Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis


Summary

Background In familial adenomatous polyposis the only curative treatment is colectomy, and the choice of operation lies between restorative proctocolectomy (RPC) and colectomy with ileorectal anastomosis (IRA). The RPC procedure carries a higher morbidity but, unlike IRA, removes the risk of subsequent rectal cancer. Since the course of familial adenomatous polyposis is influenced by the site of mutation in the polyposis gene, DNA analysis might be helpful in treatment decisions.

Methods We evaluated the incidence of rectal cancer in polyposis patients who had undergone IRA, and examined whether the requirement for subsequent rectal excision because of cancer or uncontrollable polyps was related to the site of mutation.

Findings Between 1956 and mid-1995, 225 patients registered at the Netherlands Polyposis Registry had undergone IRA. In 87 of them, a pathogenetic mutation was detected. 72 patients had a mutation located before codon 1250 and 15 patients after this codon. The cumulative risk of rectal cancer 20 years after surgery was 12%, and at that time 42% had undergone rectal excision. The risk of secondary surgery was higher in patients with mutations in the region after codon 1250 than in patients with mutations before this codon (relative risk 2.7, p<0.05).

Interpretation On this evidence, IRA should be the primary treatment for polyposis in patients with mutations before codon 1250, and RPC in those with mutations after this codon.


See Commentary page 422
underwent RPC. In all cases the diagnosis of FAP was confirmed by the presence of more than 100 adenomatous polyps and/or the identification of a mutated APC gene. The surgical operations were done in hospitals all over the Netherlands. Before 1990, in most centres, the preferred treatment of polyposis patients with few rectal polyps was IRA.

For risk assessment, patients who had an IRA were studied with respect to their risk of developing rectal cancer or requiring excision of the rectum. The data were analysed by survival analysis methods. Observation time was up to the date of last contact, death, the date of diagnosis of rectal cancer, the date of rectal excision, or the closing date of the study. Differences in risk of undergoing rectal excision were tested for statistical significance by the log rank test. Mutation studies of the APC gene conducted in the families registered at the Dutch Polyposis Registry have been described elsewhere.15,16

Results

Of the 230 patients who had an IRA, 5 had follow-up of less than one year after surgery and were excluded. The remaining 225 had a mean follow-up of 11 yr (range 1–38). Mean age at surgery was 28·3 yr (range 11–70). 16 of these patients developed a rectal cancer (mean age 45 yr; range 29–61). Of these 16 patients, information on screening was available in 12: 11 had undergone surveillance within the previous 12 months. The interval since the last endoscopic examination ranged from 3 to 14 months (mean 8·8 months). Figure 1 shows the cumulative risk of developing rectal cancer by years of follow-up after surgery. At 10, 15, 20, and 25 years after surgery the cumulative risks were 3·9% (95% confidence interval 0·9–6·8%), 10·4% (4·5–16·3%), 12·1% (5·4–18·8%), and 25·8% (6·6–45·1%). Seven of the 16 rectal cancer patients died, six from the cancer and one from postoperative complications. In 45 of the 225 patients the rectum had to be removed because of recurrent polyps (n=29, mean age: 33 yr) or rectal cancer (n=16). The cumulative risk of rectal excision 10, 15, and 20 years after IRA was 15·0% (95% CI 9·6–20·3%); 25·8% (6·6–45·1%). Seven of the 16 patients the rectum had to be removed because of recurrent polyps or rectal cancer (n=29, mean age: 33 yr) or rectal cancer (n=16). The cumulative risk of rectal excision 10, 15, and 20 years after IRA was 15·0% (95% CI 9·6–20·3%), 32·2% (23·9–40·6%), and 42·2% (30·0–54·4%).

Mutation analysis

DNA analysis was conducted in 105 of the 150 polyposis families and the pathogenic mutation was detected in 56 families. 32 of these families had at least one member who underwent an IRA. 21 families including 72 patients with an IRA (group A) had a mutation before codon 1250 and the remaining 11 families including 15 individuals with an IRA (group B) had a mutation after this codon. 14 of the patients from group A and eight of the patients from group B required rectal excision because of rectal cancer of uncontrollable polyps. The cumulative risk of rectal excision by years of follow-up after surgery was significantly higher in group B than in group A (relative risk 2·7; log rank test p<0·05) (figure 2).

Discussion

Although non-steroidal anti-inflammatory drugs may have some beneficial effect on colonic adenomas,17 prophylactic surgery of the colon is still the only curative treatment for polyposis. Restorative proctocolectomy might seem the ideal operation. By removal of all or nearly all the large-bowel mucosa the risk of cancer can be almost completely avoided. There are disadvantages, however, and the most important are the greater morbidity and duration of convalescence than with IRA and the possible failure of the pouch—a complication that requires an ileostomy. Because most of the FAP patients who need surgery are between 15 and 25 years of age, such a procedure would seriously interfere with their education and the development of social relationships. Selection of patients for IRA or RPC must therefore depend on the balance of pros and cons—the morbidity and the possible failure of RPC versus the risk of cancer in the remaining rectum after IRA. Several reports from the 1980s indicated that the risk of rectal cancer gradually increases with time and amounts to 10–55% after 20 years of follow-up.12,13 One recent large-scale study from the Scandinavian countries covering 294 patients indicated a rectal cancer risk of 9% and 13% after 20 and 25 years of follow-up, respectively.18 These data are in agreement with the results of the St Mark’s Polyposis Registry.19 The present study, which covered a comparable number of patients, yielded about the same risk at 20 years of follow-up. A Japanese study comprising 320 patients showed a much higher risk, 37% after 20 years.10 An update of the St Mark’s series reveals that the risk of rectal cancer increases sharply after the age of 50 years and is as high as 29% at age 60.20

Possible explanations for the discrepancies in incidence of rectal carcinoma between centres may include differences in the length of the rectal stump, the age at colectomy, and the quality of follow-up after surgery. In addition, variation in the definition of “uncontrollable” polyps between centres may contribute to the differences in rectal carcinoma incidence. The confidence intervals for the risks reported for a follow-up of 20 years or longer
are very wide in most series (because of the small number of patients with such a long follow-up) and, in fact, the differences between the studies may fall within these limits. Could the rectal cancers have been prevented by regular rectoscopy? Almost all the patients with rectal cancer in the present series were under close surveillance and the interval since the last examination had been less than one year. The St M ark’s experience also indicated that the patients who developed rectal cancer were good compliers and most had undergone surveillance within the past six months.10

The risk of rectal cancer is not the only factor in the choice of operation. An important consideration is the likelihood that, after IRA, a patient will later require rectal excision. In our series, 20 years after IRA almost half the patients had needed rectal excision for rectal cancer or for polyps that could not be controlled by polypectomy. If we were able to identify the patients who would need secondary surgery after IRA, such patients could be selected for a more definitive primary surgical procedure (RPC). Several studies have shown that the course of the disease in families with polyposis due to a mutation in the region after codon 1250 on exon 15, especially at codon 1309, tends to be more aggressive than in families with mutations before this codon.6–10 Patients from such families may be at greater risk of recurrent polyps and rectal cancer after IRA. To test this hypothesis we evaluated the cumulative risk of rectal excision in a subgroup of patients with a known mutation. We found that the risk of rectal excision in patients with a mutation after 1250 is indeed higher than that in patients with a mutation before this codon.

We conclude that the results of DNA testing in relation to the phenotypic expression in the patient and family could be helpful in surgical decision-making. In patients with a mutation in the region after codon 1250, who are at high risk of rectal excision after IRA, RPC is the treatment of choice; whereas in patients with a mutation before codon 1250 colectomy and IRA is the preferred treatment.

We thank I S J van Leeuwen-Cornelisse for collecting the family material, M E J Gerrits and M E Velthuizen for assembling the clinical information and maintaining the databases, and I Seeger-Wolf for reviewing the English text.

References


