A decision analysis of surveillance for colorectal cancer in ulcerative colitis

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Abstract

Background—Patients with long standing, extensive ulcerative colitis have an increased risk of developing colorectal cancer.

Aims—To assess the feasibility of surveillance colonoscopy in preventing death from colorectal cancer.

Patients—A hypothetical cohort of patients with chronic ulcerative colitis.

Methods—The benefits of life years saved were weighted against the costs of biannual colonoscopy and proctocolectomy, and the terminal care of patients dying from colorectal cancer. Two separate Markov processes were modelled to compare the cost-benefit relation in patients with or without surveillance. The cumulative probability of developing colorectal cancer served as a threshold to determine which of the two management strategies is associated with a larger net benefit.

Results—If the cumulative probability of colorectal cancer exceeds a threshold value of 27%, surveillance becomes more beneficial than no surveillance. The threshold is only slightly smaller than the actual cumulative cancer rate of 30%. Variations of the assumptions built into the model can raise the threshold above or lower it far below the actual rate. If several of the assumptions are varied jointly, even small changes can lead to extreme threshold values.

Conclusions—It is not possible to prove that frequent colonoscopies scheduled at regular intervals are an effective means to manage the increased risk of colorectal cancer associated with ulcerative colitis.

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Patients with long standing, extensive ulcerative colitis have an increased risk of developing colorectal cancer.[1–7] After 40 years about 30% of all patients with pancolitis have developed colorectal cancer,[4–7] compared with a 6% cumulative risk over lifetime for such cancer in the general population.[8] Because of the increased risk of cancer, surveillance colonoscopy in long standing pancolitis has been widely recommended.[9–11] The rationale of surveillance colonoscopy is to detect cancer at an early stage when treatment is more likely to be curative. Mucosal dysplasia is considered a premalignant lesion that over a time period of

three to five years can lead to full blown cancer. The presence of dysplasia in biopsy specimens obtained through surveillance colonoscopy suggests that a patient undergoes prophylactic proctocolectomy to achieve primary cancer prevention. Little evidence exists, however, that surveillance is truly efficacious and cost effective in preventing deaths from colorectal cancer. No randomised controlled trial has been performed in the attempt to define the role of surveillance colonoscopy in colorectal cancer prevention. The prevalence of extensive ulcerative colitis is relatively small, and even large medical centres committed to the study of inflammatory bowel disease rarely follow more than 200 patients at any given point in time. It is not likely that a randomised clinical trial will be conducted soon to provide conclusive evidence in favour of or against surveillance. Considering the obstacles to a clinical resolution, the aim of the present study was to utilise the techniques of medical decision analysis in trying to assess the feasibility and usefulness of surveillance.

Methods

In the surveillance of patients with ulcerative colitis, the benefit of life years saved needs to be weighted against the costs of colonoscopy, proctocolectomy, and the terminal care of patients dying from colorectal cancer. Two separate Markov processes were modelled to compare the cost-benefit relation in patients with or without surveillance by biannual colonoscopy. The cumulative probability of developing colorectal cancer served as a threshold to determine which of the two management strategies is associated with a larger net benefit.[12]

MARKOV MODEL

The present analysis deals with a hypothetical cohort of patients, who are presently 50 years old and who were first diagnosed with ulcerative colitis 10 years ago. Medical events are modelled as transitions of patients among a predefined set of health states, the occurrence of each transition being governed by a probability value (fig 1).[13] The time frame of the analysis is divided into equal increments of two years duration, during which patients may cycle from one state to another. The white rectangles of fig 1 represent permanent states in the true sense of a Markov process, as subjects remain in these states at least for the complete
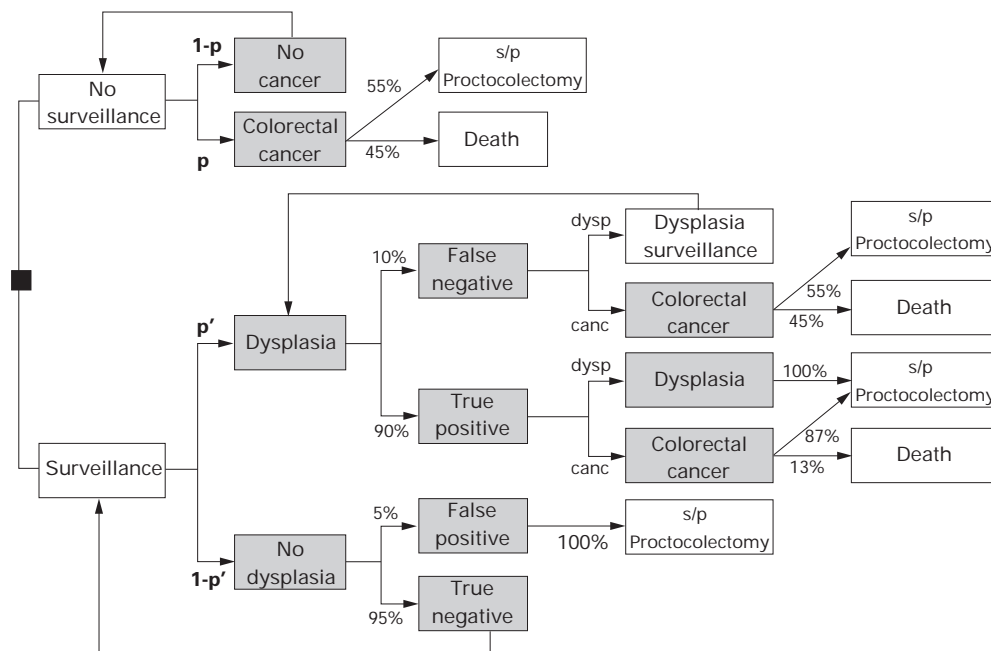

Figure 1 Markov state diagram of surveillance and no surveillance for colorectal cancer. The white rectangles represent true Markov states where subjects remain for the complete length of a cycle. The shaded rectangles represent intermediate states, which subjects can enter and leave during one cycle before settling in a true Markov state. The transition p represents the incidence rate of cancer per cycle, p' represent the incidence of high grade dysplasia. In patients with high grade dysplasia, dysp represents the fraction of patients with dysplasia alone, while canc represents the fraction of high grade dysplasia accompanied by cancer.

length of a two year cycle. The grey rectangles symbolise intermediate states of patients with or without surveillance. Subjects can enter and leave these intermediate states during one cycle before settling in a permanent Markov state.

The upper of part of fig 1 shows the natural history in patients without surveillance. Patients may develop cancer with a probability p or may stay cancer free with a probability 1−p. In the case of colorectal cancer, patients may survive after a proctocolectomy or die from colorectal cancer. After a cycle of two years, patients without cancer are re-entered into the analysis and are reassessed for the potential development of colorectal cancer. The same pathway is followed during each subsequent cycle.

The lower part of fig 1 shows the natural history in patients undergoing surveillance. The probability p' of developing high grade dysplasia is higher than the probability p of developing cancer. In patients with high grade dysplasia, the outcome of surveillance is determined by the rate of false negative and true positive

test results. If a false negative test concerns the presence of dysplasia alone, patients will continue to be followed in the surveillance programme and will be given another chance of a correct diagnosis during the next cycle of surveillance. A false negative test of high grade dysplasia accompanied by cancer will result in survival through timely proctocolectomy or death from colorectal cancer. The outcome of proctocolectomy in a patient with a true positive test also depends on whether the patient has dysplasia alone or dysplasia accompanied by cancer. Lastly, in patients without dysplasia, colonoscopy plus biopsy can result in false positive and true negative tests. A false positive test leads to proctocolectomy, while patients with a true negative test continue to be followed by surveillance colonoscopy. In addition to the states shown in fig 1, the population in each state is subjected to natural attrition by the annual age specific death rate of the US population.[14]

TRANSITION PROBABILITIES

Table 1 lists the transition probabilities built into the model and their range tested in the sensitivity analyses. As no data are available for the sensitivity and specificity of repetitive colonoscopy plus biopsy in detecting cancer and dysplasia, we rely on previously used expert opinions and on the reported coincidence of cancer and dysplasia.[9 15 16] These rates are inflated to estimate rather sensitive and specific test characteristics of surveillance colonoscopy plus multiple biopsies. The cancer related death rates of 13% and 45% in patients with or without surveillance, respectively, are taken from a report of Connell *et al.*[17] The mortality associated with proctocolectomy is

Table 1 Baseline assumptions and range tested in the sensitivity analysis

|	Baseline model	Sensitivity analysis
Sensitivity in detecting dysplasia and CRC	90%	50–100%
Specificity of surveillance in detecting dysplasia and CRC	95%	80–100%
Case fatality rate of CRC in surveillance	13%	5–45%
Health related quality of life after proctocolectomy	95%	85–100%
Surveillance interval	2 y	1–5 y
Time lag between dysplasia and CRC	3 y	1–5 y
Costs per surveillance colonoscopy	$911	$200–$1500
Costs of proctocolectomy	$8300	$4150–$16 600
Costs of terminal care per patient with CRC	$34 100	$17 050–$68 200
Average annual income	$24 294	$10 000–$50 000
Annual discount rate	3%	–

CRC, colorectal cancer.
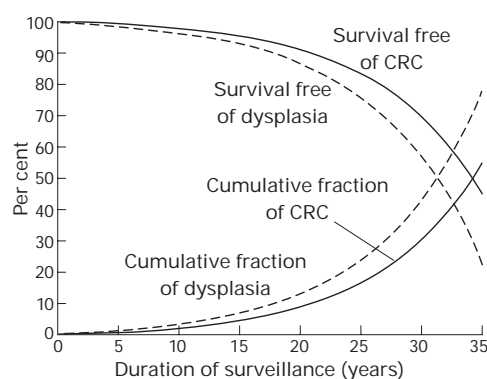
Figure 2　Cumulative fraction of patients with dysplasia or colorectal cancer (CRC), and surviving fraction of patients remaining free of dysplasia or colorectal cancer. Cumulative fractions were calculated using equations (1) and (3) with $\%CRC_{30y} = 30\%$, lag = three years, survival = 100% − cumulative fraction.

assumed to be negligible in comparison with the cancer related death rates.

Between the second and fourth decade after the first diagnosis of ulcerative colitis, the cumulative fraction of patients with colorectal cancer rises in an exponential fashion (%CRC): $\%CRC = e^{k.time} - 100\%$ (1)

If the cumulative fraction %CRC after a given time is known, equation (1) can be solved to calculate the time constant k. For instance, data from the literature suggest that 30% of all patients with pancolitis will have developed cancer over a time period of 30 years between the beginning of the second and the end of the fourth decade after the onset of the disease.[4–7] The time dependent increase in the occurrence of colorectal cancer corresponds to the transition probability p for the development of cancer per one cycle length. It is calculated as the difference between two values of equation (1) at two consecutive time points one cycle length apart: $p = \%CRC_2 - \%CRC_1 = e^{k.time} (e^{k.cycle} - 100\%)$ (2)

From long term follow up data, Lashner *et al* have estimated an average time lag of three years between the first occurrence of dysplasia and the subsequent development of cancer.[18 19] Hence, the time dependence of the cumulative probability of dysplasia can be modelled as: $\%DYS = e^{k(time+lag)} - 100\%$ (3) where the time constant k is given by equation (1). The time dependent increase in the occurrence of dysplasia corresponds to: $p' = \%DYS_2 - \%DYS_1 = e^{k(time+lag)} (e^{k.cycle} - 100\%)$ (4)

Figure 2 shows the time dependent increase in the occurrence of dysplasia or cancer and the survival function of patients who remain free of either one. The proportional breakdown of false negative and true positive colonoscopies into dysplasia (dysp) and cancer (canc), as depicted in the Markov process of fig 1, is calculated as the proportional difference between p' and p from equations (4) and (2), respectively: $canc = (p' - p)/p'$ and $dysp = 1 - canc = p/p'$ (5)

The outcomes of the two competing management strategies of surveillance versus no surveillance depend on the fraction p of patients with cancer and the fraction p' of patients with dysplasia. As shown by equations

(1) to (4), both fractions depend on the time constant k calculated from the cumulative fraction of patients with colorectal cancer. Therefore, a threshold value of cumulative cancer rate can be found through iteration, for which both management strategies yield an identical net benefit. The threshold value will change in relation to the transition probabilities or the assumptions regarding costs and benefits built into the model. A very low threshold would speak much in favour of surveillance, as this value would be easily surpassed by the actual cumulative lifetime probability of developing colorectal cancer. The higher the threshold value, the less convincing the argument would be in favour of endoscopic surveillance.

COSTS AND DISCOUNTING

Table 1 summarises the cost estimates used in the present analysis. The expenses for surveillance cover both physician fees and facility costs arising from colonoscopy plus histological examination. The expenses also include potential complications of colonoscopy requiring hospitalisation, such as bleeding and perforation. The two complications are assumed to occur in *0.15%* and 0.2% of the procedures, respectively.[20] The costs represent the payments by the US Health Care Finance Administration (HCFA) during the fiscal year 1998. The cost estimates of proctocolectomy and terminal care of patients with colorectal cancer are taken from a publication by Provenzale *et al*.[21]

The benefit of surveillance is measured in terms of life years gained. The status post proctocolectomy is weighted by a percentage decrease in health related quality of life (HRQL). Its value depends, in part, on whether HRQL is assessed by previously asymptomatic patients or patients with severe symptoms of pancolitis or colorectal cancer. The HRQL associated with prophylactic proctocolectomy has not been analysed. After proctocolectomy for persisting severe symptoms of colitis it was found to vary between 80% and 100%.[22 23] For the purpose of the present analysis, a baseline estimate of 95% is assumed. The value of life is estimated by the human capital approach, using the average annual income in the United States.[24 25] Future costs and benefits are both discounted by an annual rate of 3%.[26]

Results

Under baseline assumptions, the two strategies of surveillance or no surveillance yield an identical net benefit, if the cumulative rate of colorectal cancer reaches a value of %CRC = 27% after 30 years of surveillance. If the actual cumulative rate of colorectal cancer exceeds this value, management of ulcerative colitis by biannual surveillance colonoscopy becomes more beneficial than no surveillance. Vice versa, an expected cumulative rate lower than this threshold would speak against surveillance. As indicated above, the cumulative probability of colorectal cancer reported in the literature exceeds this baseline threshold value and would thus seem to support a management
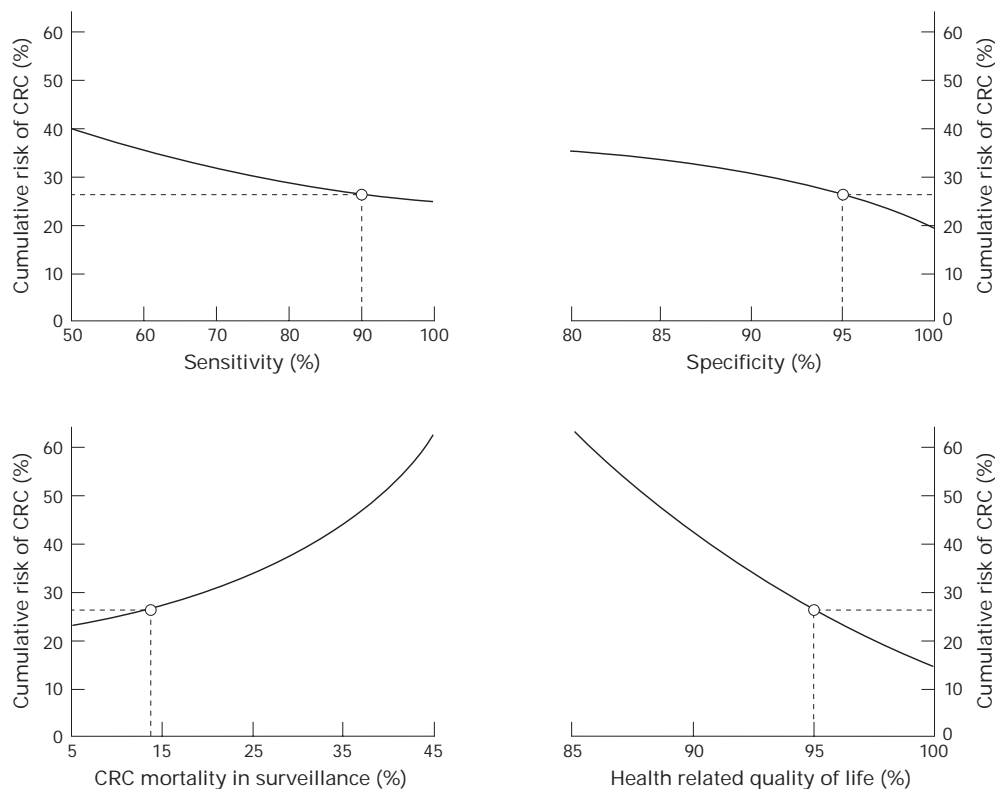
Figure 3   One way sensitivity analyses of the threshold value for cumulative cancer risk. CRC, colorectal cancer.

strategy based on biannual surveillance. As the threshold value is only slightly less than the actual cumulative cancer rate of 30%, one may expect that slight variations of the assumptions built into the model will easily raise the threshold above the cumulative cancer rate.

The influences of the assumptions built into the model on the threshold value are tested in multiple sensitivity analyses, where each assumption is varied over a broad range. Compared with other parameters, the outcome of the model is less sensitive to the cost estimates used in the model. Smaller expenses for the endoscopic procedure change surveillance into a more favourable management strategy and reduce the threshold in its favour. For instance, varying the cost of colonoscopy between $200, $500, and $1500 results in changes of the threshold value between 18%, 21%, and 35%, respectively. A rise in the costs of proctocolectomy makes surveillance a less favourable strategy, while expensive terminal care has an opposite effect. For instance, halving or doubling the costs of proctocolectomy changes the threshold to 24% or 32%, respectively. Halving or doubling the costs of terminal care changes the threshold to 29% or 23%, respectively. As higher incomes translate into larger benefits associated with gained life years, an annual income of $50 000 leads to a threshold value of 19%.

Any increase in the time lag between the first occurrence of dysplasia and cancer reduces the amount of life years saved. A long time lag results in a larger fraction of patients who undergo proctocolectomy only for dysplasia, but who would have remained cancer free for a long time period. Overall the influence of this phenomenon is relatively small, however. Varying the time lag from one to five years changes the threshold by only 1%. If one assumes that the benefit of surveillance and its associated reduction in cancer related mortality remain unaffected by increasing the interval of surveillance, any decrease in the frequency of endoscopic procedures has an effect similar to reducing the costs of the endoscopic procedure. For instance, decreasing the frequency from once per two years to once per three or four years, decreases the threshold to 19% and 14%, respectively, as it makes surveillance a more cost effective strategy.

The upper two panels of fig 3 display how the threshold is influenced by the sensitivity and specificity of colonoscopy plus biopsy in detecting dysplasia or cancer. Changes in the sensitivity by 10% have little influence on the threshold. As the sensitivity decreases, the fraction of false negative tests increases and more patients die from colorectal cancer. Changes of specificity by 5% also exert relatively little influence on the threshold. A decrease in the specificity leads to a larger fraction of false positive tests and more patients undergoing unnecessary proctocolectomy associated with a reduction in HRQL. Any type of less efficacious surveillance characterised by a low sensitivity or specificity value is associated with a higher threshold.

The lower two panels of fig 3 display how cancer related mortality associated with a surveillance programme and how reduction in HRQL after proctocolectomy affect the threshold. High mortality rates from colorectal cancer despite surveillance negate the benefit of any such strategy and raise the threshold.
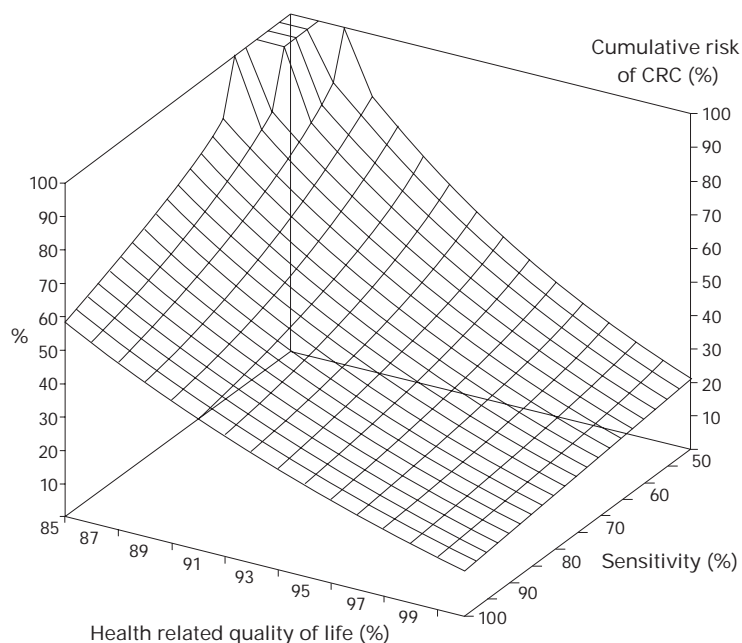
Figure 4   Two way sensitivity analysis of the threshold value for cumulative cancer risk. CRC, colorectal cancer.

HRQL = 98%, sensitivity = 95%, and specificity = 98%. The resulting threshold value %CRC = 16% lies well below the cumulative lifetime probability. On the other hand, a set comprising of mortality = 16%, HRQL = 90%, sensitivity = 85%, and specificity = 90% is associated with a threshold of 59% outside the cumulative lifetime risk of most ulcerative colitis patients to ever develop colorectal cancer. Both sets of assumptions are by no means extreme and seem to fall within a reasonable range that might be expected by a widely distributed surveillance programme.

Discussion

The present cost-benefit analysis compares the outcomes of ulcerative colitis managed with or without endoscopic surveillance to prevent death from colorectal cancer. The analysis yields a threshold for the cumulative cancer risk, which would render surveillance colonoscopy the preferred management strategy. A low threshold speaks in favour of surveillance, whereas a high threshold argues against it. The calculated value for the threshold is compared with the actual risk of developing colorectal cancer. Beginning only 10 years after the onset of ulcerative colitis, the cumulative risk of colorectal cancer has been reported to reach 30% over the next 30 years, that is, 40 years after the first diagnosis of the disease.[4–7] Under baseline assumptions, the cost-benefit analysis yields a threshold of 27%. Varying individual probability values and cost estimates can raise the threshold far above or lower it far below the true cumulative cancer risk. If several of the assumptions built into the model are varied jointly, even small changes can lead to extreme threshold values. As such sensitivity analyses show, one can conceive similarly reasonable sets of assumptions that result either in excessively high or low thresholds. The decision analysis fails to yield a clear cut answer about the usefulness of surveillance colonoscopy in ulcerative colitis.

Three prior decision analyses have also addressed the question of endoscopic surveillance in ulcerative colitis. Using a decision tree and threshold analysis, Gage compared the expected utilities of prophylactic proctocolectomy versus surveillance colonoscopy in a patient with ulcerative colitis since 20 years.[27] The threshold indicated the cumulative risk of colorectal cancer, above which prophylactic proctocolectomy became the favoured management option. It varied between 16% and 89% depending on the postoperative mortality, as well as the sensitivity and specificity of the surveillance colonoscopy. Provenzale *et al* used a Markov model to assess the increase in life expectancy obtained through prophylactic colectomy, surveillance colonoscopy, and expectant management.[15] In a cohort of 30 year old patients with ulcerative colitis since 10 years, prophylactic proctocolectomy increased life expectancy by 2–10 months compared with surveillance, and by 1.1–1.4 years compared with expectant management. In a separate analysis, Provenzale *et al* calculated an incremental cost effectiveness ratio of $4700 per life

Among all parameters tested in the univariate sensitivity analyses, the reduction in HRQL after proctocolectomy exerts the strongest influence on the threshold. Without any influence of proctocolectomy on HRQL, surveillance becomes a much favoured strategy. On the other hand, a reduction of HRQL by only 15% results in threshold values that exceed by far the cumulative cancer rates observed in patients with ulcerative colitis. The sensitive response of the threshold to changes in HRQL reflects the fact that surveillance results in an increased rate of proctocolectomy. The benefit of life years gained becomes largely negated if these life years are associated with a notably reduced HRQL.

Until now, all analyses dealt with responses of the threshold to univariate changes of one parameter at a time. Figure 4 depicts the example of a two way sensitivity analysis where two parameters, such as sensitivity and HRQL, are varied simultaneously. Each point of the three dimensional mesh represents a threshold value dependent on the values of the two parameters shown on the x and y axes. The rise in the threshold associated with a decrease in the sensitivity or HRQL alone becomes more accentuated if both parameters decrease simultaneously, and it can reach unrealistically high values of 100%. Similar two way sensitivity analyses apply to the simultaneous variation of any two other parameters, such as HRQL plus specificity, sensitivity plus specificity, or HRQL and cancer related mortality under surveillance.

The simultaneous variations of three or four parameters yield even larger fluctuations in the threshold. One can conceive similarly reasonable sets of assumptions that result in excessively high or low thresholds. Figure 1 and table 1 show the baseline parameters. Simultaneous variations of all four parameters from fig 3 lead to a second set of values that is slightly different from the baseline set, such as mortality = 10%,

year saved through surveillance every five years, compared with a strategy of no surveillance.[21] A decrease in the surveillance interval to four and three years resulted in incremental cost effectiveness ratios of $83 400 and $111 600, respectively, per additional life year gained. The authors recommended the implementation of a surveillance programme, because it would increase life expectancy and because its incremental cost effectiveness ratio compared favourably with screening strategies for tuberculosis or cervical cancer and other medical interventions, such as heart transplantation.

Our analysis differs from these previous studies in several aspects. Using the human capital approach, the cost-benefit analysis balances the cost of surveillance, surgery, and terminal care against the benefit of life years saved.[24] Similar to the studies by Provenzale *et al* but different form the study by Gage, a Markov process is used to assess the time dependent behaviour of cancer risk in ulcerative colitis.[15 21] Rather than expressing our results as utilities, costs, or incremental cost effectiveness ratios, the outcomes of the competing treatment strategies are compared in terms of an overall threshold probability. The threshold value relates to a clinically available parameter, such as cumulative cancer risk in long standing ulcerative colitis. This relation between the threshold and the cancer risk makes it easier to appreciate the outcome of the analysis. The decision in favour or against surveillance does not need to rely on abstract economic cost parameters or extraneous comparisons with unrelated types of medical interventions.

Would another or more complex type of decision analysis yield a different outcome? A more detailed analysis could include, for instance, operative mortality associated with proctocolectomy, patient compliance with a surveillance programme, and the impact of surveillance itself on HRQL in ulcerative colitis. Rather than analyse the transition from normal colon to dysplasia, one could break down the single state of dysplasia into two separate states of low grade and high grade dysplasia. Similarly, the state of colorectal cancer could be broken down into cancers of different Dukes's stages. Modelling the natural history of colorectal cancer in a more detailed fashion is largely compromised by a lack of reliable clinical data for most of these additional states and their associated transition probabilities. Instead of adding precision to the model, any expansion of the set of assumptions built into the model would only increase its range of variation. The current set of parameters in the model can already lead to fluctuations of the threshold between 0% and 100%.

Gastroenterologists by the nature of their profession like to do surveillance colonoscopy and tend to favour reports that recommend such strategy. Authors and readers alike prefer clear cut and easy decision rules. The term "medical decision analysis" alludes to a technique that can calculate the most appropriate decision rule. Unfortunately, medical decision analysis fails to resolve the clinical dilemma of endoscopic surveillance in ulcerative colitis. Small variations in several of the assumptions built into the model result in thresholds that seemingly speak in favour of or against surveillance. In order to provide more narrow estimates regarding the usefulness of surveillance, decision analysis would have to rely on very precise clinical evidence that is currently missing. None of several clinical trials has been able to provide unequivocal evidence in favour of surveillance.[28–32] The major reason for this failure relates to the prohibitively large number of patients with ulcerative colitis who need to be followed over a prolonged time period, before statistically sound results could be obtained.

In conclusion, medical decision analysis fails to show that surveillance colonoscopy would be beneficial in long standing ulcerative colitis. Presently, there are also no clinical data to support the contention that surveillance colonoscopy is a cost effective means to prevent death from colorectal cancer in patients with ulcerative colitis. These statements are not meant to belittle the general contribution of colonoscopy in protecting against death from colorectal cancer. Patients do benefit from screening colonoscopy and colonoscopic pursuits of newly developed symptoms or suspicious findings. However, it is not possible to prove that frequent colonoscopies scheduled at regular intervals are an effective means to manage the increased risk of colorectal cancer associated with ulcerative colitis.

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