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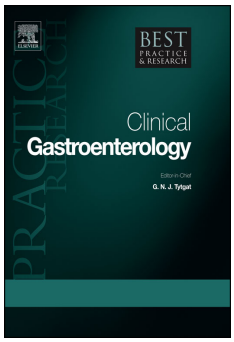

Cost Effectiveness of Surveillance in GI practice

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Abstract

Gastrointestinal (GI) diseases are among the leading causes of death in the world. To reduce the burden of GI diseases, surveillance is recommended for some diseases, including for patients with inflammatory bowel diseases, Barrett's oesophagus, precancerous gastric lesions, colorectal adenoma, and pancreatic neoplasms. This review aims to provide an overview of the evidence on cost-effectiveness of surveillance in GI practice, specifically focussing on the aforementioned diseases. We searched the literature and reviewed 21 studies. Despite heterogeneity of studies in terms of setting, study population, surveillance strategies and outcomes, most reviewed studies suggested at least some surveillance of patients with these GI diseases to be cost-effective. For some high-risk conditions frequent surveillance with 3-month intervals was warranted, while for other conditions, surveillance may only be cost-effective every 10 years. Further studies based on more robust effectiveness evidence are needed to inform and optimise surveillance programmes in GI practice.

Keywords: gastrointestinal diseases, cost-benefit analysis, surveillance, early diagnosis, review

Introduction

Gastrointestinal (GI) diseases are responsible for considerable morbidity and mortality worldwide. Causing almost 8 million deaths annually, GI diseases are among the leading causes of death in the world.[1] Not surprisingly, they have a large associated economic burden. In the United States (US), 10% of deaths occur due to GI diseases, and associated costs have been estimated at around $142 billion per year.[2] Alarmingly, the incidence and prevalence of major GI conditions such as gastroesophageal reflux disease, inflammatory bowel diseases (IBD) and GI cancers are increasing, particularly in North-American and European countries.[1, 3]

Many GI diseases are curable if detected in early stages, or even preventable. For instance, diseases like gastric and colorectal cancer have well-detectable and treatable precursor states that allow for disease prevention.[1] Patients with precursor lesions are often at higher risk for recurrent lesions and cancer, which suggests that lesion removal with frequent subsequent examination may prevent disease. Other GI conditions such as IBD and Barrett's oesophagus may also increase the risk of other diseases including cancer.[4-6] Therefore, as discussed in the other chapters of the current issue, surveillance is common in current GI practice. It has been recommended by international guidelines for patients with diverse conditions, including Barrett's oesophagus, ulcerative colitis (UC), Crohn's disease and pancreatic neoplasms.[7-10]

Surveillance is very similar to screening in that both refer to the early identification of potential unrecognized disease with the aim to prevent poorly treatable disease. Often, the same tests can be used. Similar to screening, surveillance may have both health benefits (e.g. deaths averted) and harms (e.g. false-positive or false-negative test results, complications due to tests, overdiagnosis and overtreatments). The main difference between screening and surveillance is that the former targets healthy populations, while surveillance generally targets patients who are at increased risk of a specific

disease. Because of the similarity of the concepts of screening and surveillance, the same approach can be used for their evaluation.

One possible approach to evaluate screening and surveillance programmes is the “balance approach” introduced by Harris et al.[11] In this approach, evaluation of a programme is based on the evidence for the magnitude of health benefit, magnitude of harm, and the required resources.[11] The approach considers the balance between benefits and harms and determines whether the magnitude of net benefits justifies the required use of resources for a specific programme. With rapidly increasing health care costs in Western countries, efficient allocation of scarce resources is becoming increasingly important criterion for health policy evaluation.

Cost-effectiveness is a popular concept to summarize the relationship between the monetary inputs for implementing a healthcare intervention, its consequent health expenditure effects, and the health outcomes. Cost-effectiveness can be determined using cost-effectiveness analysis (CEA). CEA is a form of decision analysis which enables policy makers to identify the most effective interventions considering the limited available resources and to determine which one provides the highest value for money.[12-14] The advantage of CEA is that it integrates harms, benefits and cost of health care strategies into a single outcome measure. CEA results often take the form of a cost-effectiveness ratio, which estimates the cost of an intervention to attain one unit of a health outcome (e.g. quality-adjusted life years gained).[15] This may be reported either comparing (1) an intervention such as surveillance to the situation without the intervention, or regular care (i.e. the average cost-effectiveness ratio) or (2) comparing each surveillance strategy with the next most effective one (i.e. incremental cost-effectiveness ratio (ICER)). The relative uniformity in outcomes from cost-effectiveness studies allows for comparative analysis both of alternative interventions for a single disease, as well as for different organs and diseases.[15]

This paper aims to provide an overview of the evidence on cost-effectiveness of surveillance in GI practice as measured by ICERs. It will focus on IBD, Barrett's oesophagus, gastric precancerous lesions, colorectal polyps and neoplasia in the pancreas.

Review methods

To achieve the objective of the review, we searched the following six electronic databases to find the relevant studies which have been published from 2000 to June 2016; Ovid Medline, Ovid Embase, The Cochrane library, The British National health System Economic Evaluation Database (NHS EED), the American Economic Association's electronic database (EconLit) and Cost-Effectiveness Analysis Registry (CEA Registry) (see Appendix 1, for search algorithm used in Ovid Medline). The search was limited to papers published in English language. We excluded studies without a reference scenario of no surveillance. The database was supplemented by expert suggestions and by reviewing reference lists from all discovered previous literature reviews. All reported costs were converted to US$ ($) using historical conversion rates.

Results

Our search resulted in reviewing 21 studies which evaluated the cost-effectiveness of surveillance strategies in the GI conditions described below. The majority of studies took a third party payer perspective (i.e. incorporating only direct costs) with 3% discount rates for benefits and cost. For studies which adopted a societal perspective or alternative discount rates, this was explicitly noted (Table 1-5 footnotes).

Inflammatory Bowel Diseases

Four studies which investigated the cost-effectiveness of surveillance of patients with inflammatory bowel diseases (IBD) were included. All were Markov modelling studies. Study settings included the Netherlands, US and Canada. The studies were heterogeneous with respect to the study population, and the surveillance tests and intervals evaluated. Two studies considered patients with UC, one IBD in general (including both UC and Crohn's disease), and one study included patients with concomitant IBD and Primary Sclerosing Cholangitis (PSC). (Table 1).

Both studies which considered UC patients found that surveillance was cost-effective. Rubenstein et al.[16] analysed the cost-effectiveness of different surveillance strategies for men at age of 35 years with a 10-year history of UC. They considered two population subgroups, patients with and without medication of 5-Aminosalicylates (5-ASA) and found surveillance in both to be cost-effective. In patients with 5-ASA, the most effective strategy under a willingness-to-pay threshold of $100,000 was colonoscopy surveillance every 3 years (ICER: $63,387 per quality-adjusted life years (QALY)). Without 5-ASA, the optimal strategy was annual colonoscopy (ICER: $69,105 per QALY). In the other study, Konijeti et al.[17] used chromo-endoscopy and colonoscopy as surveillance tests. Both tests were cost-effective, but the analysis suggested that chromo-endoscopy with targeted biopsies was more effective and less costly than colonoscopy with random biopsies at all intervals.

The Negron et al.[18] study, which considered patients with IBD-PSC, also found that surveillance colonoscopy was cost-effective compared to no surveillance (for 2-yearly surveillance strategy the ICER of $37,522 per QALY was reported). In that study, annual surveillance was not cost-effective (ICER: $174,650 per QALY). Lutgens et al.[19] compared the cost-effectiveness of surveillance strategies of the American Gastroenterological Association (AGA) and the British Society of Gastroenterology (BSG) for patients with IBD. AGA recommends annual surveillance for patients with PSC and biennial surveillance for patients without PSC, while BSG guidelines distinguish three risk groups and recommend annual, biennial and every 5-year surveillance. Although both strategies were equally effective, the BSG surveillance strategy was more cost-effective due to a lower number of colonoscopies (ICER: $11,130 per QALY).

Table 1. Overview of cost-effectiveness studies of surveillance in patients with IBD

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (year)[¶]	Cost ($)	Effectiveness (QALY)	ICER
Rubenstein 2009[16]	US	35-year-old men with chronic UC	Until age 90 or death	QALY	None	-	71,000	20.07	NA
					Colonoscopy	1-10 *	NR	NR	≤ 69,105 *
					Colonoscopy plus 5-ASA	1-2	NR	NR	≥147,503
					Colonoscopy plus 5-ASA	3-10 *	NR	NR	≤63,387 *
Konijeti 2014[17]	US	Patients with population-based age distribution and ≥8 years history of UC	Until age 90 or death	QALY	None	-	100,200	13.18	NA
					Chromo-endoscopy with targeted biopsies	1-10 ¥	103,100-125,00	13.10-13.36	17,150 ¥
					Colonoscopy with random biopsies	1-10 #	103,900-128,000	13.06-13,34	Dominated
Negron 2014[§] [18]	Canada	35-year old patients with 10-year history of	Life time	QALY	None	-	101,663	9.84	NA
					Colonoscopy	5	104,517	10.03	15,021
						2	107,894	10.12	37,522
						1	114,880	10.16	174,650

		well-controlled IBD and recent PSC diagnosis							
Lutgens 2014[19]	Netherlands, US	40-year-old patients with IBD for 10 years	40 years	QALY	BSG	1, 3 or 5¤	NR	24.16	11,130
					AGA	1 or 2ǂ	NR	24.16	Dominated

AGA: American Gastroenterological Association, ASA: aminosalicylate, BSG: British Society of Gastroenterology, IBD: inflammatory bowel disease, ICER: incremental cost-effectiveness ratio, NR: not reported, NA: not applicable, PSC: primary sclerosing cholangitis, QALY: quality adjusted life year, UC: ulcerative colitis.

¶ The numbers in this column show different intervals of surveillance strategies which have been evaluated in the study, e.g. 1-10 means that intervals of 1 year, 2 years, 3 years etc. up to 10 years were evaluated.

* The optimal strategy with a willingness-to-pay threshold of $100,000 was at intervals of 1 and 3 years for colonoscopy alone and colonoscopy plus 5-ASA, respectively.

¥ The optimal strategy was at an interval of 10 years for chromo-endoscopy with the presented ICER.

Colonoscopy with random biopsies were dominated by the chromo-endoscopy strategy at all intervals.

§ A societal perspective with 5% discount rate for benefit and cost was adopted.

¤ Surveillance interval depended on the risk profile of the patients.

ǂ Annual surveillance for patients with PSC and biennial surveillance for patients without PSC.

Barrett's oesophagus

We included 8 studies on surveillance in Barrett's oesophagus (BO) from the US, Netherlands, United Kingdom (UK) and Australia. All studies were Markov modelling studies evaluating endoscopy with biopsy as the surveillance modality. The studies were heterogeneous in terms of the study population (all BO patients, BO patients without dysplasia (BO-ND), BO patients with low-grade dysplasia (BO-LGD), and high-grade dysplasia (BO-HGD)), health outcomes (QALY, life year (LY), and life expectancy) and surveillance intervals. (Table 2) With one exception, all studies suggested surveillance to be cost-effective up to varying level of intensity.

Studies which considered all BO patients reported conflicting results. Sonnenberg et al.[20] estimated that surveillance endoscopy and biopsy every 2 years was cost-effective compared to no surveillance (ICER: $16,965 per LY), while another study representing a UK setting suggested that endoscopic surveillance with 3-year, 1-year and 3-month intervals for patients with BO-ND, BO-LGD and BO-HGD respectively, was not cost-effective compared to no surveillance (dominated).[21]

Four studies assessed the cost-effectiveness of endoscopic surveillance in patients with BO-ND. All studies suggested that surveillance was cost-effective. Kastelein et al [22] evaluated various surveillance strategies with different intervals for a cohort of 55-year-old men with BO-ND, to find that with a willingness-to-pay threshold of €35,000, the optimal strategy was surveillance endoscopy every 5 years, with radiofrequency ablation if BO-ND patients developed HGD (ICER: $6,604 per QALY). Gordon et al. [23] suggested that 2-yearly endoscopic surveillance for NO-BD patients and more intensive surveillance if patients developed dysplasia was also cost-effective according to Australian standards (ICER: $60,858 per QALY), although probabilistic sensitivity analysis suggested that the likelihood of cost-effectiveness was only 16%. Two other studies from the US found for 50-year-old patients that endoscopic surveillance with biopsy every 5 and 3 years, respectively, was cost-effective with ICERs of $22,011 [24] and $86,434 per QALY.[25]

Studies looking specifically at BO-LGD patients also found surveillance to be cost-effective. Kastelein et al.[22] suggested that the optimal cost-effective strategy was surveillance every 3 years, with radio-frequency ablation (RFA) for patients who developed HGD (ICER: $40,664 per QALY). In another study, Inadomi et al.[24] suggested that annual endoscopic surveillance was cost-effective compared to no surveillance (ICER: $23,010 per QALY).

Finally, three US studies evaluating surveillance in BO-HGD patients also estimated that this was cost-effective. Shaheen et al.[26] estimated that a regressive endoscopic surveillance strategy of 3-month intervals in the first year, 6-month intervals in the second year (if no further HGD were detected) and 1-year subsequent intervals had an ICER of $32,053 per QALY compared to no surveillance. Sonnenberg et al.[27], suggested annual surveillance endoscopy was cost-effective (ICER: $6,797 per LY). Inadomi et al.[24] found that a similar strategy to Shaheen et al. with three-month intervals during the first year and subsequent 1 year intervals would be cost-effective for patients with HGD at baseline (ICER: $18,945 per QALY).

Table 2. Overview of cost-effectiveness studies of surveillance in patients with Barrett's oesophagus

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval[¶]	Cost ($)	Effectiveness (QALY/LY/LE)	ICER
Patients with general BO									
Sonnenberg 2002[20]	US	60-year-old patients with long segment BO	NR	LY	None	-	2,061	NR	NA
					Endoscopy plus oesaphogectomy for HGD	2y	6,262	NR	16,965
Somerville 2008[#][21]	UK	55-year-old men with BO	20 years	QALY	None	-	5,312	12.03	NA
					Endoscopy	3y for ND, 1y for LGD, 3m for HGD	6,964	11.98	Dominated
Patients with BO-ND									
Kastelein 2015[§][22]	The Netherlands	55-year-old men with BO-ND	NR	QALY	None	-	7,119	12.62	NA
					Endoscopy plus RFA for HGD and early OAC	1-5y	8,774-18,842	12.87-12.90	6,604[¥1]
					Endoscopy plus EMR followed by RFA for HGD and early OAC	1-5y	9,059-19,276	12.87-12.90	Dominated

					Endoscopy plus oesophagectomy for HGD and OAC	1-5y	17,456-29,607	12.54-12.64	Dominated
Gordon 2014[§][23]	Australia	50-year-old patients with BO-ND	Until age 80 years or death	QALY	None	-	5,226	12.04	NA
					Endoscopy	2y for ND, 6m for LGD, treatment of HGD and EAC	14,659	12.190	60,858
Inadomi 2009[24]	US	50-year-old patients with BO-ND	Until age 80 years	QALY	None	-	471*	15.2*	NA
					Endoscopy and ablation for dysplasia	1y, 5y after another exam finds ND	10,816*	15.67*	22,011
Das 2009[25]	US	50-year-old patients with BO-ND	Until age 80 years	QALY	None	-	2,894	17.959	NA
					Endoscopy	3y for ND, 1y for LGD, 3m for HGD	13,016	18.076	86,434
Patients with BO-LGD									
Kastelein 2015[§][22]	The Netherlands	55-year-old men with BO-LGD	NR	QALY	None	-	27,258	10.95	NA
					Endoscopy plus RFA for HGD and early OAC	1-5y	33,202-52,607	11.91-12.27	40,664[¥2]

					Endoscopy plus EMR followed by RFA for HGD and early OAC	1-5y	35,306-56416	11.91-12.27	Dominated
					Endoscopy plus oesophagectomy for HGD and OAC	1-5y	63,636-68,949	11.33-11.34	Dominated
Inadomi 2009[24]	US	50-year-old patients with BO-LGD	Until age 80 years	QALY	None	-	687*	14.7*	NA
					Endoscopy	1y	16,334*	15.38*	23,010
Patients with BO-HGD									
Shaheen 2004[26]	US	50-year-old Caucasian males with BO-HGD	Until death	QALY	None	-	748	13.9	NA
					Endoscopy	3m during first year, 6m during second year if no further HGD detected, 6m and 1y thereafter	34,724	14.96	32,053
Sonnenberg 2003[27]	US	60-year-old patients with	NR	LE	None	-	14,178*	71.59*	NA
					Endoscopy	1y	18,732*	72.26*	6,797

		BO-HGD			Endoscopy plus NSAID	1y	21,267*	72.82*	4,526
Inadomi 2009[24]	US	50-year-old patients with BO-HGD	Until age 80 years	QALY	None	-	1,859*	12.4*	NA
					Endoscopy	3m during first year, 1y thereafter if no further HGD	48,084*	14.84*	18,945

BO: Barrett's oesophagus, EMR: endoscopic mucosal resection, HGD: high-grade dysplasia, ICER: incremental cost-effectiveness ratio, LDG: low-grade dysplasia, LY: life year, NA: not applicable, ND: no dysplasia, NR: not reported, NSIAD: nonsteroidal anti-inflammatory drugs, OAC: oesophageal adenocarcinoma, QALY: quality adjusted life year, LE: life expectancy, RFA: radiofrequency ablation.

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study, e.g. 1-5y means that intervals of 1 year, up to 5 years were evaluated.

1.5% discount rate for benefit and 6% for cost were adopted.

§ 5% discount rate was adopted.

¥ The ICER of the optimal strategy with regards to the willingness-to-pay threshold of 35,000 Euro is reported in the table.

1. The optimal strategy was surveillance every 5 years for patients with LGD and treatment of patients who developed HGD or OAC with RFA. According to international standards, 4-yearly surveillance was also cost-effective (ICER: $78,273).
2. The optimal strategy was surveillance every 3 years for patients with LGD and treatment of patients who developed HGD or OAC with RFA. According to international standards, annual surveillance was also cost-effective (ICER: $94,501).

* The values were estimated from graphs.

Colorectal adenomas

We found four studies assessing the cost-effectiveness of surveillance programmes in patients with adenomas. All four studies were modelling studies and evaluated colonoscopy for surveillance. Similar to BO, health outcomes and surveillance intervals were different across studies. (Table 3)

Three studies simulated cohorts of 50-year-old patients with adenomas. First, Saini et al.[28] evaluated different surveillance intervals for these patients depending on the level of patient's risk to develop new adenomas and colorectal cancer. They found that colonoscopy surveillance every 3 years for high-risk patients and 10 years for low-risk patients (3/10 strategy) was cost-effective compared to 10-yearly surveillance for all patients (ICER: $5,743 per QALY). Although effective, a 3/5 strategy was much more costly (ICER: $296,266 per QALY). In another study, Arguedas et al.[29] considered colonoscopy surveillance every 3 years and if no further adenomas were found, surveillance resumed every 5 years. They estimated that this strategy had an ICER of $27,970 per LY compared to no surveillance. Finally, Shaukat et al.[30] estimated that colonoscopy surveillance every 3 or 5 years depending on whether large adenomas (≥10 mm) were found or not, to be cost-effective (ICER: $20,600 per LY). The fourth study[31] simulated a group of 60-year-old adenoma patients. The study suggested that even a single colonoscopy surveillance after 1 year was cost-effective with an ICER of $66,136 per LY.

Table 3. Overview of cost-effectiveness studies of surveillance in patients with colorectal adenomas

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (year)[¶]	Cost ($)	Effectiveness (QALY/LY)	ICER
Saini 2010[28]	US	50-year-old patients with adenomas	Until death	QALY	None*	10	1775	17.57	NA
					Colonoscopy	3 for HR patients 10 for LR patients[¥]	1,831	17.58	5,743
					Colonoscopy	3 for HR patients 5 for LR patients[¥]	3,170	17.58	296,266
					Colonoscopy	3 for both HR and LR patients[¥]	4,936	17.58	dominated
Arguedas 2001[29]	US	50 year-old patients with adenomas	10 years	LY	None	-	1014	8.45	NA
					Colonoscopy	3 and 5[#]	1572	8.48	27,970
					Celecoxib chemoprevention	-	11503	8.49	1,715,199
Shaukat 2009[30]	US	50 year-old patients with adenomas	Until age of 100 years or death	LY	None	-	2,796	18.64	NA
					Colonoscopy	3 for large adenoma (≥10 mm), 5 for small or no adenoma (<10 mm),	4,579	18.72	20,600
Hassan	Italy	60-year-old patients	Lifetime	LY	None	-	NR	NR	NA

2009[§][31]		with adenomas			Colonoscopy	Once after 1 year	NR	NR	66,136

ICER: incremental cost-effectiveness ratio, HR: high risk, LY: life year, LR: low risk, NA: not applicable, QALY: quality adjusted life year.

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study.

* This is similar to screening of average-risk patients as recommended in the United States.

¥ HR patients: patients with >2 adenomas or advanced adenomas (adenomas ≥1 cm, villous, or with high-grade dysplasia), LR patients: patients with 1–2 small (<1 cm) tubular adenomas.

If any adenoma was detected in the surveillance colonoscopy, the next colonoscopy was done in 3 years, if no adenomas were detected, the colonoscopy was repeated 5 years later.

§ Not-discounted rate was reported.

Neoplasia in the pancreas

Three studies evaluated the cost-effectiveness of surveillance strategies for neoplasia in the pancreas. All were simulation modelling studies and conducted in the US. Again, studies evaluated varying study populations, health outcomes and surveillance strategies.(Table 4)

Two out of three studies focused on familial pancreatic cancer. Rubenstein et al. [32] simulated a cohort of 45-year-old men with chronic pancreatitis who had at least a first-degree relative with pancreatic cancer. Two surveillance strategies including 6-monthly endoscopic ultrasound (EUS) plus fine needle aspiration and EUS alone were both not cost-effective compared to no surveillance. Rulyak et al.[33] considered a cohort of 100 members of familial pancreatic cancer kindreds who underwent EUS at age of 50 years. Any abnormal findings in EUS were followed up using endoscopic retrograde cholangiopancreatography and, if cancer was confirmed, total pancreatectomy. The results suggested this strategy to be cost-effective compared to regular care (ICER: $16,855 per LY).

A third study considered surveillance after curative treatment of pancreatic cancer.[34] The investigators simulated patients who had recent neoadjuvant therapy and pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. They found that clinical evaluation of the patients and CA 19-9 assay every 6 months was cost-effective (ICER: $5,364 per LY). The alternative strategy, clinical evaluation with CA19-9 and routine abdominal/pelvic computed tomography and chest X-ray every 6 months was dominated. More intensive surveillance strategies were not cost-effective.

Table 4. Overview of cost-effectiveness studies of surveillance for pancreatic neoplasia

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (months)¶	Cost ($)	Effectiveness (QALY/LY)	ICER
Rubenstein 2007[32]	US	45-year-old men with chronic pancreatitis and ≥1 FDR with pancreatic cancer	Until age 90 or death	QALY	None	-	2,983	18.57	NA
					EUS and FNA	6	42,521	17.94	Dominated
					EUS	6	186,089	14.54	Dominated
					Prophylactic total pancreatectomy	NA	199,911	14.28	Dominated
Rulyak 2003[33]	US	50-year-old patients with family risk (unspecified)	Life time	LY	None	-	3,271	17.20	NA
					EUS and ERCP (if the EUS result was positive)	once	9,677	17.58	16,855
Tzeng 2013[34]	US	Patients who recently received neoadjuvant therapy and pancreatico-duodenectomy for PDAC	Median follow-up of 26 months	LY	None	-	3,837	2.05	NA
					clinical evaluation and CA19-9 testing	6	7,496	2.73	5,364
					clinical evaluation and CA19-9 testing with routine abdominal/pelvic CT and CXR	6	10,961	2.73	Dominated
					clinical evaluation and CA19-9 testing	3	18,523	2.81	127,680
					clinical evaluation and CA19-	3	24,775	2.84	294,696

					9 testing with routine abdominal/pelvic CT and CXR				

CA19-9: carbohydrate antigen 19-9, CT: computed tomography, CXR: chest X-ray, EUS: endoscopic ultrasound, ERCP: endoscopic retrograde cholangiopancreatography, FDR: first-degree relative, FNA: fine needle aspiration, ICER: incremental cost-effectiveness ratio, LY: life year, NA: not applicable, PDAC: Pancreatic ductal adenocarcinoma, QALY: quality adjusted life year.

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study.

Gastric precancerous conditions

Surveillance of gastric precancerous conditions was considered in two studies. Again these two studies used simulation modelling to evaluate endoscopic surveillance, and varied in terms of study populations, health outcomes and surveillance strategies. (Table 5)

Both studies suggested that endoscopic surveillance was cost-effective for patients with gastric precancerous lesions. One Portuguese study modelled a group of 50-year-old patients with extensive gastric atrophy or intestinal metaplasia who underwent endoscopic surveillance and biopsy every 3, 5 or 10 years.[35] This study found that surveillance every 3 years was cost-effective (ICER: $24,204 per QALY). Endoscopic surveillance strategies with intervals of 5 and 10 years were dominated by a non-surveillance strategy. Another study simulated a population of 60-year-old patients with only gastric intestinal metaplasia, and found that annual surveillance endoscopic may be cost-effective with an ICER of $72,519 per LY compared to no surveillance.[36]

Table 5. Overview of cost-effectiveness studies of surveillance in patients with gastric precancerous conditions

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (years)¶	Cost ($)	Effectiveness (QALY/LY)	ICER
Arei 2014*[35]	Portugal	50-year-old patients with extensive gastric atrophy or intestinal metaplasia	25 years	QALY	None	-	172	13.607	NA
					Endoscopy	10	2,400	13.268	Dominated
					Endoscopy	5	1,972	13.565	Dominated
					Endoscopy	3	2,091	13.687	24,204
Hassan 2010[36]	Italy	60-year-old patients with gastric intestinal metaplasia	10 years	LY	None	-	583	NR	NA
					Endoscopy	1	3,552	NR	72,519

ICER: incremental cost-effectiveness ratio, LY: life year, NA: not applicable, NR: not reported, QALY: quality adjusted life year

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study.

* A societal perspective was adopted.

Discussion

In this review, we searched the literature on cost-effectiveness of surveillance for a variety of GI diseases, including IBD, BO, gastric precancerous lesions, colorectal adenomas and diverse patients with a high risk of pancreatic neoplasia in the pancreas. We included 21 modelling studies from high income-countries of which more than one-third considered surveillance in BO (8 studies) and few studies considered other GI diseases (2-4 studies per disease each). Although studies differed in terms of settings, study populations, surveillance strategies and health outcomes, most reviewed studies suggested that at least some surveillance of patients with BO, IBD, precancerous gastric lesions, colorectal adenoma, and with increased risk of pancreatic neoplasia may be cost-effective. Cost-effective surveillance strategies generally used endoscopy, except in patients with resected pancreatic cancer, where clinical evaluation and carbohydrate antigen 19-9 testing was used instead. Surveillance intervals varied from 3 months for patients with BO-HGD up to 10 years for patients with ulcerative colitis.

At the disease level, there was considerable heterogeneity in cost-effective surveillance intervals depending on the risk for and fatality of the preventable disease. Apart from one study in UC patients finding only 10-year surveillance cost-effective, for most IBD patients 1-5 year surveillance colonoscopy was found to be cost-effective, with the intervals varying by study and depending on additional risk characteristics. For BO, again with one exception,[21] all studies found endoscopic surveillance with biopsy to be cost-effective, with minimum cost-effective intervals varying from 2-5 years for BO-ND, to 1-3 years for BO-LGD patients, to 3-12 months for BO-HGD patients. Surveillance colonoscopy was generally found to be cost-effective in the studies retrieved for patients with colorectal adenomas with intervals of 3-5 years, however, one study found that 5 year surveillance may not be cost-effective in low-risk patients,[28] and another study suggested that one-time only colonoscopy after 1 year may be cost-effective.[31] For patients with increased risk of pancreatic neoplasia, follow-up clinical evaluation

plus CA19-9 essay every 6 months was deemed cost-effective after pancreatic cancer therapy,[34] while the evidence for cost-effectiveness of endoscopic examination for patients with a family history of pancreatic cancer was conflicting. Finally, precancerous gastric lesions seemed to deserve surveillance endoscopy every 1-3 years.[35, 36]

Surveillance of patients with IBD, BO, colorectal adenomas, precancerous gastric lesions and neoplastic pancreatic cysts is generally recommended by current international clinical practice guidelines. Supporting organizations include the AGA, BSG, National Institute for Health and Clinical Excellence (NICE), European Crohn's and Colitis Organisation, European Helicobacter Study Group, European Society of Pathology and European Society of Gastrointestinal Endoscopy.[7, 8, 10, 37-44] None of the above expert groups except NICE considered cost-effectiveness in developing their guidelines. NICE has provided guidelines on management of IBD, BO and colorectal adenomas, [43, 44] and conducted cost-effectiveness analyses for all three conditions. Although the results from these studies were partly consistent with the studies included in this review, there were also some discrepancies. For BO patients, although the NICE analysis suggested that surveillance endoscopy every 2 years for BO-ND, every 6 months for BO-LGD, and every 3 months for BO-HGD patients would improve health outcomes, it was not considered cost-effective at a threshold of £20,000 (ICER £35,277).[43] Therefore, treatment for BO-HGD patients was recommended by NICE, but not surveillance of these patients. In our review, although Somerville et al.[21] found a similar surveillance strategy (3 year intervals for BO-ND, 1 year for BO-LGD, 3 months for BO-HGD patients) not only inefficient but even harmful (Table 2), 7 other studies all found BO surveillance to be cost-effective, often even with lower ICERs. In contrast, the NICE evaluation of surveillance in colorectal adenoma patients (colonoscopy every 5, 3 or 1 years depending on adenoma characteristics) suggested this to be cost-effective. However, while several studies in our review also found 3- to 5-year intervals to be cost-effective, the most recent study included by Saini et al. suggested that 5-year intervals may not be cost-effective for low-risk patients as mentioned before.[28, 44] Also,

the 1-year interval for high-risk patients was not studied by any of the included studies in this review. Finally, while the NICE analysis for IBD patients was restricted to high-risk patients and suggested that colonoscopy surveillance every year was cost-effective in the UK setting with a acceptance threshold of £20,000 (ICER: £17,557 per QALY),[44] in our review there were no studies included looking specifically at high-risk patients. The partly discrepant results both between studies included in this review and compared to studies used to inform UK guidelines suggest that further research is needed to clarify precisely when surveillance is appropriate.

Although most cost-effectiveness studies are concordant in suggesting that at least some surveillance in GI practice is cost-effective, they share an important caveat. All studies included here assumed that surveillance was effective in reducing disease-specific mortality. The problem with this assumption is that currently for most of the included disease no evidence exists from randomized controlled trials that this is actually the case. This lack of evidence is also explicitly acknowledged in the guidelines. It is an important limitation given all criteria for screening or surveillance state that effectiveness and net benefits of the programme should be established before considering cost-effectiveness.[11, 45] To the extent possible, where surveillance is already recommended, it should preferably be conducted in research settings to establish the effectiveness retroactively. When issuing new guidelines, policy makers should be aware that this may have ethical implications for the possibility to conduct experimental studies to establish effectiveness.

There were other limitations for the studies included in this review. All the included studies were modelling simulation analyses, the results of which depend on the model structure and assumptions regarding e.g. disease onset and progression. There is uncertainty regarding the true values for many of these parameters, which may influence outcomes substantively. Moreover, the models and assumptions represent high-income countries only. Parameters such as the risk of disease and the cost of care may

differ for low- or middle-income countries, such that the results of these analyses should be generalised with caution to other settings.

Further, the coverage of cost-effectiveness studies for some of the conditions in scope for this review was low. Given the evidence across studies was fragmented in terms of study populations, settings, and evaluated strategies, for many patient subgroups cost-effectiveness was either not assessed or assessed by only one study. Most reviewed studies also tended to evaluate only the already recommended surveillance strategies and compare them to a non-surveillance strategy. There were few studies which evaluated a range of different surveillance intervals or strategies. The strategies found to be cost-effective this way may not be optimal. As an illustrative example, for surveillance of BO patients, Das et al.[25], Shaheen et al.[26], and Inadomi et al. [24] all found that endoscopic surveillance with aforementioned intervals (Table 2) was cost-effective compared to no-surveillance strategy, however, that it was dominated by other strategies including ablation therapy without surveillance.

In conclusion, although this review suggests that surveillance in GI practice may be cost-effective for all evaluated GI conditions, for most disease the evidence was scant and the effectiveness evidence basis was weak. More research is needed on the effectiveness of surveillance to inform more comprehensive and evidence-based cost-effectiveness studies searching for optimal surveillance strategies beyond currently recommended strategies.

Summary

For many common gastrointestinal (GI) conditions, surveillance is recommended by professional societies and institutes. In this study, we searched various scientific literature databases for cost-effectiveness studies on surveillance programmes in GI conditions including inflammatory bowel disease, Barrett's oesophagus, gastric precancerous lesions, colorectal adenomas and pancreatic neoplasia. We identified a total of 21 studies, which generally suggested at least some surveillance to be cost-effective. While for high-risk conditions such as treated pancreatic cancer or BO-HGD frequent surveillance follow-up with intervals of less than 1 year was cost-effective across studies, for intermediate risk conditions such as IBD, BO-LGD, high-risk adenoma, and gastric metaplasia surveillance up to every 1-3 years was cost-effective, and for low-risk conditions such as small adenomas or BO-ND intervals of 5-10 years may represent the maximum appropriate intensity. Despite the suggestion that surveillance may be cost-effective for all the evaluated conditions, for most conditions evidence was scant and the effectiveness basis was weak. Furthermore, few studies looked for optimal surveillance strategies. To conclude, although this review suggests that surveillance may be cost-effective for some GI conditions, more research is needed on the effectiveness of surveillance to inform more evidence-based cost-effectiveness looking to optimise surveillance programmes in GI practice.

Practice points

- Current practice guidelines partly based on the expert opinion recommend surveillance for a variety of GI diseases.
- Cost-effectiveness studies suggest current surveillance practice may also be cost-effective.
- There is a lack of rigorous evidence for effectiveness and of surveillance optimization studies.

Research agenda

- Evidence is needed on the effectiveness of surveillance for GI diseases.
- Future cost-effectiveness studies should look for optimal surveillance strategies.
- Surveillance should be evaluated for low- and middle-income settings.

Conflict of interest: none

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Appendix

Appendix 1. search strategy for Ovid Medline

1	(Barrett*).tw.
2	((gastric or stomach) and (precancerous or premalignant or precursor) and (lesion* or condition*)).tw.
3	((neoplas* or cancer* or adeno* or carcino* or tumo*) and pancrea*).tw.
4	((colon OR colorect* OR sigmoid* OR bowel OR "large intestine*" OR cecum) and (cancer* OR neoplas* OR tumo* OR carcino* OR adeno* OR polyp* OR lesion*)).tw.
5	(Inflammatory bowel disease? OR IBD? OR crohn* or colitis).tw.
6	"Costs and Cost Analysis"/
7	(costs or cost eff* or cost benef* or cost anal*).tw.
8	surveillance.tw.
9	(case reports or editorial or guideline or letter or news or newspaper or article or practice guideline).pt.
10	1 or 2 or 3 or 4 or 5
11	6 or 7
12	8 and 10 and 11
13	12 not 9
14	limit 13 to English language
15	limit 14 to yr="2000 -Current"
16	limit 15 to human