ORIGINAL ARTICLE

Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis

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ABSTRACT

Objective Surveillance is recommended for Barrett's oesophagus (BO) to detect early oesophageal adenocarcinoma (OAC). The aim of this study was to evaluate the cost-effectiveness of surveillance.

Design We included 714 patients with long-segment BO in a multicentre prospective cohort study and used a multistate Markov model to calculate progression rates from no dysplasia (ND) to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and OAC. Progression rates were incorporated in a decision-analytic model, including costs and quality of life data. We evaluated different surveillance intervals for ND and LGD, endoscopic mucosal resection (EMR), radiofrequency ablation (RFA) and oesophagectomy for HGD or early OAC and oesophagectomy for advanced OAC. The incremental cost-effectiveness ratio (ICER) was calculated in costs per quality-adjusted life-year (QALY).

Results The annual progression rate was 2% for ND to LGD, 4% for LGD to HGD or early OAC and 25% for HGD or early OAC to advanced OAC. Surveillance every 5 or 4 years with RFA for HGD or early OAC and oesophagectomy for advanced OAC had ICERs of €5.283 and €62.619 per QALY for ND. Surveillance every five to one year had ICERs of €4.922, €30.067, €32.531, €41.499 and €75.601 per QALY for LGD. EMR prior to RFA was slightly more expensive, but important for tumour staging.

Conclusions Based on a Dutch healthcare perspective and assuming a willingness-to-pay threshold of €35.000 per QALY, surveillance with EMR and RFA for HGD or early OAC, and oesophagectomy for advanced OAC is cost-effective every 5 years for ND and every 3 years for LGD.

Significance of this study

What is already known on this subject?

- Endoscopic surveillance is recommended for Barrett's oesophagus to detect oesophageal adenocarcinoma at an early stage.
- Over the past years, there has been a major shift in the treatment of patients with high-grade dysplasia and oesophageal adenocarcinoma.
- Previous studies have investigated the cost-effectiveness of different surveillance intervals and treatment strategies with conflicting results.

What are the new findings?

- Endoscopic treatment with endoscopic mucosal resection and radiofrequency ablation is a cost-effective alternative for oesophagectomy in patients with high-grade dysplasia or early adenocarcinoma.
- Surveillance every 5 years with endoscopic mucosal resection for high-grade dysplasia or early adenocarcinoma, radiofrequency ablation for residual Barrett's oesophagus and oesophagectomy with neoadjuvant chemoradiotherapy for advanced adenocarcinoma is cost-effective for patients without dysplasia in long-segment Barrett's oesophagus.
- Surveillance every 3 years with endoscopic mucosal resection for high-grade dysplasia or early adenocarcinoma, radiofrequency ablation for residual Barrett's oesophagus and oesophagectomy with neoadjuvant chemoradiotherapy for advanced adenocarcinoma is cost-effective for patients with low-grade dysplasia in long-segment Barrett's oesophagus.

How might it impact on clinical practice in the foreseeable future?

- Surveillance intervals should be prolonged to 5 years for patients without dysplasia and 3 years for patients with low-grade dysplasia in long-segment Barrett's oesophagus in order to be cost-effective.
- Identification of new risk factors is needed to improve risk stratification and thereby the cost-effectiveness of surveillance with shorter surveillance intervals.

INTRODUCTION

Barrett's oesophagus (BO) is a premalignant condition in which patients have an increased risk of developing oesophageal adenocarcinoma (OAC) with an estimated incidence of 0.1–0.5% per year.[1–4] The development of OAC in BO is a gradual process, in which metaplastic epithelium with no dysplasia (ND) evolves to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and eventually OAC under the influence of chronic oesophageal acid exposure.[5] Once a patient has developed OAC, the prognosis is poor with a 5-year survival of less than 20%.[6 7] Endoscopic surveillance is therefore recommended for BO to

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detect OAC at an early stage, when curative treatment is still feasible.[8 9] Histological diagnosis of dysplasia is the golden standard for predicting neoplastic progression in BO and is therefore used for defining surveillance intervals. Current guidelines recommend surveillance every 3–5 years in patients with ND, every 6–12 months in patients with LGD and every 3 months in patients with HGD (in the absence of endoscopic therapy). Most patients with BO belong to the group with ND and have an overall low risk of neoplastic progression. The majority of patients with non-dysplastic BO will never develop HGD or OAC and die of causes not related to BO, which makes surveillance controversial in this patient group.[10] In patients with LGD, the risk of neoplastic progression is increased, which makes surveillance more effective. However, histological diagnosis of LGD is subject to considerable intraobserver and interobserver variation that limits its predictive value.[11 12]

Over the past years, there has been a major shift in the treatment of BO patients with the introduction of endoscopic treatment modalities such as endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA). EMR is used to remove visible mucosal irregularities and has a role in tumour staging, while RFA is used to eradicate residual intestinal metaplasia. Although use of RFA alone is still controversial, some studies suggest that this might be just as effective.[13 14] Nowadays endoscopic treatment with EMR and RFA is the preferred strategy for HGD and early OAC.[8 9] Recently, it was suggested that RFA might also be suitable for patients without neoplastic progression, especially for those with confirmed LGD. However, it is difficult to make a reliable diagnosis of LGD and the risk of progression may vary greatly among these patients. Therefore, no strict recommendations are made for patients with LGD.[9] Oesophagectomy is still the mainstay for curative treatment of advanced OAC, but is nowadays complemented with neoadjuvant chemoradiotherapy.[15] Chemotherapy, oesophageal stenting and brachytherapy have been added to the palliative treatment of OAC.[16]

One of the key questions in the discussion about BO surveillance is whether surveillance and (endoscopic) treatment is cost-effective. The cost-effectiveness of BO surveillance has been investigated in previous studies, where transition rates to HGD and OAC were mostly based on pooled literature data.[17–26] For a more accurate representation of the natural history of BO and its progression to OAC, true transition and misclassification rates can be calculated in a multistate Markov (MSM) model using prospectively collected follow-up data from a large cohort of patients with BO.[27] The aim of this study was to evaluate the cost-effectiveness of different surveillance intervals and treatment strategies for patients without dysplasia and LGD in long-segment BO, within a large multicentre prospective cohort study.

METHODS

Study design

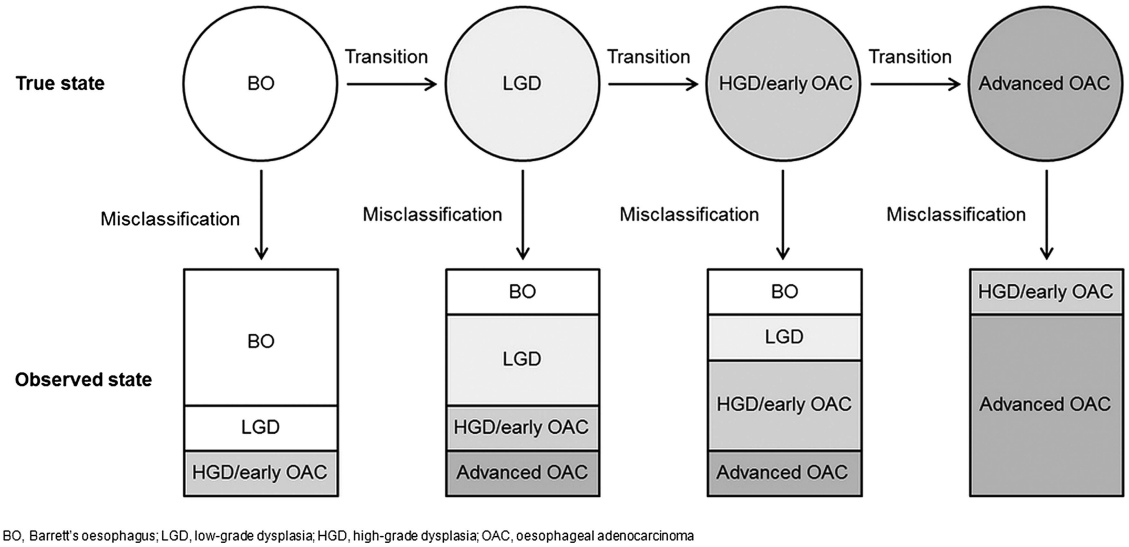
We conducted a large multicentre prospective cohort study in 3 university medical centres and 12 regional hospitals throughout the Netherlands (see online supplementary appendix 1). Between November 2003 and December 2004, 714 consecutive patients were included presenting with known or newly diagnosed BO of at least 2 cm, without a history of HGD or OAC. The diagnosis was confirmed by the presence of intestinal metaplasia. Patients were followed according to the guidelines of the American College of Gastroenterology.[9] During follow-up, incident cases of HGD and OAC were identified. Patients who developed HGD or OAC were considered to have reached an endpoint and received appropriate treatment. At each follow-up, endoscopy targeted biopsies were taken from mucosal abnormalities and four-quadrant biopsies were taken every 2 cm from the most distal to the most proximal part of the BO epithelium. Biopsies were first graded by a local pathologist and then by an expert pathologist for second opinion. After examining all biopsies, the highest degree of abnormality was reported for each endoscopy. When the local and expert pathologist disagreed on the grade of dysplasia, the slides were reviewed by a second expert pathologist. Pathologists were blinded to the diagnosis of each other and a final diagnosis was made only if at least two pathologists agreed on the grade of dysplasia. HGD and OAC limited to the mucosa (T1a) were considered as one category (HGD or early OAC) since both are treated similarly. Carcinomas invading the submucosa (T1b), muscularis propria (T2), adventitia (T3) or adjacent structures (T4) were considered as another category (advanced OAC).

Incidence, misclassification and transition rates

The incidence rates of LGD, HGD and OAC were calculated by dividing the number of incident cases by the total number of follow-up years. Since neoplastic progression is thought to be a gradual process, patients who developed HGD or OAC were supposed to have passed the stage of LGD. When LGD was not observed, the time till the development of LGD was estimated to be half of the follow-up time in patients who developed HGD or early OAC and one-third of the follow-up time in patients who developed advanced OAC. Patients who developed advanced OAC were supposed to have passed the stage of HGD. When HGD was not observed, the time till the development of HGD was estimated to be two-thirds of the follow-up time in patients with ND and half of the follow-up time in patients with LGD. Since histological diagnosis is subject to misclassification due to sampling error and interobserver variation, the histological diagnosis observed at each endoscopy may not represent the true histological diagnosis (or 'true state'). The observed state is dependent on the true state as well as the misclassification rates (figure 1). In a MSM model, misclassification rates can be estimated based on observed follow-up data.[27] The assumption was made that advanced OAC was not observed in patients with true ND and that ND or LGD was not observed in patients with true advanced OAC. The misclassification rates were used to convert observed transition rates into true transition rates. Since patients who developed HGD or OAC were excluded from further follow-up, we were not able to observe the transition rate from HGD or early OAC to advanced OAC. Therefore, we added one patient with HGD to our follow-up data who developed advanced OAC after 4 years of follow-up, based on observations in another Dutch BO cohort.[28] Although regression of dysplasia was observed in some patients, we assumed that true regression of dysplasia was not possible and that the observed regression was due to sampling error and observer variability.

Surveillance strategies

We evaluated the cost-effectiveness of 16 different surveillance strategies. The first strategy consisted of upper endoscopy in case of symptoms such as dysphagia or severe pyrosis and oesophagectomy with neoadjuvant chemoradiotherapy in patients with OAC (no surveillance). The other 15 strategies consisted of surveillance with different intervals (1–5 years) for patients with ND or LGD and endoscopic or surgical intervention for patients with HGD or OAC. Treatment strategies for patients with HGD or early OAC consisted of RFA alone, EMR followed by RFA or



BO, Barrett's oesophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; OAC, oesophageal adenocarcinoma

Figure 1 Multistate Markov model.

oesophagectomy with neoadjuvant chemoradiotherapy. We assumed that complications occurred in 2.2% after EMR, 6.5% after RFA and 22.9% after oesophagectomy and considered costs associated with additional treatment.[29–31] After endoscopic treatment with EMR or RFA, we assumed that patients returned to ND and surveillance was resumed. We assumed that 5–10% of patients had early recurrence for which they received endoscopic treatment. After endoscopic treatment, patients remained at risk for neoplastic progression. Treatment of patients with advanced OAC consisted of oesophagectomy with neoadjuvant chemoradiotherapy. Palliative treatment of OAC consisted of chemotherapy, oesophageal stenting or brachytherapy and terminal care.

Costs and quality of life

The cost-effectiveness analysis was performed from a healthcare perspective. Direct medical true costs of endoscopic and surgical procedures, neoadjuvant and palliative treatment, and inpatient and outpatient care were obtained using the 2012 reimbursement rates per diagnosis and intervention as provided by the Dutch healthcare authority (NZa).[32] Direct medical costs include costs of medical procedures, equipment, overhead, personnel and honoraria of medical specialists. Hospitals get these costs reimbursed by the health insurance. Data on quality of life (utilities) associated with different health states were derived from the published literature and were used to convert absolute life-years of survival into quality-adjusted life-years (QALYs).[33–35] Costs and utilities were discounted at an annual rate of 5%, which allows us to compare our results with those of previous studies (table 1).

Cost-effectiveness analysis

For the analysis, we used a modification of a previously published decision-analytic Markov model, which was constructed in Windows Decision Maker (beta test V.2010).[22] In this computer model, a BO cohort was simulated with as base case a 55-year-old male BO patient with ND or LGD. The natural history of the BO cohort was modelled to examine the costs of no surveillance and its effects on quality of life. Subsequently, the effect of multiple surveillance strategies was evaluated with various surveillance intervals for patients with ND or LGD and endoscopic or surgical interventions for patients with HGD or OAC. Simulation of the BO cohort started with baseline endoscopy and was continued with cycles of 3 months until death. True progression rates from ND to LGD, HGD and advanced OAC were estimated in a MSM model based on the progression and misclassification rates observed in our cohort. Death from other causes than OAC was possible in any state and was modelled as a time-dependent variable with the risk increasing with age.

Statistical analysis

Primary outcome of the study was the incremental cost-effectiveness ratio (ICER) of each surveillance strategy. The ICER is defined as the difference in cost between two surveillance strategies, divided by the change in QALYs. Whether a strategy is cost-effective depends on the willingness-to-pay threshold, which is highly variable among countries. In the Netherlands, a willingness-to-pay threshold is used of €20.000 to €80.000, depending on the severity of the condition.[36] In the USA and the UK, a willingness-to-pay threshold of €35.000 is used.[37 38] In one-way sensitivity analyses, we evaluated the effect of halving or doubling all individual input variables, while keeping the other input variables unchanged. In addition, we performed analyses using a discount rate of 3% and using transition rates of 200%, 50% and 25% of the calculated values.

RESULTS

Patient characteristics

A total of 714 patients (73% male, median age 61 years) with a median BO length of 4 cm were included and followed during surveillance with a median duration of 6 years and a total of 3992 person-years of follow-up. Most patients (74%) were already known with BO before inclusion in the study for a median duration of 5 years (table 2).

Incidence and transition rates

At baseline, 606 (85%) patients had ND and 108 (15%) LGD. In patients with ND, the observed incidence of LGD was 6% per year. In patients with LGD, the observed annual incidence was 13% for progression to HGD or early OAC and 57% for regression to ND. During follow-up, 46 (6%) patients developed HGD or early OAC and 4 (1%) patients developed advanced OAC with an annual incidence of 1.2% (95% CI 0.9

Table 1 Variables included in cost-effectiveness analysis

Variables		Base value	Reference
Transition rates (per year)			
ND to LGD		0.023	Own data
LGD to HGD/early OAC		0.043	Own data
HGD/early OAC to advanced OAC		0.250	[28]
Misclassification rates			
True state	*Observed state*		
ND	LGD	0.086	Own data
ND	HGD/early OAC	0.004	Own data
LGD	ND	0.247	Own data
LGD	HGD/early OAC	0.123	Own data
LGD	advanced OAC	0.008	Own data
HGD/early OAC	LGD	0.016	Own data
HGD/early OAC	advanced OAC	0.287	Own data
advanced OAC	HGD/early OAC	0.036	Own data
Probabilities			
Probability of surgery		0.600	Cancer register
Probability of curative treatment		0.500	Cancer register
Probability of dying from surgery		0.018	[49]
Probability of complications from surgery		0.229	[29]
Probability of complications from endoscopy		0.001	[50]
Probability of complications from EMR		0.022	[31]
Probability of complications from RFA		0.065	[30]
Costs			
Cost of endoscopy		€629	NZa
Cost of endoscopy with complication		€1677	NZa
Cost of EMR		€1925	Expert opinion
Cost of EMR with complication		€3425	Expert opinion
Cost of RFA		€6210	Expert opinion
Cost of RFA with complication		€8710	Expert opinion
Cost of staging adenocarcinoma		€2499	NZa
Cost of oesophagectomy		€17.887	NZa
Cost of oesophagectomy with complication		€38.930	NZa
Cost of postoperative follow-up, per year		€948	NZa
Cost of neoadjuvant chemoradiation		€8792	NZa
Cost of palliative chemotherapy		€3867	NZa
Cost of palliative stenting		€1215	NZa
Cost of brachytherapy		€3004	NZa
Cost of terminal care, per year		€32565	[22]
Quality of life			
Quality of life after HGD diagnosis		0.84	[33 35]
Quality of life after OAC diagnosis		0.66	[33 35]
Quality of life after endoscopic treatment (short term)		0.93	[33 35]
Quality of life after oesophagectomy (short term)		0.86	[34]
Quality of life after oesophagectomy (long term)		0.90	[34]
Duration of short-term morbidity			
After endoscopic treatment		3 days	[30]
After oesophagectomy		4 weeks	[34]
Discount rate		0.05	[22]

EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; ND, no dysplasia; NZa, Dutch healthcare authority; OAC, oesophageal adenocarcinoma; RFA, radiofrequency ablation.

Table 2 Characteristics of patients included in the Barrett's oesophagus (BO) cohort

	Cohort (n=714)
Follow-up	
Median, years (IQR)	6.1 (4.4–7.0)
Total, person-years	3992
Age	
Median, years (IQR)	61 (53–69)
Gender	
Male	520 (73%)
Female	194 (27%)
BO diagnosis	
<Inclusion	529 (74%)
≥Inclusion	185 (26%)
BO length	
Median, cm (IQR)	4 (2–6)
Baseline oesophagitis	
No	642 (90%)
Yes	72 (10%)
Baseline histology	
No dysplasia	606 (85%)
Low-grade dysplasia	108 (15%)
Mucosal abnormalities	
No	694 (97%)
Yes	20 (3%)

to 1.6) for HGD or early OAC and 0.1% (95% CI 0.0 to 0.3) for advanced OAC, which was stable over time and similar for patients with incident and prevalent BE (table 3). After neoplastic progression, 33 patients were treated with EMR. In 75% of cases, the histological diagnosis was confirmed in the EMR specimen, in 20% the histological diagnosis was downgraded and in 5% upgraded after evaluation of the EMR specimen.

The true annual transition rate was estimated to be 2.3% for ND to LGD, 4.3% for LGD to HGD or early OAC and 25% for HGD or early OAC to advanced OAC. The true incidence rate of HGD or OAC was estimated to be 0.1% per year in ND and 4.9% per year in LGD.

Surveillance in patients with ND

In patients with ND, the costs of no surveillance were €5.695 for 12.62 discounted QALYs. Surveillance every 5 years with RFA for HGD or early OAC and oesophagectomy for advanced OAC resulted in an increase in life expectancy by 0.25 QALYs and an increase in costs by €1.324, representing an ICER of €5.283 per QALY. Surveillance every 4 years resulted in an additional increase in life expectancy by 0.02 QALYs and an additional increase in costs by €802, representing an ICER of €62.619 per QALY. Strategies with surveillance intervals shorter than 4 years provided substantial higher costs with similar or less QALYs gained (table 4).

Strategies using EMR prior to RFA had similar effects on QALYs compared with strategies using RFA alone, but were slightly more expensive. Strategies using oesophagectomy were much more expensive with less QALYs gained. However, use of RFA alone is still controversial and EMR contributed significantly to tumour staging, which may justify the slightly higher costs. In summary, when assuming a willingness-to-pay threshold of €35.000 per QALY, surveillance every 5 years with EMR followed by RFA or RFA alone for HGD or early OAC and oesophagectomy with neoadjuvant chemoradiotherapy for advanced OAC is a cost-effective strategy for long-segment BO

Table 3 Observed annual incidence rates in patients with Barrett's oesophagus

Transition	Observed	Cases interpolated	Total	Follow-up in patient-years	Incidence rate with 95% CI
ND to LGD	180	27	207	3640	5.7% (4.9 to 6.5)
LGD to HGD/early OAC	18	28	46	350	13.1% (9.6 to 17.5)
LGD to ND	198	–	198	350	56.6% (49.0 to 65.0)
ND/LGD to HGD/early OAC	42	4	46	3990	1.2% (0.9 to 1.6)
ND/LGD to advanced OAC	4	–	4	3992	0.1% (0.0 to 0.3)

HGD, high-grade dysplasia; LGD, low-grade dysplasia; ND, no dysplasia; OAC, oesophageal adenocarcinoma.

with ND. When assuming a willingness-to-pay threshold of €80.000 per QALY, surveillance every 4 years is cost-effective (figure 2).

Surveillance in patients with LGD

In patients with LGD, the costs of no surveillance were €21.806 for 10.95 discounted QALYs. Surveillance every 5 years with RFA for HGD or early OAC and oesophagectomy for advanced OAC resulted in an increase in life expectancy by 0.96 QALYs and an increase in costs by €4.756, representing an ICER of €4.922 per QALY. Surveillance every 1–4 years resulted in an additional increase in life expectancy, but at increasing costs (table 4). EMR followed by RFA for patients with HGD or early OAC had similar effects on QALYs compared with strategies using RFA alone, but costs were slightly higher. Oesophagectomy was much more expensive with less QALYs gained. When assuming a willingness-to-pay threshold of €35.000 per QALY, surveillance every 3 years with EMR followed by RFA or RFA alone for HGD or early OAC and oesophagectomy with neoadjuvant chemoradiotherapy for advanced OAC is a cost-effective strategy for long-segment BO with LGD. When assuming a willingness-to-pay threshold of €80.000 per QALY, surveillance every year is cost-effective.

Sensitivity analysis

The most critical variables in the cost-effectiveness analysis were the true progression rates. When progression rates were doubled, surveillance every 2 years was cost-effective for long-segment BO with ND and every year for LGD with ICERs of €27.073 and €17.973 per QALY (table 5). When progression rates were halved, surveillance every 5 years was cost-effective for both ND and LGD with ICERs of €29.802 and €7.631 per QALY. When progression rates were only 25% of the calculated values, surveillance was only cost-effective for LGD, with intervals of 5 years and an ICER of 11.753 per QALY. Changes in costs and quality of life data had less impact on the cost-effectiveness of surveillance. When using a discount rate of 3% instead of 5%, results were similar.

DISCUSSION

In this large prospective study, we evaluated the cost-effectiveness of different surveillance intervals and treatment strategies in patients with long-segment BO. Assuming a willingness-to-pay threshold of €35.000 per QALY, endoscopic surveillance is cost-effective with intervals of 5 years, EMR followed by RFA for HGD or early OAC, and oesophagectomy with neoadjuvant chemoradiotherapy for advanced OAC in patients with non-dysplastic BO. Surveillance every 3 years is cost-effective for patients with LGD. For patients with ND, the results of our study correspond to recommendations made in current guidelines.[8 9] For patients with LGD, however, surveillance is recommended with intervals of 6–12 months, while according to our study intervals should be at least 3 years in order to be cost-effective. When histology is used as the only predictor for

Table 4 Cost-effectiveness of different surveillance intervals and treatment strategies in patients with Barrett's oesophagus

	No dysplasia			Low-grade dysplasia		
Strategy	Costs	QALYs	ICER	Costs	QALYs	ICER
No surveillance	€5.695	12.62		€21.806	10.95	
Surveillance every 5 years with RFA	€7.019	12.87	€5.283	€26.562	11.91	€4.922
Surveillance every 5 years with EMR followed by RFA	€7.247	12.87	x	€28.245	11.91	x
Surveillance every 5 years with oesophagectomy	€13.965	12.64	x	€50.909	11.33	x
Surveillance every 4 years with RFA	€7.821	12.89	€62.619	€28.964	11.99	€30.067
Surveillance every 4 years with EMR followed by RFA	€8.086	12.89	x	€30.856	11.99	x
Surveillance every 4 years with oesophagectomy	€15.229	12.63	x	€51.835	11.34	x
Surveillance every 3 years with RFA	€9.005	12.90	€105.755	€32.071	12.09	€32.531
Surveillance every 3 years with EMR followed by RFA	€9.277	12.90	x	€34.238	12.09	x
Surveillance every 3 years with oesophagectomy	€16.890	12.61	x	€52.851	11.34	x
Surveillance every 2 years with RFA	€10.984	12.90	€324.420	€36.242	12.19	€41.499
Surveillance every 2 years with EMR followed by RFA	€11.286	12.90	x	€38.779	12.19	x
Surveillance every 2 years with oesophagectomy	€19.325	12.59	x	€53.960	11.34	x
Surveillance every year with RFA	€15.074	12.89	x	€42.086	12.27	€75.601
Surveillance every year with EMR followed by RFA	€15.421	12.89	x	€45.133	12.27	x
Surveillance every year with oesophagectomy	€23.686	12.54	x	€55.159	11.34	x

EMR, endoscopic mucosal resection; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted-life-years; RFA, radiofrequency ablation; x, strategy dominated by alternative.

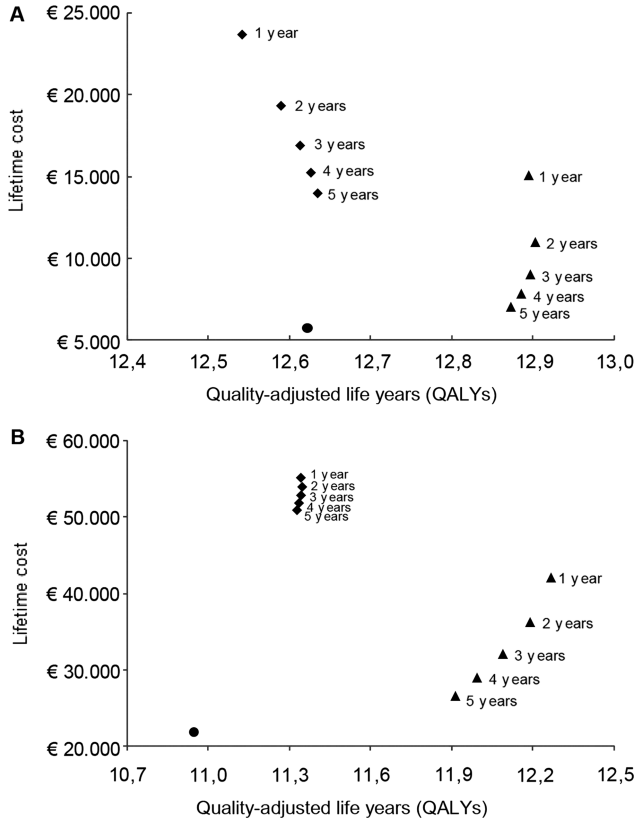


Figure 2 Lifetime costs and quality-adjusted life-years associated with different surveillance strategies in patients with no dysplasia (A) or low-grade dysplasia (B).

neoplastic progression, surveillance intervals should be prolonged to 3 years in patients with LGD to be cost-effective. However, with prolongation of the surveillance intervals, the risk of interval carcinomas may increase. Identification of additional risk factors may improve risk-stratification and thereby the cost-effectiveness of surveillance with short intervals.

Previous studies investigating the cost-effectiveness of BO surveillance have shown highly variable results, mainly due to different assumptions about progression rates and quality of life associated with different health states. Surveillance was reported to be cost-effective in four studies with surveillance intervals ranging from 2 to 5 years.[20 21 23 24] However, in four other studies surveillance was not cost-effective with sometimes even higher costs and less quality of life than without surveillance.[17 19 22 26]

Over the past years there has been a major shift in the treatment BO patients with the introduction of endoscopic treatment strategies. We therefore included EMR and RFA in this cost-effectiveness analysis.[8 9] An advantage of EMR is that it not only removes mucosal abnormalities suspect for dysplasia, but also allows for evaluation of tissue invasion.[39 40] RFA is used in addition to EMR for complete eradication of BO, but may also be used as a single-treatment modality.[30 41] Previous studies have shown that RFA is effective in eradicating HGD, early OAC and complete segments of BO with low complication rates.[30 41–43] The current study shows that RFA is also cost-effective, which corresponds to the results of previous studies.[17–26] Some recent studies suggested that RFA might also be cost-effective in patients with confirmed LGD.[43 44] However, it is hard to make a reliable diagnosis of LGD that limits its feasibility. Therefore, we did not include RFA as a treatment strategy for LGD. Use of EMR in addition to RFA was associated with similar effects on quality of life, but was slightly more expensive. As a result, strategies using EMR followed by RFA were dominated by strategies using RFA alone. In two recent retrospective studies, it was shown that use of EMR before RFA had no additional benefit, which suggests that RFA alone might be a suitable treatment for patients with HGD or early OAC.[13 14] However, use of RFA alone is still controversial, and although use of additional EMR might be slightly more expensive, it allows for evaluation of tissue invasion and is therefore useful for tumour staging. The current study shows that in 25% of patients histological diagnosis was changed after evaluation of the EMR specimens and in some patients another treatment strategy was preferred based on these results. We therefore believe there is an additional role for EMR prior to RFA, which also corresponds to recommendations in current guidelines.[8 9]

The cost-effectiveness of a surveillance strategy not only depends on the costs and effects on quality of life, but also on

Table 5 Cost-effectiveness of different surveillance intervals in case of higher or lower transition rates (sensitivity analysis)

	Transition rates 200%			Transition rates 50%			Transition rates 25%		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
No dysplasia									
No surveillance	€9.886	11.89		€3.501	12.87		€2.443	12.95	
Surveillance every 5 years with RFA	€9.731	12.54	x	€5.864	12.95	€29.802	€5.357	12.97	€126.139
Surveillance every 4 years with RFA	€10.510	12.60	€12.560	€6.667	12.95	x	€6.152	12.97	x
Surveillance every 3 years with RFA	€11.624	12.67	€16.152	€7.868	12.95	x	€7.352	12.96	x
Surveillance every 2 years with RFA	€13.473	12.74	€27.073	€9.883	12.94	x	€9.376	12.95	x
Surveillance every year with RFA	€17.403	12.78	€87.727	€10.411	12.93	x	€13.510	12.94	x
Low-grade dysplasia									
No surveillance	€24.747	9.44		€19.772	11.84		€18.636	12.26	
Surveillance every 5 years with RFA	€29.778	10.76	€3.817	€24.548	12.46	€7.631	€23.503	12.68	€11.753
Surveillance every 4 years with RFA	€32.095	10.90	€16.398	€27.034	12.48	€135.848	€26.027	12.67	x
Surveillance every 3 years with RFA	€35.053	11.11	€14.100	€30.249	12.50	€206.087	€29.287	12.65	x
Surveillance every 2 years with RFA	€39.024	11.39	€14.080	€34.540	12.50	€670.480	€33.626	12.62	x
Surveillance every year with RFA	€44.671	11.70	€17.973	€40.499	12.49	x	€39.634	12.58	x

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted-life-years; RFA, radiofrequency ablation; x, strategy dominated by alternative.

the willingness-to-pay threshold.[22] We considered a willingness-to-pay threshold between €20.000 and €80.000 per QALY with special emphasis on the threshold of €35.000 per QALY, which is used in the UK and the USA.[36–38] The most critical variables in the cost-effectiveness analysis were the true progression rates. We used advanced statistical techniques to estimate these rates from prospectively collected follow-up data. The incidence rate of OAC was estimated at 0.1% per year, which corresponds to the results of recent population-based studies that confirms that our model is a good reflection of the natural history of neoplastic progression in BO.[2] For patients with LGD, the incidence rate of OAC was estimated at 4.9% per year. Previous studies have shown highly variable results for LGD with incidence rates of 0–26% and 1.7% in a recent meta-analysis.[45] The estimated progression rate in the current study was higher than in the meta-analysis, which can be explained by the fact that we only included patients with long-segment BO, that LGD diagnosis was made only when at least two pathologists agreed on the diagnosis and that patients were under strict surveillance. When progression rates were halved, surveillance every 5 years was cost-effective for ND and LGD. When progression rates were 25% of the calculated values, surveillance was only cost-effective for LGD. Changes in other variables such as costs and quality of life data had less impact on outcome.

One of the strengths of this study is that the transition rates were estimated based on follow-up data from our own large prospective BO cohort instead of using pooled literature data. Transition rates based on pooled literature data are likely to overestimate the true incidence rate of neoplastic progression due to publication and selection bias. Transition rates based on large epidemiological studies are likely to underestimate the true incidence rate of neoplastic progression since these patients are not necessarily under strict surveillance, which is of major importance to detect HGD or early OAC. With the use of our own follow-up data, we obtained a more accurate representation of the natural history of BO and its progression to OAC. In addition, patients with OAC were stratified according to TNM stage. As a result, endoscopic intervention could be applied to patients with HGD as well as patients with early OAC. Furthermore, we incorporated new treatment strategies such as EMR and RFA for HGD or early OAC, neoadjuvant chemoradiotherapy for patients who underwent oesophagectomy and chemotherapy, oesophageal stenting and brachytherapy for palliative treatment.

Our study also has some limitations. Although progression rates were estimated based on prospective follow-up data, the number of patients who developed HGD or OAC was relatively low, which limits the accuracy of the estimate. When longer follow-up becomes available, a more reliable estimate can be made. Second, we were not able to observe the transition from HGD or early OAC to advanced OAC since these patients were excluded from further follow-up and received appropriate treatment. Instead, we used data from another Dutch BO cohort. Third, we only included patients with BO of at least 2 cm and therefore our results cannot be applied universally to all patients with BO. Since long-segment BO is associated with a higher risk of neoplastic progression, we believe that our cohort is representative for the clinically relevant population with patients with long-segment BO, which are the patients who are most likely to benefit from surveillance. Finally, we did not include any other risk factors other than histology. To date histological diagnosis of dysplasia is the only accepted predictor for neoplastic progression and is therefore used for defining surveillance intervals. Other potential risk factors are insufficiently validated in large studies and are therefore not yet ready for use. However, when new risk factors become available they can be used to identify patients at high risk for neoplastic progression. By targeting surveillance to those at high risk, the cost-effectiveness of surveillance can be improved. In previous studies, we have already shown promising results of chemoprevention with proton pump inhibitors, non-steroidal anti-inflammatory drugs and statins and use of biomarkers such as p53.[46–48] When new risk factors become available, our model needs to be updated for a more personalised surveillance strategy.

In conclusion, this study shows that surveillance every 5 years with EMR followed by RFA for HGD or early OAC and oesophagectomy with neoadjuvant chemoradiotherapy for advanced OAC is a cost-effective strategy in patients with long-segment BO without dysplasia, assuming a willingness-to-pay threshold of €35.000 per QALY. In patients with LGD, surveillance every 3 years with EMR followed by RFA for HGD or early OAC and oesophagectomy with neoadjuvant chemoradiotherapy for advanced OAC is cost-effective. In the future, new risk factors or biomarkers may identify patients at high risk for neoplastic progression and thereby improve the cost-effectiveness of BO surveillance.

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Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis

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