COLON CANCER

Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect

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Background: In view of the high risk of developing a new primary colorectal carcinoma (CRC), subtotal colectomy rather than segmental resection or hemicolectomy is the preferred treatment in hereditary non-polyposis colorectal cancer (HNPCC) patients. Subtotal colectomy however implies a substantial decrease in quality of life. To date, colonoscopic surveillance has been shown to reduce CRC occurrence.
Aims: To compare the potential health effects in terms of life expectancy (LE) for patients undergoing subtotal colectomy or hemicolectomy for CRC.
Methods: A decision analysis (Markov) model was created. Information on the 10 year risk of CRC after subtotal colectomy (4%) and hemicolectomy (16%) and stages of CRCs detected within a two year surveillance interval (32% Dukes' A, 54% Dukes' B, and 14% Dukes' C) were derived from two cohort studies. Five year survival rates used for the different Dukes stages (A, B, and C) were 98%, 80%, and 60%, respectively. Remaining LE values were calculated for hypothetical cohorts with an age at CRC diagnosis of 27, 47, and 67 years, respectively. Remaining LE values were also calculated for patients with CRC of Dukes' stage A.
Results: The overall LE gain of subtotal colectomy compared with hemicolectomy at ages 27, 47, and 67 was 2.3, 1, and 0.3 years, respectively. Specifically for Dukes' stage A, this would be 3.4, 1.5, and 0.4 years.
Conclusions: Unless surveillance results improve, subtotal colectomy still seems the preferred treatment for CRC in HNPCC in view of the difference in LE. For older patients, hemicolectomy may be an option as there is no appreciable difference in LE.

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant disorder predisposing to cancer. It has been estimated that 2–5% of all cases of colorectal cancer (CRC) are due to HNPCC.[1–3] Identification of the DNA mismatch repair (MMR) genes responsible for the disease has facilitated diagnosis of HNPCC and made it possible to identify carriers of the mutated gene within a family. These carriers have a high risk of developing CRC, endometrial cancer, and other cancers associated with HNPCC. One of the hallmarks of the syndrome is the occurrence of multiple tumours in an individual. These include multiple primary CRCs or the combined occurrence of CRCs, endometrial cancer, and other related cancers.[4 5] The risk of developing a metachronous CRC was estimated to be 20–30% within 10 years after treatment of the first CRC.[6] This forms the basis for the recommendation to perform colectomy with an ileorectal anastomosis (that is, subtotal colectomy) in patients with CRC due to an MMR gene defect.

Recently, a number of studies on the effectiveness of periodic examination of the colorectum have been published.[7 8] Järvinen *et al* reported that surveillance led to a 56% reduction in the CRC rate in a group of screened mutation carriers compared with a group of carriers that did not undergo surveillance examinations.[7] A recent study on 114 Dutch families showed that regular colonoscopic surveillance leads to the identification of mainly local tumours.[9]

Subtotal colectomy performed for CRC leads to a significant reduction in quality of life (QOL) compared with the general population.[10] The SCOTIA group prospectively compared the difference in QOL after subtotal colectomy and segmental resection in sporadic CRC. They concluded that segmental resection was associated with fewer bowel function problems and therefore was the preferred treatment in left sided malignant colonic obstruction.[11]

In view of the above findings the question rises whether subtotal colectomy remains the preferred treatment in HNPCC patients with a primary CRC. The main goal of this study was to compare the potential health effects in terms of life expectancy (LE) between patients that underwent subtotal colectomy followed by surveillance of the rectum, and those that underwent a more conservative surgical procedure (that is, segmental resection or hemicolectomy) followed by surveillance of the remaining bowel.

METHODS

Markov model

A Markov model was constructed using DATA 3.5 (TreeAge Software, Inc., Williamstown, Massachusetts, USA) to compare different treatment strategies for CRC in HNPCC patients. In brief, a model was constructed comprising the possible health states of a patient (patient with a Dukes' A, B, or C tumour). Subsequently, all relevant possible health transitions were recognised. The likelihood of transferring from the original health state to the next over time is reflected by transition probabilities—that is, the chance of transition from one state to another state (for example, patients may develop a second tumour after surgery for their

Abbreviations: HNPCC, hereditary non-polyposis colorectal cancer; CRC, colorectal cancer; MMR, mismatch repair; QOL, quality of life; LE, life expectancy

first CRC). The state to state transition was characterised by a probability distribution (based on the chance of developing a second CRC derived from literature study). The model follows a hypothetical cohort of mutation carriers over time and tracks the annual incidence of CRC by stage and mortality. Short term mortality associated with surgery was also incorporated.

Remaining LE was calculated after three different types of surgical approaches for CRC: (1) proctocolectomy with ileoanal anastomosis that was assumed to eliminate all risk of CRC and the need for postoperative surveillance; (2) subtotal colectomy with ileorectal anastomosis followed by surveillance of the rectum; and (3) partial colectomy—that is, segmental resection or hemicolectomy followed by surveillance of the remaining bowel. Surveillance was defined as colonoscopy every two years after segmental resection or hemicolectomy and flexible sigmoidoscopy of the remaining rectal segment every two years after subtotal colectomy. Primary model outcome was the LE. In addition, we differentiated between survivals with various parts of the colon intact. Remaining LE values for a mutation carrier were calculated after the three different types of surgical procedures at the age of CRC detection of 27 years, 47 years, and 67 years.

Data sources and assumptions

The probabilities and pertaining sources used in the Markov model are listed in table 1.

Risks of a metachronous CRC after surgery

(1) Proctocolectomy was assumed to eliminate all risk of CRC.

(2) The risk of rectal cancer after subtotal colectomy varies across studies and ranges from 3.4% to 10% every 10 years.[9 12] On the basis of the most recent study, the risk of rectal cancer after subtotal colectomy was assumed to be 4% after 10 years.

(3) The risk of a metachronous tumour after partial colectomy varies from 15% to 30%.[6 9] On the basis of our own recent data, we estimated the risk of CRC after segmental resection at 16% after 10 years.

Colorectal cancer stages

Information on the stages of CRCs when detected by surveillance was derived from two large scale studies from the Netherlands and Finland. The distribution of the stages detected $\leqslant 2$ year after a negative surveillance examination while on the Dutch or Finnish surveillance program were used, as shown in table 1 (Dukes' A 32%, Dukes' B 54%, and Dukes' C 14%).

Table 1 Probabilities and sources of the Markov model

Variable	Value (%)	Ref
10 year risk of a metachronous CRC after:		
Proctocolectomy	0	
Subtotal colectomy with ileorectal anastomosis	4	9 12
Segmental resection or hemicolectomy	16	9
Distribution of screen detected CRC stages		7–9
$\leqslant 2$ year		
Dukes' A	32	
Dukes' B	54	
Dukes' C	14	
Colorectal cancer 5 year survival rates		13
Dukes' A	98	
Dukes' B	80	
Dukes' C	60	
Mortality rate associated with colorectal surgery	0.5	14–18

CRC, colorectal cancer.

Survival and mortality

Information on colorectal carcinoma survival was derived from recent studies on survival in HNPCC patients.[13 14] Five year survival rates were assumed to be 98% in the case of Dukes' A, 80% for Dukes' B, and 60% for Dukes' C.[13] We assumed a preoperative mortality rate of 0.5%.[15–18]

RESULTS

If cancer is detected while on the surveillance program, proctocolectomy with ileoanal anastomosis will lead to the greatest LE of 34.8 years for a mutation carrier at age 27 years. Subtotal colectomy with ileorectal anastomosis leads to an LE of 33.9 years whereas segmental resection or hemicolectomy leads to an LE of 31.6 years. The benefit of subtotal colectomy compared with segmental resection or hemicolectomy decreases as CRC is detected at an older age. The LE gain of subtotal colectomy compared with segmental resection or hemicolectomy is 2.3 years at age 27 years, one year at age 47 years, and 0.3 years at age 67 years.

If the first CRC detected while on the screening program is a Dukes' stage A carcinoma, proctocolectomy with ileoanal anastomosis will lead to the greatest LE of 47.1 years for a mutation carrier at age 27 years. Subtotal colectomy with ileorectal anastomosis leads to an LE of 45.8 years whereas segmental resection or hemicolectomy leads to an LE of 42.4 years. The LE gain of subtotal colectomy compared with segmental resection or hemicolectomy is 3.4 years at age 27 years, 1.5 years at age 47 years, and 0.4 year at age 67 years. Note however that this survival is conditional on the tumour being Dukes' stage A. Information on exact stage is not available prior to operation and therefore the survival benefit cannot be considered representative. In table 2, the LE values of all possible surgical options are shown for different Dukes' stages.

DISCUSSION

Since the identification of the genes responsible for HNPCC, clinicians are more aware of this condition and, consequently an increasing number of families are recognised. An important question is whether the clinical management of CRC, associated with HNPCC, should differ from that of sporadic CRC. Until now, there was general agreement that subtotal colectomy was the preferred surgical treatment for a patient from a well defined HNPCC family with an early CRC. The rationale for this recommendation is the significant risk of developing a subsequent metachronous CRC, reported by several research groups.[6 9] However, a recent study showed that periodic colonoscopic examinations of family members at high risk for HNPCC led to a significant reduction in the CRC rate.[7] The vast majority of tumours, detected by surveillance, were in an early stage. Another recent study showed that subtotal colectomy in patients with familial adenomatous polyposis led to a significant reduction in QOL compared with the general population.[10] With respect to this observation, it should be realised that QOL may be better after subtotal colectomy in HNPCC patients than in patients with familial adenomatous polyposis because in the latter group usually only the rectum (10–15 cm) is preserved.

Based on the results of these recent studies, we wondered whether subtotal colectomy is still the treatment of first choice. To address this problem we performed a decision analysis study and compared the health effects between the main surgical options. Of note however was the fact that the cancer risks used in our model were drawn from retrospective studies and therefore possible bias may have occurred. At a time when a decision should be made on the best surgical approach, the exact pathological staging of the tumour is unknown. Intensive surveillance has been shown to lead to the detection of mainly local tumours (that is, Dukes' A and

Table 2 Life expectancy of patients with colon cancer depending on treatment offered and age at first detection

	Life expectancy from first detection onwards		
	Age 27 y	Age 47 y	Age 67 y
Hemicolectomy overall*	31.6	20.6	10.5
Subtotal colectomy overall	33.9	21.6	10.8
Proctocolectomy overall	34.8	21.9	10.8
Hemicolectomy Dukes' A	42.4	27.4	13.7
Subtotal colectomy Dukes' A	45.8	28.9	14.1
Proctocolectomy Dukes' A	47.1	29.4	14.2
Hemicolectomy Dukes' B	29.1	19.0	9.8
Subtotal colectomy Dukes' B	31.1	19.8	10.0
Proctocolectomy Dukes' B	31.8	20.1	10.0
Hemicolectomy Dukes' C	16.9	11.3	6.2
Subtotal colectomy Dukes' C	17.6	11.6	6.2
Proctocolectomy Dukes' C	18.0	11.7	6.2

*Overall takes into account a distribution of Dukes' stages A, B, and C of 32%, 54%, and 14%, respectively.

B) and therefore this is the most likely to expect. However, Dukes' stage C tumours are still detected in a small proportion of subjects while on the program. Therefore, we made the calculations in our model both for a cohort of patients with a distribution of colorectal tumours as actually encountered in surveillance programs as well as for a cohort of patients that would enter the model with a Dukes' A tumour. The results of our study showed that in young patients, subtotal colectomy and protocolectomy lead to a significant increase in LE compared with segmental resection or hemicolectomy. The earlier the stage at which cancer was detected and the younger the patient at diagnosis, the greater was the benefit of subtotal colectomy and proctocolectomy. Besides LE, the risk of a secondary surgery weighs in the decision on surgical treatment. Assuming a constant risk of 16% every 10 years after partial colectomy, patients that develop a primary CRC below the age of 60 years have a 20–60% risk of secondary surgery for a new CRC whereas the risk of rectal cancer after subtotal colectomy is approximately four times lower. On the basis of our findings and these latter considerations, we consider subtotal colectomy as the preferred treatment in young patients at high risk of HNPCC. Although proctocolectomy was associated with the largest increase in LE, we do not consider this option in HNPCC patients because of the worse functional results after this type of surgery compared with the results reported after subtotal colectomy.[19] However, if the primary cancer lies in the rectum, conventional hemicolectomy or subtotal colectomy do not apply. In these cases proctocolectomy with an ileoanal anastomosis appears to be the treatment of first choice.

In older patients (for example, >60 years) proctocolectomy and subtotal colectomy lead to only a slight increase in LE, even if the tumour is detected in the most favourable stage (that is, Dukes' stage A). Also, in older patients, the lifetime risk of developing a second CRC is relatively low. As a consequence, in these patients we consider segmental resection as an appropriate surgical option. In general, subtotal colectomy should be avoided in a patient with a history of poor sphincter function. When choosing partial colectomy, it is very important to rule out the occurrence of a synchronous tumour. Unfortunately, studies on QOL after different surgical treatments do not specifically consider HNPCC patients.[11] For these patients, the risk of a synchronous or metachronous tumour after a limited resection might have a considerable impact on QOL due to fear of cancer. This argument may also be used in decision making.

For detection of CRC in patients with a suspected family history of HNPCC, immunohistochemical expression analysis of MMR proteins and/or microsatellite instability analysis on biopsies taken at colonoscopic examinations are useful tools to confirm the presence of microsatellite instability. In view of the above results, it may be of interest to a patient to use these molecular genetic tools before deciding on surgical treatment.

In conclusion, although intensive surveillance of HNPCC patients reduces the incidence of CRC and overall mortality, there remains a substantial risk of developing (mainly early) CRC while on a program. If CRC is detected while on a program, in young patients (<60 years) subtotal colectomy seems to be the treatment of choice in view of the difference in life expectancy between the two options and the possible decrease in cancer fear as the risk of secondary cancer decreases. In older patients, segmental resection is also an appropriate option and should be discussed with the patient. Large prospective clinical studies should be considered to confirm our findings. Also, future studies should address how the fear of a second cancer after limited surgery influences quality of life.

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