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Cost-Effectiveness Analysis on Endoscopic Surveillance Among Western Patients With Barrett's Esophagus for Esophageal Adenocarcinoma Screening

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Abstract: Incidence of esophageal adenocarcinoma (EAC) has risen rapidly over the past decades in Western countries. As a premalignant lesion, Barrett's esophagus (BE) is an established risk factor of EAC. This study estimated the impact of surveillance endoscopy for BE on population's survival upon EAC by a whole-population cost-effectiveness analysis among modeled Western population.

Possibilities and survival payoffs were retrieved through literature searching based on PubMed database. Patients with BE were classified as adequate surveillance (AS), inadequate surveillance (IAS), and no surveillance groups. Direct cost of endoscopy per person-year was estimated from diagnosis of BE to before diagnosis of EAC in the whole-population model, whereas the payoff was 2-year disease-specific survival rate of EAC.

AS for patients with BE had lower cost-effectiveness ratio (CER) than that of IAS group, as well as lower incremental cost-effectiveness ratio (6116€/% vs 118,347€/%). Prolonging the surveillance years could decrease the yearly cost in whole population and also relevant CERs, despite increased total cost. Increasing the proportion of participants in AS group could improve the survival benefit. The maximal payoff was up to 2-year mortality reduction of 2.7 per 100,000 persons by spending extra €1,658,913 per 100,000 person-years.

A longer endoscopic surveillance among BE subpopulation plan can reduce yearly budget. Attempt to increase the proportion of AS participants can induce decline in population mortality of EAC, despite extra but acceptable expenditure. However, regarding optimal cost-effectiveness, further studies are still required to identify a high-risk subpopulation out of BE patients for endoscopic surveillance.

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Abbreviations: AS = adequate surveillance, BE = Barrett's esophagus, CER = cost-effectiveness ratio, EAC = esophageal adenocarcinom, HGD = high-grade dysplasia, IAS = inadequate surveillance, ICER = incremental cost-effectiveness ratio, IDD = indefinite dysplasia, IM = intestinal metaplasia, LGD = low-grade dysplasia, NBE = no Barrett's esophagus or unknown, NS = no surveillance.

INTRODUCTION

Incidence of esophageal adenocarcinoma (EAC) has risen rapidly among all age group over the past 3 decades in the Western countries by certain estimates,[1] and especially in North America and Europe.[2] In Europe and the United States, the adenocarcinoma became the predominant histological subtype of esophageal carcinomas.[3] Data from the Surveillance Epidemiology and End Results program in the United States assessed the period 2001 to 2005, and found EAC represented 55.5% of all esophageal carcinomas.[4] In contrast, squamous cell carcinoma is the predominant histological subtype of esophageal cancers in Asia such as Japan and China and other countries.[3]

Despite advances in multimodality treatment, the prognosis for EAC remains relatively poor.[3,5] However, endoscopic surveillance of Barrett's esophagus (BE) is considered to provide an opportunity of detecting EAC at early stage.[6,7] Early detection may lead to much better survival outcome and save premature death. As a premalignant lesion, BE is an established risk factor of EAC, and therefore patients with BE are defined as a high-risk subpopulation for EAC.[8] Despite that, screening and surveillance for BE have not become a mandatory strategy for identifying and monitoring the high-risk subpopulation.[9,10] In addition, based on the endoscopic surveillance of BE condition, a follow-up study found the complete endoscopic resection of BE with high-grade dysplasia (HGD) and early EAC would be an effective, safe, and durable treatment.[11]

Recently, Verbeek et al[12] have reported a promising results that adequate surveillance (AS) by regular endoscopy on BE patients could increase the proportion of detected early-stage EAC and significantly improve the survival, comparing to patients with inadequate surveillance (IAS) or no surveillance (NS). Solaymani-Dodaran et al[13] found that approximately 2% among patients with BE would die of esophageal cancer within 10 years, but patients with BE died more frequently of other causes. As known, the prevalence of BE among population is $<10\%$, but BE can induce higher incidence of EAC than no Barrett's esophagus or unknown (NBE) condition.[14] Moreover, $<10\%$ of patients with EAC were known to have BE before.[2]

In the areas with high incidence of EAC, the endoscopic surveillance can achieve effective results of early diagnosis in

cost-effective manner.[3] However, in Western population with the nature of relative low incidence of EAC, whether the endoscopic surveillance on confirmed BE patients after a screening endoscopic test can also demonstrate a cost-effectiveness result is fairly controversial, and short in relevant assessment. In addition, merely a small group of patients diagnosed with BE may finally develop EAC.[15] It is another concern on the cost-effectiveness of endoscopic surveillance on patients with BE. An endoscopy with multiple biopsies is not cheap, costing approximately $800 in the United States by a previous estimate.[16] Thus, to examine this issue, we aimed to estimate the cost-effectiveness of endoscopic surveillance on patients with BE for improving survival outcome of EAC patients in a whole-population model for Western population.

MATERIALS AND METHODS

Cost-Effectiveness Decision Tree

The decision tree simulates a whole-population model including cancer-free persons (Figure 1). The possibilities of terminals and survival payoff are retrieved from literature search in PubMed through the search strategy as, "('barrett's oesophagus'[All Fields] OR 'barrett esophagus'[MeSH Terms] OR ('barrett'[All Fields] AND 'esophagus'[All Fields]) OR 'barrett esophagus'[All Fields] OR ('barrett's'[All Fields] AND 'esophagus'[All Fields]) OR 'barrett's esophagus'[All Fields]) AND (esophageal[All Fields] AND ('adenocarcinoma'[MeSH Terms] OR 'adenocarcinoma'[All Fields]))." The studies on Western population, which reported the prevalence of BE, incidence of EAC among patients with BE or subpopulation without BE, and the EAC-related survival outcome of AS, IAS, and NS groups among patients with BE, as well as subpopulation without BE, were eligible for possibility retrieval.

First, the population is classified as BE patients and NBE subpopulations at a chance node. The prevalence of BE among general population is estimated as 1.6% by certain estimate.[17] Among BE patients, they enter 3 surveillance plans at a decision node, namely AS, IAS, and NS. The definitions of AS and IAS is referred to report from Verbeek et al.[12] AS was defined as $\geq$1 endoscopy every 3 years for BE with only intestinal metaplasia (IM), $\geq$1 endoscopy every year for BE with indefinite dysplasia (IDD) or low-grade dysplasia (LGD), and $\geq$1 endoscopy every 3 months for HGD.[12] IAS was defined as $\leq$1 endoscopy every 4.5 years for BE with IM, $\leq$1 endoscopy every 1.5 years for BE with IDD/LGD, and $\leq$1 endoscopy every 4.5 months for BE with HGD.[12] The proportions of these 3 groups are retrieved as 57%, 15%, and 28% in a Western population, respectively.[12] Particularly, the proportion of AS participants is considered as a variable, which is estimated in sensitivity analysis. Besides, among NBE population, NS endoscopy is performed in present model. For above 4 groups, all are divided into 2 terminal nodes at the chance nodes. The 2 terminals are incident EAC and EAC-free. Among BE patients from Western population, the incidence of EAC is 6.1 per 1000 person-years, whereas that is 1.0 per 1000 person-years among NBE persons.[18,19]

Cost (Per Person-Year)

The cost of each surveillance protocol is defined as yearly expenditure (€) for surveillance endoscopies per person. The period of surveillance is defined as from diagnosis of BE to before diagnosis of EAC. The cumulative times of endoscopies are influenced by the length of surveillance plan (Table 1). One endoscopy is counted for primary diagnosis of BE in AS, IAS, and NS groups. The calculation of endoscopy times is according to the definition of AS, IAS, and NS among patients with BE, namely in AS group, 1 endoscopy every 3 years for IM without

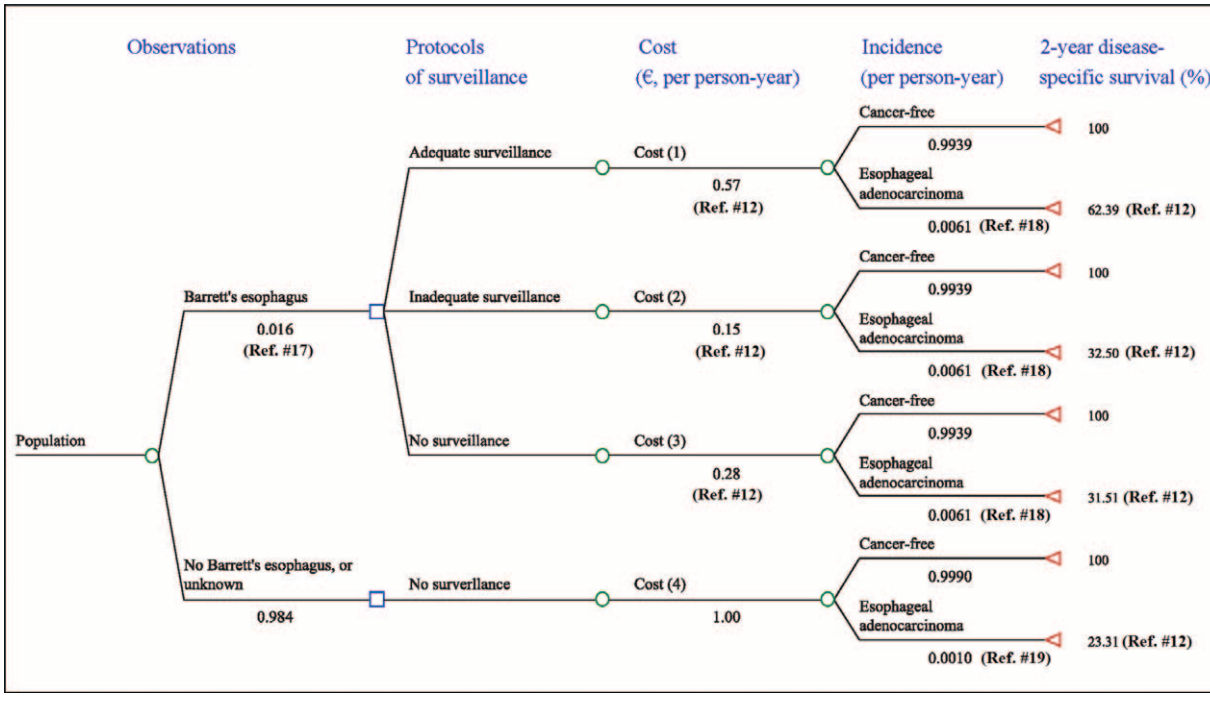

FIGURE 1. Cost-effectiveness decision tree model of endoscopic surveillance for esophageal adenocarcinoma among patients with definite Barrett's esophagus.

TABLE 1. Estimated Cost Per Person-Year of Each Surveillance Protocol

Strategy	**AS-BE**									**NS-BE**
Years of surveillance	2	3	4	5	6	7	8	9	10	Any
Times of endoscopies										
Diagnosis	1	1	1	1	1	1	1	1	1	1
Surveillance										
IM ($p = 0.4551$)	1	1	1	2	2	2	2	3	3	0
IDD/LGD ($p = 0.3072$)	2	3	4	5	6	7	8	9	10	0
HGD ($p = 0.2377$)	8	12	16	20	24	28	32	36	40	0
Cumulative times of endoscopies*	3.97	5.23	6.49	8.20	9.46	10.72	11.97	13.69	14.95	1.00
Cost (€, per person-year)†	1588.44	1394.43	1297.42	1312.03	1261.09	1224.71	1197.42	1216.65	1195.62	=800/y
Strategy	**IAS-BE**									**NS-NBE**
Years of surveillance	2	3	4	5	6	7	8	9	10	Any
Times of endoscopies										
Diagnosis	1	1	1	1	1	1	1	1	1	0
Surveillance										
IM ($p = 0.4551$)	0	0	0	1	1	1	1	2	2	0
IDD/LGD ($p = 0.3072$)	1	2	2	3	4	4	5	6	6	0
HGD ($p = 0.2377$)	5	8	10	13	16	18	21	24	26	0
Cumulative times of endoscopies*	2.50	3.52	3.99	5.47	6.49	6.96	7.98	9.46	9.93	0
Cost (€, per person-year)†	998.28	937.60	798.28	874.69	864.95	795.71	798.28	840.73	794.69	0

AS = adequate surveillance, BE = Barrett's esophagus, HGD = high-grade dysplasia, IAS = inadequate surveillance, IDD = indefinite dysplasia, IM = intestinal metaplasia, LGD = low-grade dysplasia, NBE = no Barrett's esophagus or unknown, NS = no surveillance, p = possibility.

* The times of endoscopies during surveillance were weighted the possibility of each grade of histology.

† Cost for surveillance was defined as the expenditure on endoscopies from diagnosis of BE to before diagnosis of esophageal adenocarcinoma.

dysplasia, 1 endoscopy every year for IDD and LGD, and 1 endoscopy every 3 months for HGD are performed respectively. In IAS group, estimates are the maximal times of endoscopies by the definition. Therefore, the IAS is performed in the manner of 1 endoscopy every 4.5 years for IM, every 1.5 years for IDD/LGD, and 4.5 months for HGD. For NBE participants, none endoscopy with diagnosis or surveillance aims is counted for estimate. To ease understanding, every endoscopy together with biopsy and pathology is simply priced at €800. The cumulative cost is calculated by summing the weighted costs of each group (Table 2).

TABLE 2. Calculation of Cost Per Person-Year of the Endoscopic Surveillance for Barrett's Esophagus Patients in a Whole-Population Model

Items	**Possibility and Cost**				**Cumulative Cost (€) ($CC_{(y)}$)***
Diseases (d)	BE			NBE	
Prevalence of BE ($p1$)	0.0160			0.9840	
Protocol of surveillance (i)	AS	IAS	NS	NS	
Proportion of participation ($p2$)	0.5714	0.1517	0.2769	1.0000	
Cost per person-year (€) ($C_{(y)}$)					
2-y surveillance	1588.43	998.29	400.00	0.00	18.72
3-y surveillance	1394.42	937.60	266.67	0.00	16.21
4-y surveillance	1297.42	798.29	200.00	0.00	14.69
5-y surveillance	1312.02	874.70	160.00	0.00	14.83
6-y surveillance	1261.10	864.94	133.33	0.00	14.22
7-y surveillance	1224.71	795.73	114.29	0.00	13.64
8-y surveillance	1197.42	798.29	100.00	0.00	13.33
9-y surveillance	1216.64	840.73	88.89	0.00	13.56
10-y surveillance	1195.63	794.70	80.00	0.00	13.21

AS = adequate surveillance, BE = Barrett's esophagus, C = cost per person-year, CC = cumulative cost per person-year among whole population, d = disease of Barrett's esophagus, i = protocol of surveillance, IAS = inadequate surveillance, NBE = no Barrett's esophagus or unknown, NS = no surveillance, p = possibility; y = years.

* $CC_{(y)} = \mathrm{sum}(p1 \times \mathrm{sum}(C_{(y)} \times p2_{(i)}))$.

TABLE 3. Calculation of Survival Payoff of the Endoscopic Surveillance for Barrett's Esophagus Patients in a Whole-Population Model

Items	Possibility and Survival Payoff			
Diseases (d)	BE			NBE
Prevalence of BE ($p1$)	0.0160			0.9840
Protocol of surveillance (i)	AS	IAS	NS	NS
Proportion of participation ($p2$)	0.5714	0.1517	0.2769	1.0000
Incidence of EAC ($p3$)	0.0061	0.0061	0.0061	0.0010
2-y disease-specific survival (%) ($s1$)	62.39	32.50	31.51	23.31
Survival payoff (EAC) ($sp1 = s1 \times p3$)	0.3806	0.1983	0.1922	0.0233
Possibility of cancer-free ($p4$)	0.9939	0.9939	0.9939	0.9990
2-y disease-specific survival (%) ($s2$)	100.00	100.00	100.00	100.00
Survival payoff (cancer-free) ($sp2 = s2 \times p4$)	99.3900	99.3900	99.3900	99.9000
Cumulative survival payoff of each group ($sp_{(i)}$)*	57.0118	15.1082	27.5708	99.9233
Cumulative survival payoff of BE and NBE ($sp_{(d)}$)†	1.5951			98.3245
Final survival payoff of the model (sp)‡	99.9196			

AS = adequate surveillance, BE = Barrett's esophagus, d = disease of Barrett's esophagus, EAC = esophageal adenocarcinoma, i = protocol of surveillance, IAS = inadequate surveillance, NBE = no Barrett's esophagus or unknown, NS = no surveillance, p = possibility, s = survival, sp = survival payoff.

* $sp_{(i)} = (sp1 + sp2) \times p2$.

† $sp_{(d)} = \text{sum}(sp_{(i)})$.

‡ $sp = \text{sum}(sp_{(d)})$.

Survival Payoff

The payoff of each terminal node is estimated of 2-year disease-specific survival possibility. The possibility of EAC-free group is 1.00, whereas the possibilities of incident EAC patients are 0.6239, 0.3250, 0.3151, and 0.2331 in AS-BE, IAS-BE, NS-BE, and NS-NBE groups, respectively.[12] The cumulative survival payoff of a population is the sum of all the 8 terminal nodes weighted by possibilities at each chance node (Table 3). Where suitably, the cumulative payoff is translated to 2-year disease-specific survival rate (%) or 2-year disease-specific mortality of EAC (per 100,000 persons).

Cost-Effectiveness and Incremental Cost-Effectiveness Analysis

Among patients with BE in a 5-year surveillance plan, the cost-effectiveness ratios (CERs) of AS, IAS, and NS are calculated and plotted with an acceptability curve. Incremental cost-effectiveness ratios (ICERs) are compared between AS and IAS groups, with reference to NS group. One-way sensitivity is performed by adjusting the length of surveillance plan and the proportion AS participants among BE patients. In whole-population models, the CER curve of different surveillance length is plotted with a fitting curve in the precondition of above-mentioned proportions of participants. The length of surveillance plan ranges from 2 to 10 years with a 1-year step. Likewise, the CER curve of different proportions of AS participants is plotted. Given a consistent 10% of IAS participants in a 5-year surveillance model, the proportions of AS participants range from 0% to 90% with a 10% step.

ETHICS

This cost-effectiveness analysis was completely based on published literature, whereas neither human nor animal was directly involved in research. Therefore, the protocol of the present study was not submitted to any ethics committee or institutional review board for approval.

RESULTS

In a 5-year surveillance model, comparison among AS, IAS, and NS groups for patients with BE demonstrates AS group requires greater cost per person-year but lower CER, compared with IAS group (Figure 2). Moreover, ICER of AS group is obviously preferable to that of IAS group, 6116 (€/%) vs 118,347 (€/%) (Figure 2).

In whole-population models provided the proportions 57%, 15%, and 28% for AS, IAS, and NS groups, the costs for endoscopic surveillance per person-year gradually decreases

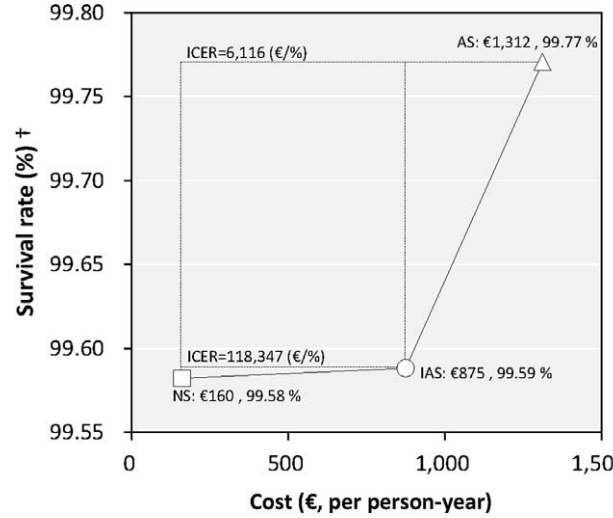

FIGURE 2. Lower cost-effectiveness ratio (CER) is found in adequate surveillance (AS) group than that in inadequate surveillance (IAS) group. Likewise, referring to no surveillance (NS) group, incremental CER (ICER) is lower in AS group than in IAS group. The precondition of this cost-effectiveness analysis is 57% participants with AS, 15% with IAS, and 28% without surveillance among all Barrett's esophagus patients. †Two-year disease-specific survival percentage of esophageal adenocarcinoma.

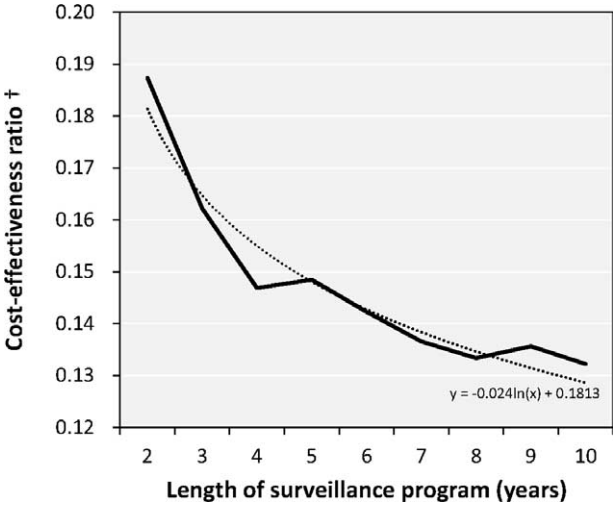

FIGURE 3. Cost-effectiveness ratio (CER) decreases along with prolonged surveillance in a whole-population model, given 57% participants with adequate surveillance, 15% with inadequate surveillance, and 28% without surveillance among all BE patients. †CER = € per person-year for endoscopies/2-year disease-specific survival percentage of esophageal adenocarcinoma.

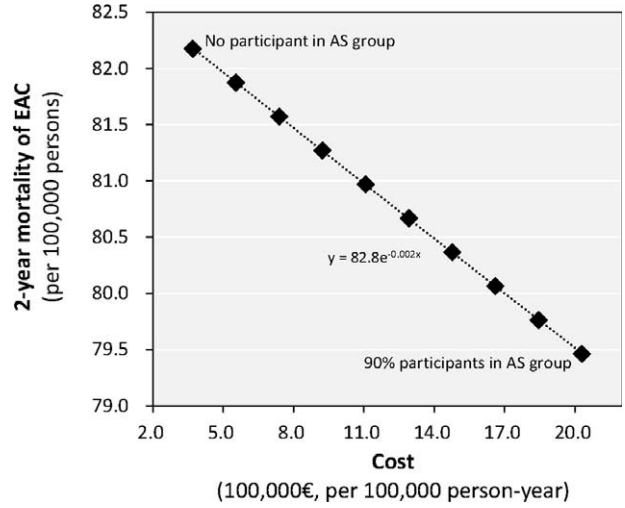

FIGURE 4. One-way sensitivity analysis on proportion of participants among Barrett's esophagus (BE) patients in a whole-population model for 5-year surveillance. In this one-way sensitivity analysis, the proportion of BE patients in inadequate surveillance group was consistent at 10% level, whereas the proportion of BE patients participating in adequate surveillance group ranged from 0% to 90% by every 10% steps. AS = adequate surveillance; EAC = esophageal adenocarcinoma.

along with the prolonged surveillance durations (Tables 2 and 3). It implies that a longer surveillance plan can decrease yearly budget burden, despite factually increased overall costs to complete entire surveillance plan. Therefore, the CERs correspondingly decrease along with prolonged surveillance plans (Figure 3).

Given a consistent 10% proportion of IAS participants among BE patients in a 5-year surveillance plan of whole-population model, one-way sensitivity analysis is performed by ranging the proportion of BE patients in AS group from 0% to 90% with a step of 10%. Increasing the proportion of AS participants not only raises the yearly cost (Figure 4), but also decreases the 2-year mortality of EAC with gradually increasing CERs (Figure 5). ICER analysis shows each extra €184,324 per 100,000 person-years will be able to reduce the 2-year EAC-related mortality of 0.3 per 100,000 persons. On the whole, the maximal payoff is up to 2-year mortality reduction of 2.7 per 100,000 persons by spending extra €1,658,913 per 100,000 person-years.

DISCUSSION

This study estimates the cost-effectiveness performance of endoscopic surveillance for Western patients with BE to improve the overall population survival benefit. The results show that adequate endoscopic surveillance for patients with BE is able to be more cost-effective than IAS. Prolonging the surveillance years can decrease the yearly cost in whole population, despite increased total cost. Increasing the proportion of participants in AS group can improve the survival benefit of a population with acceptable extra expenditure.

The incidences of EAC are clearly different between the Western and Eastern countries because the risk factors, such as obesity and gastroesophageal reflux associating with BE development, are more prevalent in the Western countries.[1,3] BE can induce a significant lifetime risk of developing HGD and EAC.[20,21] Meanwhile, the 5-year survival rate following a diagnosis of EAC is <15% by certain estimates.[22,23] Moreover, the increase of early EAC is obviously associated with advantage in overall outcome.[12] Therefore, theoretically, active screening and surveillance for BE can lead to greater proportion of early EAC and improve overall survival.

Although the present analysis indicates the cost-effectiveness of endoscopic surveillance for patients with BE is reasonable and acceptable to some extent, more selective subgroup with higher risk of developing EAC can possibly

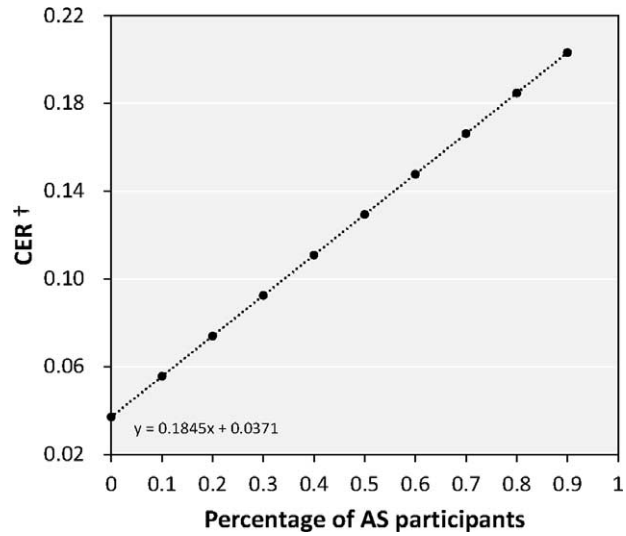

FIGURE 5. Cost-effectiveness ratio (CER) increases along with proportion of adequate surveillance (AS) participants, given a consistent 10% participants with inadequate surveillance in a 5-year surveillance plan. †CER = € per person-year for endoscopies/2-year disease-specific survival percentage of esophageal adenocarcinoma.

improve the cost-effectiveness of surveillance. Surveillance endoscopy of nondysplastic Barrett's esophagus that fails to detect IM, or negative surveillance, is known to occur in clinical practice.[24] Duits et al[25] found LGD in BE had a markedly increased risk of malignant progression, but the vast majority of patients diagnosed of LGD at community could be downstaged after expert pathological review and had a low progression risk. Negative surveillance occurs frequently in short-segment nondysplasia BE, whereas a <1 cm segment of nondysplasia BE is diagnosed, a significant proportion of patients may go on to have continuously undetected IM on consecutive surveillance endoscopic examinations without intervention.[24] A recent report suggested that endoscopic surveillance of patients with nondysplasia BE was unlikely to be cost-effective for the majority of patients.[26]

Therefore, the grade of dysplisia may be an independent factor influencing the cost-effectiveness of surveillance strategy for BE patients.[27] A narrow indication for endoscopic surveillance merely covers BE patients with proven HGD can be an alternative choice for candidate selection in Western population regarding the nature of low incidence. Moreover, molecular biomarkers labeled high-risk subgroups of dysplastic BE are expected to narrow the candidates of surveillance, but prospective validation studies are required before clinical application.[28,29] In addition, the post genome-wide association analysis in the Barrett's and Esophageal Adenocarcinoma Consortium genome-wide association study did not find any common genetic variants within components of the miRNA biogenesis core pathway to likely modulate susceptibility to esophgeal adenocarcinoma or BE.[30] Further studies may be therefore necessary and warranted to identify simple clinical biomarkers for the selection of a high-risk subpopulation to develop EAC.

There are several limitations of this study requiring to be carefully considered. First, a cost-effectiveness model is not as perfect as Markov model, which is able to simulate a better virtual population. The risk of developing EAC is expected to decrease over time with negative or stable results by endoscopy. Correspondingly, the interval of surveillance can be alternated over time based on negative or stable results by endoscopy. However, present cost-effectiveness model is unable to simulate this transition. Second, present analysis only involves direct medical cost of endoscopy during surveillance. Direct medical costs, such as treatment during surveillance and postdiagnosis of EAC, are not counted into model. Radiofrequency ablation of BE with confirmed LGD can reduce risk of developing HGD and adenocarcinoma.[31] The treatment of early or locally advanced EAC may differ greatly and influence the medical cost largely.[32] Therefore, more participants in AS group can lead to detecting more early diseases and reduce postdiagnosis medical cost. Third, the survival payoff defined as disease-specific survival rate is also not the prefect one. During the endoscopic surveillance of patients with BE, additional incident cases of other tumors located as upper digestive tract, such as gastric cancer and stromal gastrointestinal tumor, can improve the overall survival outcome in endoscopic surveillance groups. Finally, the 2-year outcome point was not efficient enough compared with 5-year follow-up observational results. The present cost-effectiveness estimate was dependent on current available published literature. Through literature searching in PubMed database, there was no report containing the 5-year disease-specific survival outcome. Thus, longer follow-up and Markov model may provide more robust assessment on endoscopic surveillance among patients with BE.

In summary, AS for patients with BE is a more cost-effective approach than IAS to improve population survival outcome. A longer surveillance plan can reduce yearly budget. The total expenditure for surveillance of patients with BE and its survival payoff are reasonable due to the fairly low prevalence of BE among whole population. Attempt to increase the proportion of AS patients can induce decline in population mortality of EAC, despite extra but acceptable expenditure. However, regarding optimal cost-effectiveness, further studies are still required to identify a high-risk subpopulation out of BE patients for endoscopic surveillance.

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