveness per patient of the 'EGFR testing strategy' compared to the 'no-testing strategy' was estimated to be approximately JP¥122,000 (US$1180; US$1 = JP¥104 as of February 2014) and 0.036 QALYs. The ICER was then calculated to be around JP¥3.38 million (US$32,500) per QALY gained. These results suggest that the 'EGFR testing strategy' is cost-effective compared with the 'no-testing strategy' when JP¥5.0 million to 6.0 million per QALY gained is considered an acceptable threshold. These results were supported by the sensitivity and scenario analyses.
Conclusion: The combination use of gefitinib and EGFR testing can be considered a cost-effective first-line therapy compared to chemotherapy such as carboplatin–paclitaxel for the treatment for NSCLC in Japan.

1. Introduction

Lung cancer is the most common cause of death from cancer worldwide, representing nearly 20% of all cancer deaths [1]. In Japan, lung cancer is the leading cause of death, accounting for more than 70,000 deaths in 2013, and both the morbidity and mortality continue to increase [2]. Thus, lung cancer is one of the most important public health issues.

Approximately 80% of all lung cancer cases are non-small cell lung cancer (NSCLC). The majority of patients with NSCLC are diagnosed at an advanced stage [3,4]. Standard first-line therapy for advanced NSCLC consists of systemic platinum-based doublet chemotherapy, including cisplatin or carboplatin, combined with taxanes, pemetrexed and gemcitabine. Although several combinations are used, none has yet shown superiority [5–7].

Recently, targeted therapies have been developed to provide alternative treatment options for this disease. Gefitinib is an orally administered epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) which was first approved in Japan in 2002. In 2004, two pivotal studies revealed that the presence of genetic mutation in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR-TKI [8,9]. Subsequently, four randomized Phase 3 clinical trials, including the Iressa Pan-Asia Study (IPASS), assessed gefitinib as first-line therapy for advanced NSCLC patients with EGFR mutation [10–13]. In the subgroup of patients with EGFR mutation, progression-free survival (PFS) was

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significantly longer and the response rate was significantly higher with gefitinib than with platinum-based doublet chemotherapy. Further, patients receiving gefitinib had a lower incidence of severe adverse events compared to those receiving chemotherapy. Nevertheless, the final results of IPASS confirmed that there was no difference in overall survival (OS) between gefitinib and carboplatin–paclitaxel (CBDCA + PTX) [14]. On the basis of this evidence, the Pharmaceuticals and Medical Devices Agency (PMDA) approved revised labeling for gefitinib that limited its indications to locally advanced or metastatic NSCLC patients with EGFR mutations in 2011.

The Japanese national health insurance system provides universal coverage to all citizens. However, as in other developed countries, burgeoning medical costs caused by the aging population and the evolution of novel but costly health care technologies is an emerging social problem. The medical costs for cancer treatment continues to increase, and at about JP¥3812 billion (US$37 billion; US$1 = JP¥104 as of February 2014) represented 13.5% of all medical costs in 2012 [15]. The current labeling for gefitinib for NSCLC requires EGFR mutation testing for all patients to identify eligible treatment candidates. It is therefore important to justify this additional cost. To our knowledge, however, no such cost-effectiveness analysis of gefitinib has yet been conducted in Japan.

Here, we evaluated the cost-effectiveness of combination use of gefitinib and EGFR mutation testing as first-line therapy for NSCLC patients in Japan.

2. Methods

2.1. Decision model structure

We compared the cost-effectiveness of the two treatment strategies from the perspective of healthcare payer (Fig. 1). In the 'EGFR-testing strategy' (strategy 1), testing for EGFR mutations was performed before treatment was determined; patients who tested positive for EGFR mutation received gefitinib as first-line treatment, and those who tested negative received CBDCA + PTX as first-line treatment. We assumed that 32% of patients tested positive [16]. In the 'no EGFR-testing strategy' (strategy 2), genetic testing was not conducted, and all patients were treated with CBDCA + PTX. The treatment-related costs and outcomes for patients without EGFR mutation in both strategies were assumed to be the same as they all received CBDCA + PTX as first-line therapy. Therefore, only the EGFR testing fee was included as the difference in the two treatment strategies.

The measure of this cost-effectiveness analysis was incremental cost-effectiveness ratio (ICER). Quality-adjusted life-years (QALYs) gained was used as an outcome to calculate the ICER. In this analysis, willingness-to-pay (WTP) was set to JP¥5.0 million to 6.0 million (US$48,100 to 57,700) for one additional QALY based on a Japanese study [17]. We adopted a 2% discount rate per year for both costs and outcomes [18].

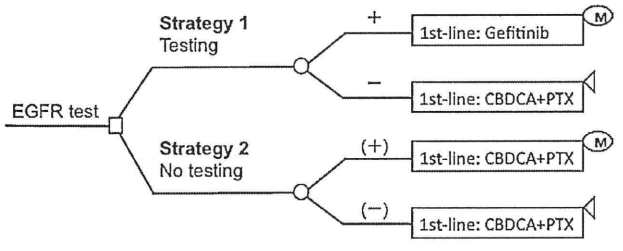

Fig. 1. Treatment strategies evaluated in this analysis. CBDCA + PTX, carboplatin–paclitaxel; EGFR, epidermal growth factor receptor; M, Markov model.

2.2. Patients and treatment

For this analysis, the base-case patient population was assumed to be Japanese patients who were 18 years of age or older, had histologically confirmed stage IIIB or IV NSCLC with an ECOG performance status from 0 to 2, and had no history of chemotherapy.

The patients were assumed to receive either of the therapies below according to the Japanese drug package inserts, identical to the regimen used in IPASS:

- gefitinib (250 mg/day, administered orally) until disease progression,
- paclitaxel (200 mg/m^2, administered intravenously) followed by carboplatin (at a dose calculated to produce an area under the concentration-time curve of 6.0 mg/ml/min, administered intravenously) in cycles of once every 3 weeks up to 6 cycles.

2.3. Disease modeling

We constructed the Markov model including three health states for analysis: progression-free survival, progressive disease, and death (Online Data Supplement Fig. 1). Patients move from one state to another during each cycle length of 3 weeks. The time horizon of 5 years was adopted to reflect the limited remaining life of the patients. Weibull curves were extrapolated to fit to Kaplan–Meier survival curves of IPASS [10,14]. The scale parameter (λ) and shape parameter (γ) were estimated using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). These parameters were used to measure the probabilities of transition at the time point of cycle t, according to the following formula [19]: $P(t) = 1 - \exp[\lambda(t-1)^{\gamma} - \lambda t^{\gamma}]$. The fitted Weibull curves for patients with EGFR mutation and the estimated parameters are provided in the Online Data Supplement Fig. 2 and Table 1.

2.4. Costs and utility

Costs were estimated from the health care payer's perspective; therefore, only direct medical costs were included. The medical costs considered in this model included drugs, outpatient chemotherapy, EGFR testing, disease monitoring and hospital administration (Table 1). To calculate the cost of each drug, we assumed a body surface area of 1.73 m^2 and glomerular filtration rate of 97.6 ml/min based on the median age of patients in IPASS [10]. For the first cycle of treatment, the patients were considered to be hospitalized. Premedication for CBDCA + PTX consisting of dexamethasone, granisetron, ranitidine, and diphenhydramine was to be used according to the regimen used at the Cancer Institute Hospital of the Japanese Foundation of Cancer Research (JFCR) [20]. Treatment regimens used after disease progression in IPASS varied, as they were at the physician's discretion. Therefore, we applied the costs of docetaxel monotherapy after disease progression as the base case. The costs of terminal and best supportive care were expected to be the same in both strategies, so they were not included in this analysis. Costs were calculated according to the Japanese 2012 drug tariff and medical care based on fee for service [21,22].

Because health utility measurements were not available in IPASS, utility scores for each state were adapted from other literature [23,24]. In our study, utility values were adjusted according to response rate, types of Common Terminology Criteria (CTC) grade 3/4 adverse events, route of administration and disease progression (Table 2). CTC grade 2 hair loss was also included as it has been reported to have a deleterious impact on health-related quality of life (HRQoL) [23–25].

Table 1
Costs and number of times of healthcare services per patient cycle.

Parameter	Unit cost (JP¥ [US$])	Gefitinib		Carboplatin + paclitaxel			Subsequent therapy
		1st cycle	Subsequent cycle	1st cycle	2nd to 6th cycle	After 6th cycle	
Drug costs [21]							
Gefitinib	6526.2 [62.8]	21	21				
Carboplatin	66,806 [642.3]			1	1		
Paclitaxel	112,043 [1077.3]			1	1		
Premedication	7464.5 [71.8]			1	1		
Subsequent treatment[a]	111,895 [1075.9]						1
Outpatient chemotherapy [22]							
Outpatient service fee	690 [6.6]		1		1	1	1
Prescription fee	420 [4.0]		1				
Prescription fee for anticancer drug	700 [6.7]		0.75				
Outpatient chemotherapy	5800 [55.8]				1		1
Intravenous drip fee	950 [9.1]			1	1		1
Preparation in sterile environment	500 [4.8]			1	1		1
EGFR testing fee [22]	21,000 [201.9]	1					
Disease monitoring [22]							
Blood drawing fee	160 [1.5]		1		1	1	1
Peripheral blood test fee	210 [2.0]	1	1	1	1	1	1
Peripheral blood test diagnostic fee	1250 [12.0]	0.75	0.75	0.75	0.75	0.75	0.75
Biochemical test fee	1210 [11.6]	1	1	1	1	1	1
Biochemical test diagnostic fee	1440 [13.8]	0.75	0.75	0.75	0.75	0.75	0.75
Tumor marker test fee	4000 [38.5]	0.75	0.75	0.75	0.75	0.75	0.75
CT scan with a contrast medium	14,500 [139.4]	0.5	0.5	0.5	0.5	0.5	0.5
CT scan diagnostic fee	4500 [43.3]	0.75	0.75	0.75	0.75	0.75	0.75
Hospital fee [22]							
From 1st to 14th day	20,160 [193.8]	14		14			
From 15th day	17,580 [169.0]	7		7			
Total (JP¥[US$]/cycle)		580,413 [5580.9]	155,908 [1499.1]	610,126 [5866.6]	211,476 [2033.4]	17,913 [172.2]	137,058 [1317.9]

CT, computed tomography; EGFR, epidermal growth factor receptor.
[a] The cost of docetaxel therapy (60 mg/m^2 per cycle) was used in the base-case.