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Leerdam, M.E. van; Latchford, A.

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Can innovation in endoscopic therapy alter clinical outcomes in patients with familial adenomatous polyposis?



Authors

Monique E. van Leerdam^{1,2}, Andrew Latchford^{3,4}

Institutions

- 1 Department of Gastroenterology and Gastro-intestinal Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands
- 2 Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands
- 3 Polyposis Registry, St. Marks's Hospital, Harrow, United Kingdom
- 4 Department of Surgery and Cancer, Imperial College London, London, United Kingdom

Bibliography

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author

Monique E. van Leerdam, AVL-NKKI-Department of Gastroenterology, Plesmanlaan 121 Amsterdam 1066, Netherlands
m.v.leerdam@nki.nl

Familial adenomatous polyposis (FAP) is a rare autosomal dominant inherited disease caused by a pathogenic mutation in the *APC* gene with a prevalence of about 1 in 8500 to 10,000 births [1]. Patients with “classical FAP” do have a typical phenotype and develop 100 to 1000 adenomas throughout the colon. If left untreated, colorectal cancer will occur at a median age 35 to 45 years. Prophylactic surgery, usually either resection of the colon with an ileo-rectal anastomosis (IRA) or resection of the colon and rectum with an ileo-pouch anal anastomosis (IPAA), is offered to mitigate this risk of cancer. Timing and type of prophylactic surgery depends on the number, size, and histology of the adenomas and should be personalized.

Most reports have shown that a rectal polyp count >20 predicts future rectal excision and most guidelines advise performing proctocolectomy with IPAA when there are >20 adenomas in the rectum. Other known independent risk factors for progressive rectal disease that should be taken into account are colonic polyp count >500, *APC* mutation at codons 1250 to 1250, and age <25 years at time of surgery [2, 3].

About 15% to 20% of patients with FAP do have a “de novo” *APC* mutation and are diagnosed due to presentation with symptoms [1, 3]. The prevalence of colorectal cancer in patients with FAP not under surveillance is high, between 50% to 70%, and the type of surgery also depends on cancer location and stage [4]. For FAP patients who undergo prophylactic surgery, the incidence of cancer in the rectum or rectal remnant

is of great concern. Based on older reports, the cumulative risk of rectal cancer is between 11% and 24% [2]. However, this encompasses an era that predated IPAA and also includes patients who in current practice would not be offered IRA.

Historical data regarding the risk of developing cancer after IRA or IPAA are difficult to interpret. There have been dramatic changes in endoscopic therapy and in particular, with the advent of cold snare polypectomy, which allows extensive therapy in a safe manner, with minimal risk of bleeding or perforation [5]. Can modern endoscopic practice and a more aggressive endoscopic therapeutic approach alter postoperative outcomes of patients with FAP? In particular, is rectal preservation possible while avoiding the development of cancer, given the functional consequences of proctectomy?

Pasquer et al describe the outcomes at three university hospitals within a French national database of patients with FAP that goes back to 1965 [6]. Data on all patients who underwent prophylactic surgery were retrospectively and/or prospectively analyzed with follow-up until 2020. In the three university hospitals, rectal preservation was preferred, independent of the number of rectal adenomas. Rectal preservation was advised if endoscopic treatment of rectal adenomas was estimated to be feasible and safe by a trained endoscopist who was expert in FAP management. Proctocolectomy was performed when the expert endoscopists estimated that endoscopic treatment was

not feasible due to the extensiveness of the polyps or if the patients was not willing to undergo close follow-up [6].

They adopted an intense therapeutic endoscopic strategy to try to eradicate all adenomas in the rectum after IRA, or the pouch after IPAA. This is indeed a novel approach. Polyps were treated with argon plasma coagulation and more recently also with cold-snare polypectomy, endoscopic mucosectomy, and submucosal dissection.

The study population included a total of 92 patients with FAP with IPAA and 197 with IRA. Mean age at the time of surgery was 29.5 years and mean follow-up was 17.1 years. During follow-up, rectal cancer occurred in 6.1% of patients with IRA (12/289) and in 1.1% in patients with IPAA. Cancer-free survival was similar in both groups and very good. Fifteen- and 25-year cancer-free survival rates were 99.5% and 96.3%, respectively, in the IRA group and 100% and 98%, respectively, in the IPAA group. Functional outcomes were better in the IRA group, as one would expect. At the end of follow-up, the mean number of stools was significantly lower in the IRA group with significantly less fecal incontinence and significantly less nocturnal leakage.

At first glance, these data look reassuring; however there are areas of concern that should be highlighted. Given the combination of retrospective and prospective data, it is difficult to establish exactly what endoscopic surveillance/therapy occurred. It is of concern that 10 of 12 rectal cancers were diagnosed at the first endoscopy in the study center, with long intervals (median of around 20 years) between operation and first endoscopy, stressing the importance of close follow-up.

During follow-up a mean of 4.4 endoscopies were performed, which looks like a low number for a median follow-up of 17 years and does not seem compatible with the described methods – no doubt non-compliance and referral bias play a role in this anomaly.

The mean number of treated adenomas at each endoscopic session was 17.8 (standard deviation [SD] 20.8) in the IRA group vs 12.9 (SD 18.8) in the IPAA group. The endoscopic complication rates are high: In about 50% of patients at least one endoscopic complication occurred.

Although there are many questions left unanswered, this study shows that rectal preservation is feasible and safe with regard to rectal cancer incidence, even for patients with more extensive polyp burden. What is unclear is whether an approach of systematic eradication of all adenomas is superior to more

selective therapy for rectal adenomas. Given the fact that the adenoma-carcinoma sequence in FAP is not accelerated, a selective approach, as outlined in the European Society for Gastrointestinal Endoscopy guidelines [2], just to treat those polyps that do progress to larger sizes (>5 mm) may well have been as “effective” yet may not expose patients to the high risk of endoscopic complications.

It is clear that endoscopic surveillance needs to be performed in a dedicated FAP center with experience in endoscopic interventions. There has been a clear change in endoscopic capabilities in terms of adenoma detection and resection. The endoscopist’s interpretation of what is “endoscopically manageable” is very different now than it was even 10 years ago. What is lacking is a clear understanding of the long-term outcomes from different approaches to address the question of what will provide the most benefit with the least risk.

Competing interests

The authors declare that they have no conflict of interest.

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