Surgery versus surveillance in ulcerative colitis patients with endoscopically invisible low-grade dysplasia: a cost-effectiveness analysis

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Background and Aims: There is uncertainty regarding the optimal management of endoscopically invisible (flat) low-grade dysplasia in ulcerative colitis. Such a finding does not currently provide an automatic indication for colectomy; however, a recommendation of surveillance instead of surgery is controversial. The aim of this study was to determine the clinical and cost-effectiveness of colonoscopic surveillance versus colectomy for endoscopically invisible low-grade dysplasia of the colon in ulcerative colitis.

Methods: A Markov model was used to evaluate the costs and health outcomes of surveillance and surgery over a 20-year timeframe. Outcomes evaluated were life years gained and quality-adjusted life years (QALYs). Cohorts of patients aged 25 to 75 were modeled, including estimates from a validated surgical risk calculator and considering none, 1, or both of 2 key comorbidities: heart failure and obstructive airway disease.

Results: Surveillance is associated with more life years and QALYs compared with surgery from age 61 for those with no comorbidities, age 51 for those with 1 comorbidity and age 25 for those with 2 comorbidities. At the current United Kingdom National Institute for Health and Care Excellence threshold of $25,800 per QALY, ongoing surveillance was cost-effective at age 65 in those without comorbidities and at age 60 in those with either 1 or more comorbidities.

Conclusions: Surveillance can be recommended from age 65 for those with no comorbidities; however, in younger patients with typical postsurgical quality of life, colectomy may be more effective clinically and more cost-effective. The results were sensitive to the colorectal cancer incidence rate in patients under surveillance and to quality of life after surgery. (Gastrointest Endosc 2017;86:1088-99.)

Ulcerative colitis (UC) is the most common type of inflammatory bowel disease. In the United Kingdom, the annual incidence is around 10/100,000, and almost 146,000 people currently have a diagnosis of UC.[1,2] The causes of UC are largely unknown, and the disease can develop at any age. It is a lifelong disease, associated with

Abbreviations: CRC, colorectal cancer; HGD, high-grade dysplasia; ICER, incremental cost-effectiveness ratio; IPAA, ileal pouch–anal anastomosis; LGD, low-grade dysplasia; NHS, National Health Service; QALY, quality-adjusted life year; UC, ulcerative colitis.

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significant morbidity. Patients with UC face a 2.4-fold increased risk of developing colorectal cancer (CRC), rising to a 4.8-fold increased risk in those with extensive disease.[3] The rate of CRC in colitis may be declining over time because of improvements in colonoscopic surveillance, more effective medical therapy, and use of population-based estimates rather than data from specialist centers.[4] The development of CRC in UC is preceded by cytologic dysplasia associated with distinct genetic abnormalities, distinguishing UC-associated CRC from sporadically occurring CRC.[5,6] Progression of inflamed mucosa is generally assumed to be from colitis without dysplasia to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and ultimately carcinoma. It has been suggested, however, that LGD may progress straight to carcinoma, leading to LGD being the definitive interventional point at which prophylactic colectomy can be considered.[7]

Colonoscopic surveillance may facilitate the detection of asymptomatic cancer or precancerous dysplastic lesions, enabling early intervention and potentially improving survival.[8] Of the different lesion types, there is uncertainty regarding the management of LGD in the normal-appearing mucosa without an associated endoscopically visible lesion, detected only by random biopsies. This has been historically termed *flat* LGD in the inflammatory bowel disease literature; however, the term *flat* in the endoscopic literature had been used to describe nonpolypoid lesions (Paris 0-II[9]) where a lesion is visible, leading to confusion. We use the term *endoscopically invisible dysplasia*, as recommended by the SCENIC guidelines[10] to describe lesions detectable only on random biopsy. Such a finding does not currently provide an automatic indication for colectomy. However, a recommendation of ongoing surveillance instead of surgery is controversial, with guidelines recommending repeat examination with chromoendoscopy and a multidisciplinary discussion with the patient when this is being considered.[8,10,11] Although the use of chromoendoscopy may reduce the rate of endoscopically invisible dysplasia, dysplasia detected by random biopsies can still occur at an appreciable rate (12.8% of all dysplasia detected per-patient) in community-based studies of chromoendoscopy.[12] Several factors must be evaluated in the decision-making process: estimates of the risk of developing a more advanced lesion or CRC after a finding of endoscopically invisible LGD vary, the patient may have undiagnosed concurrent CRC, and the risk associated with surgery depends on both age and comorbidities. Two meta-analyses have considered the risk of developing cancer after a finding of endoscopically invisible dysplasia. Thomas et al[7] estimated a risk of 14 cancers and 30 advanced neoplasias per 1000 patient years of follow-up in 2008; however, this analysis predated the availability of modern high-definition colonoscopes and more modern medical therapy. Fumery et al[13] updated this analysis in 2016, reporting a higher risk of HGD or cancer after a finding of endoscopically invisible dysplasia, at 61 advanced neoplasias per 1000 patient years.

A trade-off exists between the immediate costs of surgery and the costs of long-term surveillance. Surveillance may be a costly temporary solution if surgery ultimately becomes necessary anyway. To date, few studies have fully addressed the costs and outcomes associated with different patient management strategies for patients with UC. A small number of studies have compared no surveillance and surveillance at fixed intervals,[14-17] but no studies have considered the cost-effectiveness of ongoing surveillance versus immediate proctocolectomy.

We aimed to investigate the cost-effectiveness of surveillance after a finding of endoscopically invisible LGD versus immediate surgery, accounting for both age and the presence of comorbidities.

METHODS

A decision analytic model (Markov model) was built to evaluate the 2 alternative strategies for the management of patients with flat LGD in the United Kingdom National Health Service (NHS). The patient population modelled was individuals in whom endoscopically invisible LGD had been found at initial endoscopy and in whom follow-up endoscopy (within 3 months of diagnosis, as per European guidelines[8,18]) had failed to find evidence for multifocal LGD, an associated endoscopically visible lesion, or a more advanced form of dysplasia in the normal-appearing mucosa. It was assumed that these patients were free from comorbidities or genetic disorders associated with increased cancer risk and without a family history of CRC or a preference for surgery.

The Markov model was constructed in Microsoft Excel 2011 (Microsoft, Redmond, Wash, USA) with the structure developed by reviewing the literature on current clinical practice and conducting interviews with clinical experts at the Oxford University Hospitals NHS Foundation Trust (Figs. 1 and 2). For patients undergoing surgery, it was assumed that up to age 60 years, 75% of patients received an ileal pouch–anal anastomosis (IPAA) procedure, with the remainder receiving end ileostomy, based on current clinical practice in the Oxford University Hospitals NHS Foundation Trust. This proportion decreased to 25% from age 60 to 70 years and to 2% from age 71 years onward. Patients undergoing surveillance were assumed to receive a colonoscopy every year for the first 5 years and every 3 years thereafter, in line with expected clinical practice in the Oxford University Hospitals NHS Foundation Trust.

A hypothetical cohort of 10,000 patients transitioned between model health states over a 20-year timeframe, chosen as a reasonable timeframe over which current clinical practice could be extrapolated and thus sufficient to capture the costs and outcomes associated with both surveillance and surgery. The cycle length—how long a patient remained in a health state before transitioning—was assumed to be 3 months in all cancer, surgery, and

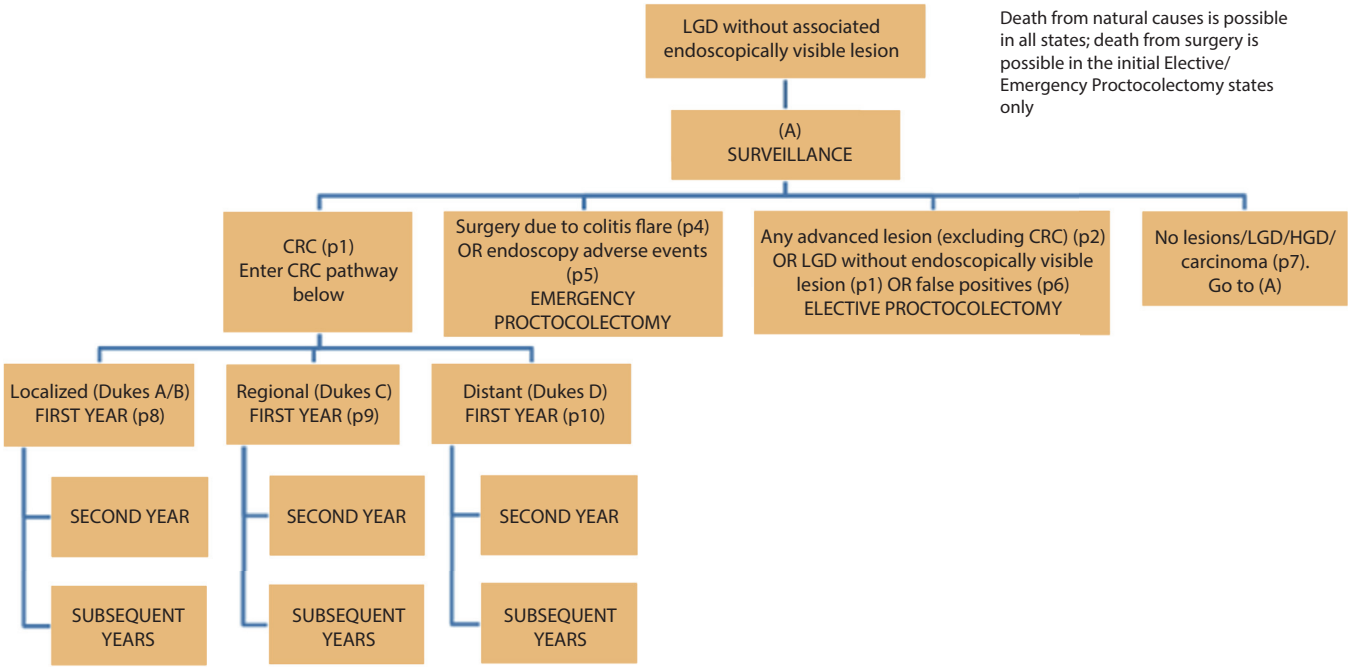

Figure 1. Surveillance model structure. *LGD,* Low-grade dysplasia; *CRC,* colorectal cancer; *HGD,* high-grade dysplasia.

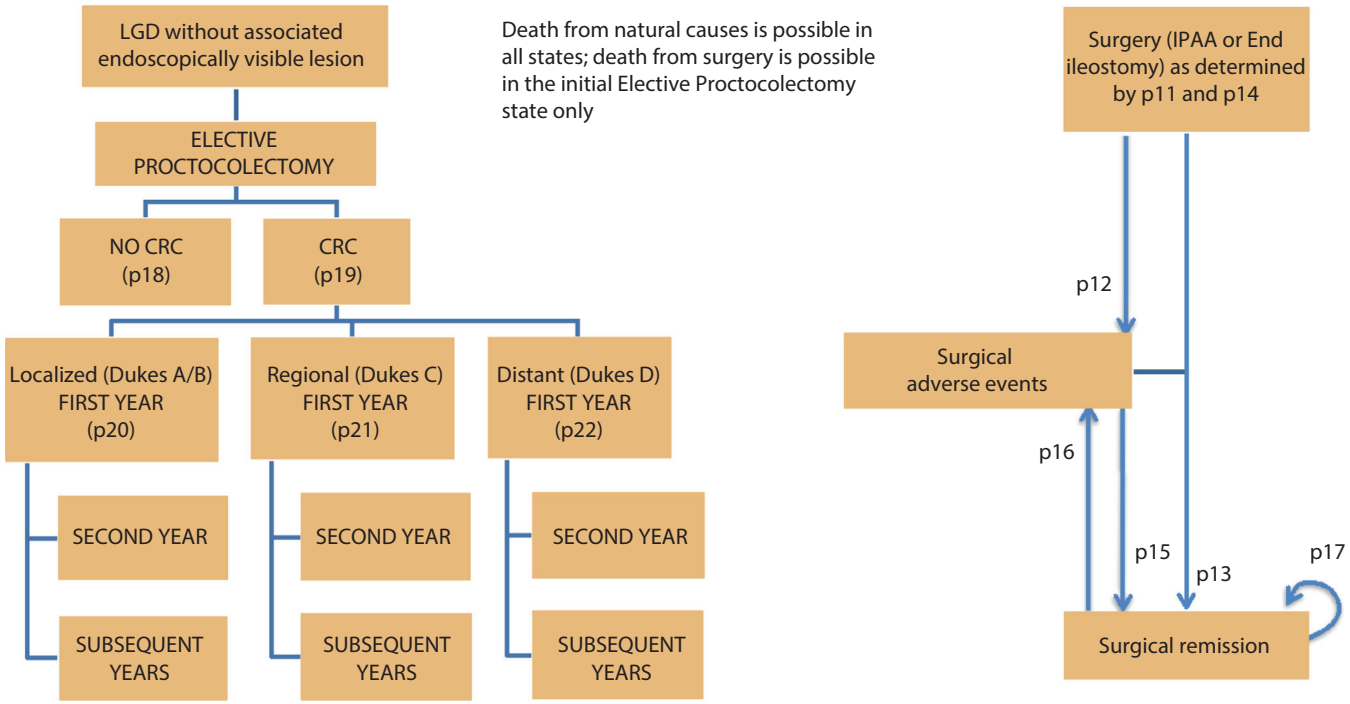

Figure 2. Immediate surgery model structure and structure of surgery component of surveillance model. *LGD,* Low-grade dysplasia; *CRC,* colorectal cancer; *IPAA,* ileal pouch-anal anastomosis.

postoperative states and for surveillance states between annual and/or 3-year surveillance (allowing for transitions to surgery because of colitis flare). Cycle lengths of 1 year and 3 years were used for annual and 3-year surveillance, respectively, in line with British and European guidelines.[8,11] Costs and health outcomes were discounted at a rate of 3.5% per annum, as per National Institute for Health and Care Excellence guidance.[19] All currencies

TABLE 1. Transition probabilities

Probability	Value	Notes	Source, ref. no.
p1a	0.0139	Annual probability of CRC	7
p1b	0.0411	Three-year probability of CRC	7
p2a	0.0159	Annual probability of any advanced lesion other than CRC	7
p2b	0.0469	Three-year probability of any advanced lesion other than CRC	7
p3a	0.0181	Annual probability of repeat finding of endoscopically invisible LGD, calculated from 1 of 13 patients in 4.2 years	20
p3b	0.0535	Three-year probability of repeat finding of flat LGD	20
p4	0.0024	Three-month probability of colitis flare needing surgery	21
p5	0.0013	Probability of perforation during endoscopy leading to surgery	22
p6	0.0024	Per endoscopy probability of false positive for dysplasia	7
p7a	1-p1a-p2a-p3a-p4-p5-p6-p24	Residual probability for annual surveillance	Residual
p7b	1-p1b-p2b-p3b-p4-p5-p6-p24	Residual probability for 3-year surveillance	Residual
p7c	1-p4-p24	Residual probability for no endoscopy cycles	Residual
p8	0.5500	Probability of Dukes A/B for cancer detected during surveillance	7
p9	0.3210	Probability of Dukes C for cancer detected during surveillance	7, 23
p10	0.1290	Probability of Dukes D for cancer detected during surveillance	7, 23
p11	Varied based on age	Probability of surgery type being IPAA	E
p12a	0.0588	Three-month probability of adverse event after IPAA	Personal communication, 24
p12b	0.0588	Three-month probability of adverse event after end ileostomy	Personal communication, 24
p13	1-p12-p23-p24	Residual probability for transition from surgery to remission	Residual
p14	1-p11	Residual probability of surgery type being end ileostomy	Residual
p15	1-p24	Residual probability for transition from surgical adverse event to surgical remission	Residual
p16a	p12a	Probability of transition to adverse event from IPAA remission	Personal communication, 24
p16b	p12b	Probability of transition to adverse event from end ileostomy remission	Personal communication, 24
p17	1-p16-p24	Residual probability for remaining in surgical remission	Residual
p18	1-p19-p23-p24	Residual probability for no CRC after immediate proctocolectomy	Residual
p19	0.0203	Probability of synchronous CRC after proctocolectomy, pooled from 2 studies using sample sizes as weights	25, 26
p20	0.7800	Probability of Dukes A/B for synchronous cancer detected after proctocolectomy	27
p21	0.2000	Probability of Dukes C for synchronous cancer detected after proctocolectomy	27
p22	0.0200	Probability of Dukes D for synchronous cancer detected after proctocolectomy	27
p23	Varied based on age, type of surgery, and comorbidities	Death from surgery	28
p24	Varied based on age	Death from other causes	29

CRC, Colorectal cancer; *LGD,* low-grade dysplasia; *IPAA,* ileal pouch–anal anastomosis; *E,* elicited from experts in the Oxford University Hospitals NHS Foundation Trust.

were converted from Great British pounds to U.S. dollars by using the exchange rate on May 24, 2017 (£1 = $1.29).

Model transition probabilities

The model transition probabilities (Table 1) give the probability of moving from one state to another in one cycle. The probabilities of developing an advanced lesion or CRC were derived from two meta-analyses.[7,13] As Thomas et al[7] reported both of these figures for patients with endoscopically invisible LGD, whereas the later meta-analysis by Fumery et al[13] reported only the incidence of advanced lesions for patients with endoscopically invisible LGD, the former meta-analysis was used as the primary source for these figures, with

TABLE 2. Model inputs

Input	Value*	Source, ref. no.
Endoscopic surveillance costs		
Diagnostic colonoscopy with biopsy (gastroenterology), day case†	$774.21	34
Outpatient face-to-face attendance, follow-up (gastroenterology)‡	$164.57	34
Drug costs		
5-aminosalicylic acid (mesalazine)§	$55.11	35
Staff costs, per hour		
Consultant gastroenterologist	$115.70	24
Inflammatory bowel disease nurse/stoma nurse	$33.22	24
Surgical costs		
Subtotal proctocolectomy with pouch formation and loop ileostomy	$8092.74	24
Proctocolectomy with ileostomy	$8092.74	24
Pouch removal, end ileostomy	$4971.29	24
Closure of ileostomy	$4971.29	24
Hospital costs		
Inpatient day	$395.17	24
Postsurgical costs		
Sigmoidoscopy (day case)	$681.17	24
Colonoscopy (day case)	$681.17	24
Metronidazole‖	$12.98	24
Ciprofloxacin‖	$8.29	24
Stoma malfunction¶	$21.65	24
Stoma supplies (1 month)	$94.53	24
Utilities		
Surveillance**	0.9410	36
Surgery††	0.8167	27, 37
Postsurgical adverse events‡‡	0.7967	27, 37
Postsurgical remission	0.9200	27
Local CRC	0.7400	38
Regional CRC	0.5900	38
Distant CRC	0.2500	38

CRC, Colorectal cancer.
*Costs from ref. 24 inflated to 2014/2015 prices.
†NHS reference cost FZ52Z.
‡NHS reference cost WF01A.
§Maximum maintenance dose, average monthly cost.
‖Average cost for a 10-day course.
¶Average cost.
**Assumed to be the same as the utility of the general population.
††Assumed to be 1 month of surgery state utility (0.61) and 2 months of postsurgical remission utility.
‡‡Assumed to be 1 month of postsurgical adverse events utility (0.55) and 2 months of postsurgical remission utility.

the latter included as a sensitivity analysis. Thomas et al[7] reported the incidence of cancer or any advanced lesion in a similar group of patients, divided into before and after LGD. After LGD refers to patients who, after a 6-month follow-up, were deemed suitable for colonoscopic surveillance. Although this decision would likely be made after 3 months in the United Kingdom NHS, this difference was not expected to have a substantive impact on the results. The model starting point was therefore the end of this 3-month period, at which higher risk patients had been referred for colectomy, and the remaining patients faced a choice between surgery and surveillance. False negatives for both dysplasia and cancer were assumed to be captured by the incidence figures in the meta-analysis.[7] False positives for dysplasia were modelled explicitly (as additional patients undergoing surgery), with probabilities derived from the meta-analysis. The derivation of these transition probabilities is described in Appendix 1, available online at www.giejournal.org.

Model inputs

Table 2 presents the model inputs. The model evaluated both the life-years and quality-adjusted life years (QALYs) accrued by each strategy. Information on the number of patients in each health state at the end of each model cycle was used to calculate life-years. QALYs were estimated by combining this life-years data with utility data extracted from the literature.[30] A United Kingdom NHS costing perspective was used. The cost of surveillance comprised the cost of an appointment with a gastroenterologist and the cost of a colonoscopy. Given that patients in the surveillance program had a previous finding of dysplasia (hence a colitis flare would likely lead to colectomy rather than medical management), patients were assumed to have received the maximum maintenance dose of 5-aminosalicylic acid.[31] Use of biological therapy was not modeled because such an indication would likely prompt colectomy. All costs were inflated to 2014/2015 prices by using United Kingdom inflation indices[32,33] and were converted from Great British pounds to U.S. dollars by using the exchange rate on May 24, 2017 of $1.29 to £1. Total costs for each strategy were calculated by summing the costs accrued in each model cycle. The total outcomes and costs for each strategy were then combined to calculate an incremental cost-effectiveness ratio (ICER) for surveillance versus surgery (ie, the cost per additional life-year or QALY gained by entering a patient into a surveillance program rather than proceeding with immediate proctocolectomy). ICERs were compared with the standard National Institute for Health and Care Excellence threshold of $25,800 per life-year or QALY gained to determine cost-effectiveness.

The base-case analysis was repeated for 6 age groups (25/35/45/55/65/75), and to account for the presence of 1, both, or neither of 2 comorbidities that are core components of the surgical risk prediction model used (peripheral edema with borderline cardiomyopathy and limiting dyspnea with moderate chronic obstructive airways

disease). Both comorbidities increased surgical risk, as did increases in age. Surgical mortality rates were calculated by using the Portsmouth predictor equation for mortality surgical risk calculator.[28] One-way sensitivity analysis was conducted for all parameters at ages 25 and 55, with no comorbidities, along with several scenario analyses (at age 55 with no comorbidities). Parameter variations reflected available evidence from the literature. All sensitivity analyses were undertaken using the results from the cost-effectiveness analysis in which QALYs were used as an outcome measure.

To explore the uncertainty around the results, a probabilistic sensitivity analysis was conducted. Probability distributions were attached to each model parameter, and 1000 simulations were conducted, with each simulation utilizing a new random draw from the probability distributions assigned to each parameter. Parameter uncertainty was quantified by using a coefficient of variation of 0.10 when these data were unavailable in the literature. This allowed 1000 ICERs to be calculated and cost-effectiveness acceptability curves to be constructed. The cost-effectiveness acceptability curves reported the proportion of the 1000 ICERs that showed either surveillance or surgery to be cost-effective at different levels of the cost-effectiveness threshold.[39]

RESULTS

Table 3 presents the results of the cost-effectiveness analysis that used QALYs (Appendix 2, available online at www.giejournal.org, presents the results using life-years). At age 25 years with no comorbidities, surveillance costs $2873 more per patient than immediate surgery, while providing 0.078 fewer QALYs. At age 65 years, surveillance costs $1014 more per patient, while providing an additional 0.041 QALYs. Surgery strictly dominates surveillance (providing more QALYs at a lower cost) for patients without comorbidities aged 25, 35, 45, and 55 years and for patients aged 25, 35, and 45 years with only 1 comorbidity. Surveillance becomes cost-effective in those with no, 1, or 2 comorbidities at 65, 60, and 60 years, respectively (Table 4).

Differences in cost-effectiveness by patient subgroup are driven by several factors. First, across almost all of the age groups and comorbidities considered, the average cost per patient of immediate surgery is around $2800 lower than the average cost of surveillance. The exception is at age 65 years, when the cost difference is between $1014 and $1206, depending on the presence of comorbidities. This is the first age group in which 75% of patients receive end ileostomy; hence, the smaller cost difference is driven by the increased cost of postsurgical remission. Most patients in this age group remain in remission for several years, whereas for the group aged 75 years, a higher proportion die within the model timeframe, hence remission costs are lower, increasing the cost difference again.

Second, as patients age, the surgical mortality rate increases and the increased quality of life experienced by surviving patients in the surveillance program begins to offset the increased mortality and morbidity caused by the development of CRC, with surveillance being cost-effective at age 65 years (no comorbidities). The disbenefit to patients in terms of immediate surgical risk and lower postsurgical quality of life is therefore offset at younger ages by the benefit of not being at risk of developing CRC and the associated high levels of morbidity and mortality. In older patients, surgical mortality is higher, and the relative impact of those who develop cancer in the surveillance arm is reduced, allowing the increased quality of life of those who avoid or delay surgery in the surveillance arm to drive the results, making surveillance cost-effective. The presence of comorbidities advances this effect in time. The same pattern of results is observed in the cost-effectiveness analysis using life-years (Appendix 2).

Alternative incidence rates of CRC and advanced neoplasia

Appendix 3 (available online at www.giejournal.org) presents an analysis in which the incidence rates for CRC and advanced neoplasia derived from the Fumery et al[13] meta-analysis are applied. Although this meta-analysis is more recent, it reports only the incidence of advanced neoplasia from invisible dysplasia; hence, an assumption was needed to derive the incidence of CRC from invisible dysplasia (see Appendix 3 for details). Fumery et al[13] report an annual incidence of advanced neoplasia from invisible dysplasia of 6.1%, more than twice the 3% figure reported by Thomas et al.[7] In the resulting cost-effectiveness analysis, surveillance becomes less cost-effective in all age groups and for any profile of comorbidities and is only cost-effective for those with 2 comorbidities at age 75.

One-way sensitivity analyses

Table 5 summarizes the one-way sensitivity analysis results for the parameter variations that had the most notable impact on the results. A reduction in the annual (or 3-year) probability of developing CRC while undergoing surveillance to 0.009 (or 0.028) leads to surveillance becoming almost cost-effective at age 25 years (ICER of $28,082 per QALY gained) and cost-effective at age 55 years (ICER of $24,529 per QALY gained). Surveillance also becomes cost-effective at ages 25 and 55 years when the utility associated with postsurgical remission after IPAA reduces to 0.885 and when the utility associated with postsurgical remission after end ileostomy reduces to 0.810. For the utility associated with inactive UC, an increase to 0.953 results in an ICER of $41,995 per QALY gained at age 55

TABLE 3. Cost-effectiveness by using QALYs of surveillance versus surgery, by age and number of comorbidities

		Comorbidities								
		0			1			2		
Age, y	Comparator	Cost/ patient	Outcomes/ patient (QALYs)	ICER, cost/ QALY gained	Cost/patient	Outcomes/ patient (QALYs)	ICER, cost/ QALY gained	Costs/ patient	Outcomes/ patient (QALYs)	ICER, cost/ QALY gained
25	Surveillance	$27,250	13.004		$27,246	12.979		$27,242	12.939	
	Surgery	$24,377	13.082		$24,336	13.006		$24,270	12.882	
	Difference	$2873	-0.078	-$36,831	$2910	-0.027	-$107,787	$2843	0.056	$50,771
35	Surveillance	$27,229	12.924		$27,225	12.899		$27,220	12.859	
	Surgery	$24,329	12.997		$24,289	12.921		$24,224	12.798	
	Difference	$2899	-0.073	-$39,707	$2936	-0.022	-$133,456	$2997	0.061	$49,126
45	Surveillance	$27,178	12.724		$27,174	12.700		$27,170	12.661	
	Surgery	$24,212	12.785		$24,172	12.711		$24,108	12.590	
	Difference	$2966	-0.061	-$48,618	$3002	-0.011	-$272,894	$3061	0.071	$43,115
55	Surveillance	$26,934	12.230		$26,930	12.205		$26,925	12.166	
	Surgery	$23,922	12.262		$23,883	12.191		$23,821	12.075	
	Difference	$3012	-0.033	-$91,277	$3047	0.014	$217,641	$3102	0.091	$34,093
65	Surveillance	$26,379	11.016		$26,373	10.990		$26,361	10.949	
	Surgery	$25,365	10.974		$25,285	10.899		$25,155	10.777	
	Difference	$1014	0.041	$24,730	$1087	0.091	$11,950	$1206	0.172	$7013
75	Surveillance	$25,290	8.340		$25,280	8.321		$25,263	8.289	
	Surgery	$22,590	8.147		$22,490	8.070		$22,326	7.945	
	Difference	$2700	0.193	$13,989	$2790	0.250	$11,161	$2937	0.344	$8539

QALY, Quality-adjusted life year; *ICER,* incremental cost-effectiveness ratio.

years. Finally, a 50% increase in the cost of IPAA leads to an ICER of $34,634 per QALY gained at age 25.

The sensitivity of the results to the probability of synchronous CRC in the immediate surgery arm also was considered, with the upper limit increased from the base case value of 2% to 19%, as reported by Bernstein et al.[40] This makes surveillance cost-effective at ages 25 and 55 years, with ICERs of $4666 and $5259, respectively. However, in the base-case analysis, for the group aged 25 years with no comorbidities, the total number of patients with CRC after 2 years in surveillance is 266, compared with 202 with synchronous cancer in the immediate surgery arm. This is the expected result: most of the synchronous cancers have been detected after 2 years of surveillance, and some additional cancers have been found. This lends credibility to the use of 2% as an estimate of synchronous cancer.

Scenario analysis

Several scenarios were considered in which multiple parameters were varied simultaneously (results presented in Appendix 4, available online at www.giejournal.org). The scenarios that had the most pronounced effect on the results were those in which the utility associated with postsurgical remission after IPAA and end ileostomy was reduced from 0.920 to 0.865 (the ICER at age 25/55 years falls to $9058/$9256 per QALY gained), and when all costs associated with surgery were increased by 25% (the ICER at age 25/55 years falls to $26,802/$57,184 per QALY gained).

Probabilistic sensitivity analysis

The cost-effectiveness acceptability curves at ages 25 and 65 years for no comorbidities are shown in Figures 3 and 4. At a cost-effectiveness threshold of $25,800 per QALY gained, the probability of surveillance being cost-effective is 39% at age 25 years and 55% at age 65 years. The probability that surveillance is cost-effective at the same threshold for all of the age groups and comorbidities considered in the base-case analysis is reported in Table 6.

DISCUSSION

This study has evaluated the cost-effectiveness of immediate surgery versus long-term surveillance in a relatively low-risk cohort of patients with UC and endoscopically invisible LGD, considering different age groups and comorbidities. Surveillance is always more expensive, and it provides more QALYs and life-years only in older patients and those with comorbidities. The age at which surveillance

TABLE 4. Age at which surveillance becomes cost-effective (ICER highlighted)

	No. of comorbidities		
Age, y	**0**	**1**	**2**
50		-$2,422,758	
51		$2,169,528	
52		$649,776	
53		$460,942	
54		$313,347	
55		$219,330	
56		$170,628	
57		$142,740	$31,920
58		$117,233	$30,703
59		$98,555	$29,639
60	-$19,390	**$18,589**	**$5844**
61	$66,694	$9386	$4709
62	$40,118	$10,108	$5264
63	$33,254	$11,119	$5980
64	$27,687		
65	**$24,506**		
66	$22,376		
67	$20,944		
68	$19,999		

ICER, Incremental cost-effectiveness ratio.

TABLE 5. Results of one-way sensitivity analysis (base-case values highlighted)

		Age, y	
Parameter	**Value**	**25**	**55**
Annual/3-year cancer probability	0.005/0.015	$9814	$10,485
	0.007/0.021	$14,643	$14,773
	0.009/0.028	$28,082	$24,529
	0.012/0.035	$263,054	$68,632
	0.014/0.041	-$36,817	-$91,547
Ileal pouch–anal anastomosis postsurgical remission utility	0.850	$6531	$5860
	0.885	$15,880	$12,522
	0.920	-$36,817	-$91,547
	0.930	-$18,899	-$27,129
	0.940	-$12,712	-$15,924
End ileostomy postsurgical remission utility	0.810	$14,776	$22,004
	0.865	$49,359	$57,930
	0.920	-$36,817	-$91,547
	0.930	-$27,945	-$62,313
	0.940	-$22,520	-$47,231
Inactive ulcerative colitis utility	0.929	-$15,290	-$21,902
	0.935	-$21,608	-$35,346
	0.941	-$36,817	-$91,547
	0.947	-$124,315	$155,164
	0.953	$90,303	$41,995
Ileal pouch–anal anastomosis surgery costs	$9702	-$108,267	-$267,590
	$14,552	-$72,542	-$179,569
	$19,403	-$36,817	-$91,547
	$24,255	-$1091	-$3526
	$29,105	$34,634	$84,495

becomes cost-effective varies between 60 and 65 years, depending on the presence of comorbidities. The incidence of CRC in the surveillance cohort and quality of life after IPAA are both important drivers of these results. Overall, the sensitivity of the results to relatively small changes in model parameters gives rise to considerable uncertainty surrounding the cost-effectiveness results, especially around the estimates for CRC incidence during surveillance. The results should therefore be interpreted with caution. Furthermore, the primary analysis is based on estimates of cancer risk in patients with endoscopically invisible dysplasia from a 2007 meta-analysis[7]; a more recent 2017 meta-analysis reported higher risk estimates for advanced neoplasia and cancer (61 vs 30 per 1000 patient years),[13] making surveillance less cost-effective in most scenarios (Appendix 3). The finding of a higher risk of advanced neoplasia when more modern studies are considered may seem counterintuitive; however, it is possible that with modern high-definition endoscopes, only "true" endoscopically invisible dysplasia remains, representing likely field cancerization[41,42] and a higher risk of further advanced neoplasia, whereas in older studies this risk may have been diluted by some low-risk visible dysplasia that was missed by older technologies. Rates of colectomy when nonpolypoid dysplasia is detected by newer technologies also may have changed risks.

Recent guidelines have considered either intensive colonoscopic surveillance or colectomy an acceptable strategy after patient discussion. Our results will inform these discussions between patients and clinicians, who will need to balance trade-offs between surgical risk and quality of life. Balancing future cancer risk with immediate surgical risk and considering cost is complex, and the suggestion that surveillance is the preferred strategy for patients aged 65 years and over, and surgery the preferred strategy for patients aged <65 years may be counterintuitive to clinicians and patients. Our model specifically considers NHS costs, and outcomes may vary in other healthcare systems. Nevertheless, our results may encourage clinicians to more

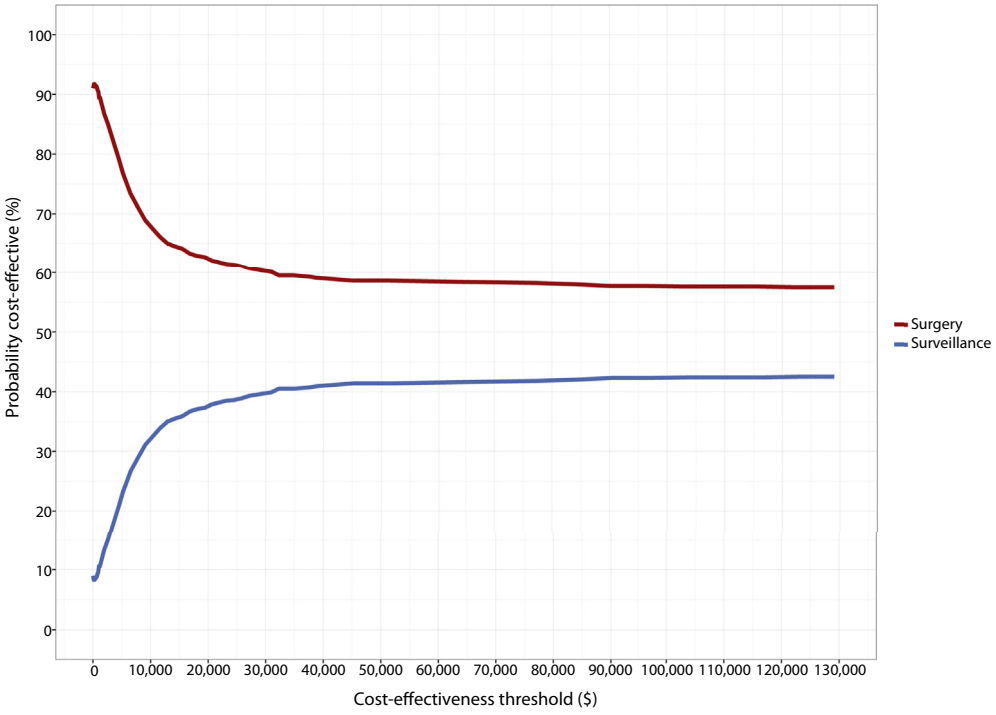

Figure 3. Cost-effectiveness acceptability curve. Patient age 25 years, no comorbidities.

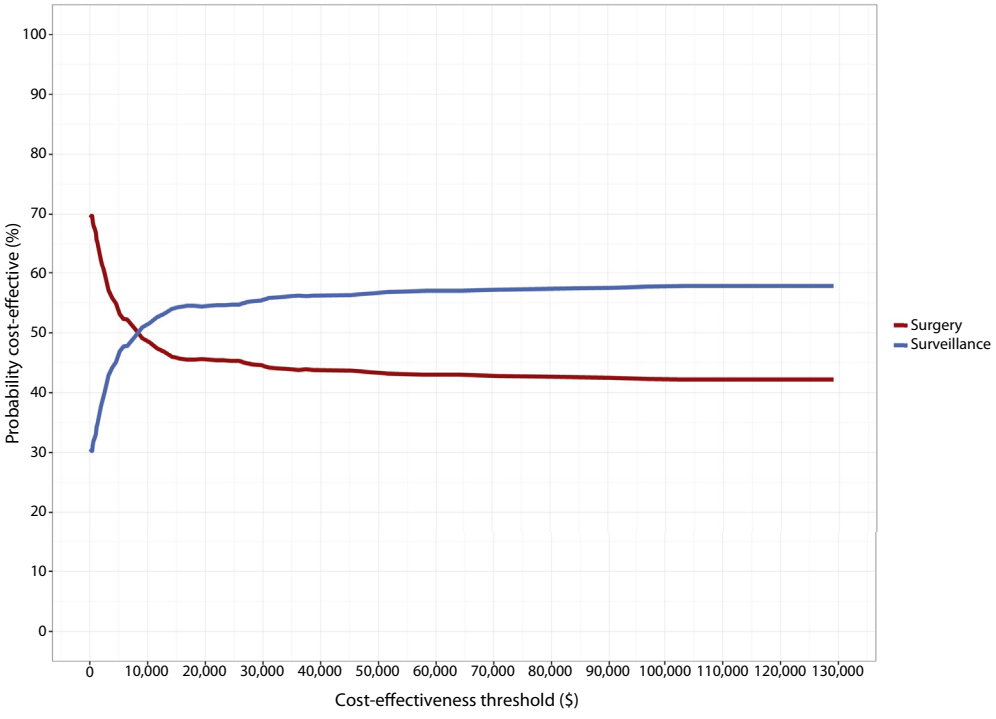

Figure 4. Cost-effectiveness acceptability curve. Patient age 65 years, no comorbidities.

actively consider the pros and cons of surgery in all but older or significantly comorbid patients.

This study has a number of strengths. First, instead of modelling the hypothetical progression to cancer from dysplasia (about which relatively little is known), "real" cancer incidence rates were used from a 2007 study that reflected the synthesis of observations from several studies.[7] Furthermore, additional analysis from a more recent meta-analysis suggests that our main estimate of cancer incidence may be conservative. Second, the use of QALYs ensures that

TABLE 6. Probability that surveillance is cost-effective at a cost-effectiveness threshold of $25,800

	No. of comorbidities		
Age, y	0	1	2
25	39%	44%	48%
35	43%	46%	50%
45	40%	47%	51%
55	42%	46%	53%
65	55%	59%	62%
75	56%	65%	71%

the impact of the different strategies on both quantity and quality of life is captured. Third, through the use of decision modelling, the multiple elements relevant to clinical decision making in this area are considered collectively and in a transparent framework. The study adds clarity to a decision that is currently considered uncertain and for which best practice is unclear, by highlighting which factors drive cost-effectiveness and illustrating the trade-offs that exist. For older patients and those with comorbidities (ie, those patients for whom surveillance is most strongly recommended), there are no major obstacles preventing a change in clinical practice—although more colonoscopies would be performed, surveillance colonoscopy in UC is already commonplace for many patients. The sensitivity of the results to utility in the postsurgical remission state and to increases in surgical costs reveal important decision factors in this setting and should be of interest in situations in which healthcare costs are expected to be higher than average or in which utility after surgery is expected to be lower than average (eg, if a patient has a preference against surgery or does not expect to adapt well to the consequences of surgery).

In terms of study limitations, the model reflects practice at a major United Kingdom inflammatory bowel disease center that is broadly in line with European Crohn's and Colitis Organisation (ECCO) and Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients (SCENIC) international guidelines; however, other geographic areas may have higher or lower thresholds for colectomy or differing surveillance strategies, which may change estimates. Second, because of limited data, the quality of life impact of repeated colonoscopies for patients in surveillance was not modelled. Third, the proportion of patients undergoing IPAA and end ileostomy at different ages was elicited from clinical experts in the Oxford University Hospitals NHS Foundation Trust. These proportions may not represent current clinical practice in other hospitals. Fourth, the 20-year model timeframe may lead to underestimates of costs and outcomes in younger patients; however, clinical practice may change during this period. We may overestimate surgical risk in young patients by using the adjusted Portsmouth predictor equation for mortality surgical risk calculator. Fifth, because of a lack of data on parameter uncertainty, an assumption was made regarding the appropriate coefficient of variation. Sixth, since the publication of the meta-analysis by Thomas et al,[7] high-definition colonoscopy and chromoendoscopy are now widely recommended in colitis surveillance, to be performed by an expert for cases in which endoscopically invisible LGD is found before colectomy is considered. This may convert some endoscopically invisible dysplasia into visible lesions. Many of the studies in this meta-analysis also pre-date current endoscopic technology and expertise. We have countered this by applying risk estimates from a recent meta-analysis that contains studies that suggest higher risks of future advanced neoplasia, leading to surgery being favored more strongly (Appendix 3). Seventh, we did not model IPAA surveillance; however, neoplasia risks in IPAA are exceptionally low, studies with long-term follow-up have questioned the value of this approach, and current guidelines only suggest "consider" of surveillance.[8,43] Eighth, the unit costs applied within the model are United Kingdom–specific, and this should be considered when the model results are generalized to settings outside the United Kingdom, where costs may be higher. Finally, we do not model the use of biological therapies, because risks are unclear in the context of invisible dysplasia. Although better control of inflammation may reduce future cancer risks, costs would be increased considerably.

Estimates of postsurgical remission utility (which reflect the reported utility of an individual, postsurgery, who has had surgery for active UC), may be different for the patients modelled in this study (who have inactive UC and dysplasia). Because our results are sensitive to postsurgical remission utility, improving the estimation of this variable may lead to surveillance becoming cost-effective at a different patient age. In addition, the impact on the results of the proportion of patients receiving IPAA or end ileostomy at different ages could be expanded to consider alternative estimates of these proportions, as could the impact of extending the 20-year model timeframe. Further work to better establish the uncertainty around the individual parameters would enable a more accurate quantification of the joint parameter uncertainty in the model and of the uncertainty around the results. This analysis would also be improved by further research that considers how the probability or expected length of postsurgical adverse events might vary with age. Finally, the studies synthesized by the meta-analysis do not treat a repeat finding of endoscopically invisible LGD as an indication for colectomy (as would be the case in the United Kingdom clinical practice), hence cancer incidence may be overestimated in the model, and the distribution of cancers may be excessively weighted toward Dukes C or D cancers.

In conclusion, surveillance appears cost-effective from age 65 years onward in patients with no comorbidities and age 60 years onward in patients with 1 or more comorbidities. For patients with a preference against surgery or for whom surgical outcomes could reasonably be expected to be worse than average, the age at which surveillance is a cost-effective treatment strategy may be significantly lower, and the results remain very sensitive to cancer incidence rates. Even with these data, however, such decisions will need to be individualized between patients and clinicians, supported by a multidisciplinary approach. It will be critical going forward in the era of biological therapy and chromoendoscopic surveillance that we redefine cancer risk estimates during colitis surveillance from large, community-based cohorts to refine future models of these strategies.

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APPENDIX 1. Derivation of transition probabilities

The annual incidence of CRC and any advanced lesion (excluding CRC) were derived from the Thomas et al[1] meta-analysis. These incidence figures were assumed to correspond broadly with the surveillance strategy being used in the model (annual surveillance for the first 5 years and 3-year surveillance thereafter); hence, the annual rate given was converted to annual and 3-year transition probabilities for use in the model. This assumption was considered reasonable because over a mean follow-up of 12 years, an average of 4.3 colonoscopies were performed, with a range of 3 to 7.6.[1] Over 12 years within the model, a maximum of 7 colonoscopies could be performed, which is within this range. Because of the data available, specific differences in cancer incidence based on sex or on the type of UC (proctitis, left-sided, or extensive) could not be explored further.

The annual incidence of CRC and any advanced lesions were derived from the Fumery et al[13] meta-analysis and the model results recalculated and included as a sensitivity analysis. Because Fumery et al report only the incidence of advanced lesions for patients with flat LGD, it was assumed that the ratio between the incidence rates for CRC and advanced lesions for all LGD also applied to flat LGD, allowing the incidence rate for CRC to be calculated for flat LGD.

The rate of endoscopy perforation was based on Bowles et al.[2] Perforation was assumed to lead to proctocolectomy: based on current clinical practice in the Oxford University Hospitals NHS Trust, these patients would likely already be in a surveillance program for dysplasia, and thus treatment was likely to be cautious. The false-positive figure for dysplasia was derived from Thomas et al.[1] Three findings of no dysplasia were made postoperatively after 1225 colonoscopies, a probability of 0.0024 per colonoscopy.[1]

Colitis flares could occur in any 3-month cycle, and were based on the 10-year colectomy probability estimated by Solberg et al.[3] This figure does not specifically address the population being modeled because it concerns the first 10 years after diagnosis of UC, but was considered to be the best available data in light of the difficulty of obtaining data specific to the population of interest.

In clinical practice, patients can be diagnosed with CRC preoperatively (by colonoscopy) or postoperatively (after colectomy for dysplasia). Because colectomy for dysplasia follows the same procedure as for CRC (involving additional removal of regional lymph nodes, confirmed by clinical experts from the Oxford University Hospitals NHS Trust), the 2 routes by which CRC is discovered were assumed to be identical for the purposes of the model, with the CRC incidence figures leading straight into the CRC pathways, despite the fact that some patients would first be suspected as having dysplasia. Patients then entered 1 of 3 states, representing Dukes A/B, Dukes C, and Dukes D staging of CRC. The distribution of patients across these stages was derived partly from the Thomas et al[1] meta-analysis, which reports the proportion of patients with Dukes A and/or B as 55%, with the remaining 45% distributed as per the ratio between Dukes C and Dukes D reported in Herrinton et al.[4] The CRC pathways were split into 3 states for each cancer stage, to reflect higher costs in the first 2 years than in subsequent years. Symptomatic CRC was not modelled because it was assumed that patients would be detected as positive for dysplasia or CRC before CRC became symptomatic.

Transition probabilities for the postsurgical pathways were derived from personal communication with the authors of Buchanan et al.[5] After surgery, patients can either progress to a postsurgical adverse events state or to a postsurgical remission state. From the adverse events state, patients enter remission, in which they can remain, or they can have further postsurgical adverse events. The cycle length used in Buchanan et al[5] is 1 month. The data provided by the authors were used to calculate the 3-month probabilities of developing adverse events after either IPAA or end ileostomy. Within the adverse events state, there was assumed to be 1 month of postsurgical adverse events and 2 months of postsurgical remission, with the costs and utilities reflecting this split accordingly, in order to retain parity with the approach taken by Buchanan et al.[5]

The proportion of patients receiving IPAA versus end ileostomy was based on expert opinion in the Oxford University Hospitals NHS Trust, with 75% of patients undergoing IPAA before age 60 years, 25% between age 60 and 70 years, and 2% above age 70 years. These proportions were assumed to be the same for patients receiving elective colectomy (for dysplasia or CRC) as for emergency colectomy resulting from perforation or colitis flare.

A proportion of those patients in the immediate surgery arm of the model were assumed to have synchronous CRC, discovered postoperatively. Estimates of synchronous CRC for patients diagnosed with flat LGD vary widely; hence, the estimate used was pooled from 2 recent studies (weighted by sample size).[6,7] The CRC distribution across Dukes stages was assumed to be lower for this group of patients as cancer was being detected at an earlier stage. The distribution used was based on Nguyen et al,[8] who estimated the distribution from a number of observational studies of LGD surveillance.

Patients could die in all states from other causes, with an additional surgical mortality rate considered for patients leaving the surgery states. The mortality rate in UC is slightly higher than in the general population, but the risk is highest in the first 2 years.[9] It was considered reasonable to assume that most patients entering the model would likely be beyond this initial period, and so

the mortality rate due to other causes was taken from the national life tables for the period 2010 to 2012,[10] with the arithmetic mean of male and female mortality at each age used. Surgical mortality rates were calculated by using the Portsmouth predictor equation for mortality surgical risk calculator.[11] Given that surgical risk varies significantly with age and the presence of comorbidities, 6 age groups were considered in the model (starting age of 25, 35, 45, 55, 65, 75 years). For each age group, information was extracted on surgical mortality rates when patients had either 0, 1, or 2 comorbidities. The 2 comorbidities considered (surgical risk at a given age was equal for either) were peripheral edema with borderline cardiomyopathy and limiting dyspnea with moderate chronic obstructive pulmonary disease.

Cancer mortality rates were estimated from the National Cancer Intelligence Network Web site, which reports 5-year survival for Dukes stages A/B/C/D.[12] Cancers were assumed to be split evenly across Dukes A and B, and so the mean of the rates for Dukes A and B was used.

APPENDIX 2. Cost-effectiveness of surveillance versus surgery using life-years, by age and number of comorbidities

APPENDIX 2 TABLE 1. Cost-effectiveness analysis results using life-years gained as an outcome measure

		No. of comorbidities								
		0			1			2		
Age, y	Comparator	Cost/ patient	Outcomes/ patient, life-years	ICER, cost/life-year gained	Costs/ patient	Outcomes/ patient, life-years	ICER, cost/life-year gained	Cost/ patient	Outcomes/ patient, life-years	ICER, cost/life-year gained
25	Surveillance	$27,250	14.150		$27,246	14.122		$27,242	14.078	
	Surgery	$24,377	14.399		$24,336	14.317		$24,270	14.181	
	Difference	$2873	-0.250	-$11,491	$2910	-0.194	-$15,001	$2843	-0.103	-$27,603
35	Surveillance	$27,229	14.062		$27,225	14.035		$27,220	13.991	
	Surgery	$24,329	14.306		$24,289	14.223		$24,224	14.088	
	Difference	$2899	-0.244	-$11,880	$2936	-0.188	-$15,617	$2997	-0.097	-$30,894
45	Surveillance	$27,178	13.846		$27,174	13.819		$27,170	13.776	
	Surgery	$24,212	14.074		$24,172	13.993		$24,108	13.860	
	Difference	$2966	-0.229	-$12,951	$3002	-0.174	-$17,252	$3061	-0.085	-$36,014
55	Surveillance	$26,934	13.306		$26,930	13.280		$26,925	13.236	
	Surgery	$23,922	13.502		$23,883	13.424		$23,821	13.296	
	Difference	$3012	-0.195	-$15,447	$3047	-0.144	-$21,160	$3102	-0.060	-$51,708
65	Surveillance	$26,379	11.985		$26,373	11.957		$26,361	11.912	
	Surgery	$25,365	12.080		$25,285	11.998		$25,155	11.864	
	Difference	$1014	-0.095	-$10,673	$1087	-0.041	-$26,524	$1206	0.048	$25,128
75	Surveillance	$25,290	9.075		$25,280	9.054		$25,263	9.020	
	Surgery	$22,590	8.982		$22,490	8.897		$22,326	8.761	
	Difference	$2700	0.093	$29,032	$2790	0.156	$17,886	$2937	0.259	$11,341

APPENDIX 3. Results by using CRC and advanced neoplasia incidence rates derived from the Fumery et al[13] meta-analysis

APPENDIX 3 TABLE 1. Cost-effectiveness of surveillance versus surgery using quality-adjusted life-years, by age and number of comorbidities

	No. of comorbidities		
Age, y	0	1	2
25	-$9745	-$10,713	-$12,750
35	-$9999	-$11,009	-$13,140
45	-$10,681	-$11,802	-$14,196
55	-$12,305	-$13,682	-$16,687
65	-$10,937	-$13,342	-$20,149
75	$74,763	$41,110	$24,279

APPENDIX 4. Main results from scenario analysis

All results are at age 55 years in the no-comorbidities group, with the listed parameters varied simultaneously and the surveillance versus surgery ICER reported. All costs are for one 3-month cycle in the state referred to.

APPENDIX 4 TABLE 1. Utility for both postsurgical remission states set to their minimum values

Parameters	Base-case values	Midpoint between base case and minimum	Minimum
Utility of postsurgical remission following IPAA	0.92	0.885	0.85
Utility of postsurgical remission following end ileostomy	0.92	0.865	0.81
Impact on ICER			
ICER at age 25 y	-$36,817	$9058	$4033
ICER at age 55 y	-$91,547	$9256	$4405

This scenario investigated the impact of the utility in postsurgical remission being overestimated for both surgical procedures simultaneously.
IPAA, Ileal pouch–anal anastomosis; *ICER,* incremental cost-effectiveness ratio.

APPENDIX 4 TABLE 2. All surgical costs increased by 12.5% and 25%

Parameters	Base-case values	Base case + 12.5%	Base case + 25%
Cost of IPAA surgery	$19,403.33	$21,828.74	$24,254.15
Cost of postsurgical IPAA complications	$802.82	$903.17	$1003.52
Cost of postsurgical IPAA remission	$12.62	$14.19	$15.76
Cost of end ileostomy surgery	$12,246.03	$13,776.79	$15,307.54
Cost of postsurgical end ileostomy complications	$343.06	$385.96	$428.83
Cost of postsurgical end ileostomy remission	$302.49	$340.31	$378.12
Impact on ICER			
ICER at age 25 y	-$36,817	-$5006	$26,802
ICER at age 55 y	-$91,547	-$17,179	$57,184

IPAA, Ileal pouch–anal anastomosis; *ICER,* incremental cost-effectiveness ratio.

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