REVIEW ARTICLE

Follow-Up Endoscopy in Gastroenterology: When Is It Helpful?

Heiko Lübbers, Reiner Mahlke, Paul Georg Lankisch, Manfred Stolte

SUMMARY

Background: The indications for follow-up endoscopy have not been established in all diseases that can be diagnosed by endoscopy.

Methods: Selective review of the literature and a survey of national guidelines.

Results: In confirmed erosive or non-erosive reflux disease, follow-up endoscopy is indicated only in the presence of complications or Barrett's esophagus. In the case of gastric ulcer or complicated duodenal ulcer, monitoring by endoscopy is mandatory. There is no consensus regarding the indication for follow-up biopsy in confirmed endemic sprue. In an acute episode of confirmed ulcerative colitis, endoscopy is indicated only if the treatment depends on the findings. In confirmed Crohn's disease, this procedure is indicated only in the presence of complications, if the findings are unclear, and before elective intestinal surgery. Those at risk of hereditary colorectal carcinoma without polyposis should undergo colonoscopy annually, starting 5 years before the youngest age of occurrence in their family or at the age of 25 years, whichever comes first.

Conclusions: With particular reference to further gastrointestinal diseases discussed in the main text, this review unfortunately shows that many of the indications for follow-up endoscopy remain to be ascertained. Controlled studies are needed to establish with sufficient certainty what really helps our patients.

The indications for follow-up endoscopy have not been defined in all cases. The aim of this review is to distinguish between essential information in this area, and that which is no longer current. The paper is based on a selective literature review with particular reference to national guidelines and their specified classes of recommendation and levels of evidence, and on a PubMed search on recommendations for follow-up endoscopy for the diseases specified below. However, since the definitions for classes of recommendation and levels of evidence can vary from guideline to guideline, we recommend consulting the guidelines directly where necessary.

Reflux disease

In confirmed erosive reflux disease/non-erosive reflux disease (ERD/NERD), follow-up endoscopy is only indicated when there are complications (ulcers, strictures) or in Barrett's esophagus (reddening of the distal mucosa of the esophagus with histological evidence of specialized intestinal metaplasia) (1, 2). Biopsies are essential during initial and follow-up endoscopy, since almost a third of all early cancers related to Barrett's esophagus are only detected histologically.

The guidelines of the German Society for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, DGVS) recommend follow-up endoscopy and biopsy where there is a degree of intraepithelial neoplasia (*Figure 1*) (1). The opinion of a second pathologist should be sought. If there is suspicion of low-grade intraepithelial neoplasia in combination with histologically or endoscopically demonstrable regenerative changes, repeat endoscopy with biopsy should be performed after 4 to 6 weeks of treatment with a proton pump inhibitor (class of recommendation B/C) (2).

As yet there are no standardized follow-up protocols for monitoring patients with Barrett's adenocarcinoma that has been treated endoscopically. It is suggested that follow-up endoscopy and biopsy should be performed every three months for the first year, every six months during the second year and annually from the third to fifth year (class of recommendation C) (2). In microscopic Barrett's esophagus, no follow-up endoscopy is recommended.

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Gastric diseases

As yet there are no consistent recommendations on the indication for follow-up endoscopies in different forms of gastritis.

This also applies to autoimmune atrophic gastritis (mucosa of the corpus of the stomach). However, in 21 265 patients with autoimmune atrophic gastritis and pernicious anemia, Ye and Nyrén (e1) found a 3.4, 2.4, and 26.4 fold increased risk for developing epidermoid cancer of the esophagus, gastric cancer and gastric carcinoid tumors, respectively. However, there was no link with adenocarcinomas of the esophagus and cardia.

Corpus dominant *Helicobacter* gastritis is a form of gastritis associated with increased risk of developing gastric cancer (e2). According to the Maastricht criteria, this constitutes an indication for *Helicobacter* eradication. Follow-up endoscopy is probably necessary if there are further risk factors, for example when there are several cases of gastric cancer in a single family (e2).

Follow-up endoscopy is mandatory in patients with a gastric ulcer or a complicated duodenal ulcer. In these cases, treatment should be monitored with a combination of urease test and histological evidence from two antrum and two corpus biopsies, respectively (class of recommendation B, level of evidence 2a, consensus) (3), using special staining techniques where necessary. When exactly monitoring should take place is not specified. At least four weeks should pass between the end of treatment with antibiotics and treatment evaluation; “negative bacterial findings” determined prior to this point in time are meaningless (3). If there is gastric scarring, extensive biopsies should be taken at least once so that a carcinoma is not overlooked (4, 5).

In case of an uncomplicated *Helicobacter* induced duodenal ulcer, follow-up endoscopy after proven *Helicobacter* eradication is not necessary (class of recommendation A/B, level of evidence 1a/2a, strong consensus) (3).

Focal atrophy and intestinal metaplasia do not need to be endoscopically monitored (class of recommendation B, level of evidence 2a, consensus) (3).

A *Helicobacter pylori* infection is a prerequisite of MALT-lymphoma (MALT = mucosa associated lymphoid tissue). In 80% of patients with a localized Stage I-1, and in 66% with a Stage I-2 MALT-lymphoma, eradication of *Helicobacter* leads to complete histological remission.

In 2.5%, follow-up endoscopies over a period of five years show early gastric cancer in spite of complete histological remission (6), so monitoring via endoscopy and biopsy is necessary even after the five year period. In patients with MALT lymphoma, the guidelines recommend follow-up endoscopy during treatment monitoring with the combination of urease test and histological evidence, two antrum and two corpus biopsies, respectively (class of recommendation B, level of evidence 2a, consensus) (3). At the moment there are no specifications concerning further intervals.

FIGURE 1

Monitoring strategies for Barrett's esophagus, modified according to (1)

Annual follow-up endoscopies are indicated in patients after endoscopic resection of early gastric cancer (7).

There are no current guidelines on whether follow-up endoscopy is necessary following resection of a gastric carcinoma. An S3-guideline is being prepared and is due to be published in 2010. Until the new guideline has been published, the authors recommend follow-up endoscopies only in symptomatic patients.

Endemic sprue

A successful gluten-free diet can be confirmed with the help of a receding antibody titer or a biopsy. However, whether a follow-up biopsy is necessary and when exactly it should be taken are the subject of controversy. It is seen as being unnecessary (8) or recommended to be performed four to six months after diagnosis (9) or after one year (10), respectively.

If treatment-resistant celiac disease is suspected, the following recommendations apply, since the macroscopic endoscopic findings return to normal before the histological changes disappear:

Endoscopic/histological follow-up in patients

- younger than 30 years of age—after one year,
- between 30 and 49 years of age—after two years,

FIGURE 2

Diagnostic procedure in suspected endemic sprue, modified according to (11); IgA, immunoglobulin A

- from the age of 50 onwards—after two years, but now including an antibody test (e3).

If the diagnosis is unclear, further procedures are determined by the antibody tests and biopsy findings (Figure 2) (11).

Whether asymptomatic patients that have the same mucosal changes as patients with symptomatic endemic sprue, should adhere to a gluten free diet remains controversial. However, if a gluten-free diet is adhered to, successful treatment must be confirmed with the help of a second biopsy (12).

If treatment fails because the gluten free diet was not adhered to, renewed dietetic consultation should follow. But if the diet is adhered to, the diagnosis needs to be verified through endoscopy with biopsies and by determining the serum tissue transglutaminase (tTG) antibodies. If the diagnosis is confirmed, video capsule endoscopy and, where necessary, double balloon enteroscopy are recommended (Figure 3) (13). These two examinations can not only help to detect persistent villous atrophy and determine how far it has impacted the

small intestine, but can also detect tumors and nonspecific findings like ulcerations of the small intestine.

Inflammatory bowel disease

In acute ulcerative colitis, follow-up biopsy is not indicated other than for therapeutic reasons. However, this is on condition that the ulcerative colitis was diagnosed with the help of a complete ileocolonoscopy, and that biopsies were taken from the terminal ileum and each colon segment (class of recommendation B) (14). The risk of colorectal carcinoma is significantly higher in ulcerative colitis compared to the normal population. In patients with (sub-)total ulcerative colitis that has been present for more than 8 years, or left-sided colitis that has been present for more than 15 years, a complete colonoscopy with serial biopsies should be performed annually during the remission phase of the ulcerative colitis (class of recommendation B) (14). This relatively rigid guideline was recently modified by the European Crohn's and Colitis Organisation (ECCO) (15). According to them, all patients with ulcerative colitis should receive a follow-up endoscopy 8 to 10 years after symptom onset to then ascertain how far the disease has progressed. In progressive colitis, follow-up colonoscopy is mandatory every two years until the 20th year after disease onset, after which annual follow-up is recommended (class of recommendation B, level of evidence 2). The ECCO guideline also recommends beginning monitoring measures in left sided and distal colitis in the 15th year after disease onset (class of recommendation B, level of evidence 2). In ulcerative proctitis, monitoring is not mandatory (class of recommendation B, level of evidence 2).

According to the current DGVS guideline, subtotal colectomy with a remaining rectal stump should be followed by annual rectoscopy, due to an increased cancer risk (class of recommendation B) (14).

In ulcerative colitis, colonoscopy with serial biopsy should preferably be performed during the remission phase (histomorphological demarcation of inflammatory/neoplastic changes difficult!) (class of recommendation C) (14). The number of biopsies taken is crucial for detecting intraepithelial neoplasia or cancerous changes (16). Diagnosis can be improved with the help of magnification chromoendoscopy (e5). However, the number of biopsies required remains a subject of debate. The DGVS consensus conference agreed on four colon biopsies in intervals of 10 cm (class of recommendation B) (14). Where there is possible intraepithelial neoplasia, endoscopic follow-up is mandatory within 3 to 6 months after intensifying anti-inflammatory treatment (class of recommendation B) (14). The data is not clear on how to proceed with a finding of low grade intraepithelial neoplasia. Extensive neoplastic lesions were frequent in some studies, rarer in others (17). As opposed to formerly, the recently published S3-guideline on colorectal carcinoma (17) no longer generally recommends proctocolectomy after a finding of low grade intraepithelial neoplasia. Instead, it recommends intensifying anti-inflammatory treatment and a follow-up endoscopy after

3 to 6 months. Anything further needs to be discussed individually with the patient. The significance of regular pouchoscopy after proctocolectomy is unclear at the moment (17).

According to former DGVS guidelines, in patients with known ulcerative colitis and an adenoma of the colon, polypectomy treatment is sufficient if no intraepithelial neoplasia in the remaining colon is found after multiple serial biopsies (class of recommendation B) (14). However, the decisive factor is the exclusion, via biopsy, of intraepithelial neoplasia in the neighbouring colonic mucosa, since a number of these patients develop colon carcinoma in this region (18, e5). According to the ECCO guidelines, an elevated dysplastic lesion should be completely removed. If there is no dysplasia in the surrounding flat mucosa, the patient should be encouraged to conscientiously make use of endoscopic follow-ups. If endoscopic resection is not possible or dysplasia is found in the surrounding flat mucosa, proctocolectomy is advisable (15).

After diagnosing Crohn's disease, follow-up endoscopy does not need to be performed every time symptoms become acute or before initiating new anti-inflammatory treatment. They are indicated when there are complications, unclear findings, and before performing elective intestinal surgery (class of recommendation D) (19).

In Crohn's disease, primary sclerosing cholangitis is seen as being a risk factor for colon carcinoma (20). After diagnosing primary sclerosing cholangitis, it should be monitored with the help of an annual colonoscopy (no class of recommendation given) (21). Where a diagnosis of primary sclerosing cholangitis in conjunction with ulcerative colitis has been made, annual monitoring should be conducted (class of recommendation B, level of evidence 3) (15).

Colonic polyps/colon carcinoma

A prophylactic proctocolectomy should be performed in patients with classic familial adenomatous polyposis (FAP). Postoperatively, annual pouchoscopy is essential, in patients with a remaining rectal stump it should be a rectoscopy every four months (class of recommendation A, level of evidence 2a, strong consensus) (17). Non-colectomized patients with attenuated familial adenomatous polyposis (aFAP) need to have a colonoscopy done annually for the rest of their life.

As the disease is autosomal dominant, the relatives of patients with FAP who are possible carriers of the mutation are at risk. After the family has received genetic counselling, this group should be subjected to predictive genetic testing from the age of 10 onwards (class of recommendation A, level of evidence 4, strong consensus). People at risk in whom the mutation has been confirmed or can not be excluded, should undergo rectosigmoidoscopy annually from the age of 10 onwards at the latest. If adenomas are found, a complete colonoscopy is mandatory and must be repeated annually till the proctocolectomy is performed (class of recommendation A, level of evidence 4, strong consensus) (17).

FIGURE 3

Recommendations for using video capsule endoscopy in endemic sprue, according to (13); tTG, tissue transglutaminase

TABLE 1

Classification of the extent of duodenal polyposis and indication for esophagogastroduodenoscopy in familial adenomatous polyposis (17)

Classification of the extent of duodenal polyposis			
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Intraepithelial neoplasia	Low-grade	Middle-grade	High-grade
Points	1	2	3
Indication for esophagogastroduodenoscopy in familial polyposis			
Spigelman	Points	Esophagogastroduodenoscopy	
I	1–4	Every 3 years ^{*1}	
II <40 years	5–6	Every 3 years ^{*1}	
II ≥40 years	5–6	Annually ^{*1}	
III	7–8	Annually ^{*1}	
IV	9–12	Surgery	

^{*1}with polypectomy when necessary

TABLE 2

Recommendation for follow-up after colonoscopic polypectomy; strength of evidence and consensus listed, classes of recommendation not listed (17, 24)

Characterization of the polyp/s (histology, other criteria)	Colonoscopy interval	Level of evidence	Consensus
Tubular adenoma • 1–2 polyps; <1 cm in size and without high-grade intraepithelial neoplasia	5 years	2b	Strong
Tubular adenoma • 3–10 polyps or • 1 polyp >1 cm or • 1 polyp with villous histology	3 years	1b	Strong
Tubular adenoma • With high-grade intraepithelial neoplasia and histologically confirmed complete resection	3 years	1b	Strong
Tubular adenoma • With high-grade intraepithelial neoplasia, but where complete removal has not been histologically confirmed	2–6 months	3b	Strong
Large flat or sessile adenomas, removed in piecemeal technique	2–6 months	3b	Strong
More than 10 adenomas* ¹ (take family medical history into account!)	<3 years	3b	Strong

*¹flat or sessile adenomas that have been removed via piecemeal technique also belong in this high risk adenoma group

People at risk with a family history of aFAP should have their first colonoscopy at the age of 15. If no polyps are found, they should have a colonoscopy annually from the age of 20 onwards (class of recommendation C, level of evidence 4, strong consensus) (17).

An FAP patient's lifetime risk of developing adenomas of the duodenal mucous membrane or even duodenal cancer, is between 80% and 90% or 3% and 4%, respectively. Growth of duodenal adenomas increases from age 40 onwards (17). From age 30 onwards, at the latest, an esophagogastroduodenoscopy should be performed every three years, concentrating particularly on the papillary region. Depending on what kind of adenoma is diagnosed, the interval should be shortened to up to one year (class of recommendation B, level of evidence 4, strong consensus) (17) (Table 1).

The hereditary nonpolyposis colorectal cancer (HNPCC) syndrome is defined according to anamnestic criteria (Amsterdam-I and -II criteria) (17). The Bethesda criteria are also used to identify further persons at risk (17). Mutation carriers (DNA mismatch repair genes) have a very high risk of developing colorectal cancer (up to 80%). For people at risk of HNPCC, annual colonoscopy is mandatory from age 25 onwards, and in any case five years before the lowest age of disease onset in the family, with (class of recommendation A, level of evidence 2a, strong consensus) or without prior surgery (class of recommendation A, level of evidence 2a, consensus) (17). The monitoring program also includes sonography, esophagogastroduodenoscopy, and gynecological examinations (17).

In addition to APC positive FAP, attenuated FAP, and HNPCC, a new, genetically defined disease class characterized by multiple colorectal adenomas has recently become known; it is caused by germline mutations in MYH—a base excision repair gene (22, 23). About one third of all patients with more than 15 adenomas have biallelic germline MYH mutations. Like patients with classic or attenuated FAP, patients with a biallelic MYH-mutation should be followed up endoscopically (23).

How to proceed after polypectomy is specified in the new S3-guideline “Colorectal Carcinoma” in its updated 2008 version (Table 2) (for recommendation classes see [17]). After completely removing neoplastic polyps (adenomas), follow-up endoscopy is mandatory. The number, size and histology of the removed adenomas should determine when follow-up colonoscopy is performed. In patients with one or two adenomas <1 cm and without higher-grade intraepithelial neoplasia, follow-up colonoscopy after five years is sufficient.

After removing flat or sessile adenomas in piecemeal technique, these patients, because of the increased rate of local recurrence and of metachronous lesions, should receive follow-up colonoscopy in shorter intervals (2 to 6 months), then after 3 years, after 5 years, or, in individual cases, earlier when necessary (level of evidence 3b, strong consensus) (17).

After a negative follow-up colonoscopy, further follow-ups are advisable in five-year intervals (level of evidence 4, strong consensus) (17). After completely removing a traditional serrated adenoma, a mixed

TABLE 3

Programmed follow-up examinations in colorectal carcinoma of UICC stages II or III (25)

Examination	Months							
	3	6	12	18	24	36	48	60
History, physical exam, CEA		X	X	X	X	X	X	X
Colonoscopy		X ^{*1}				X ^{*2}		
Abdominal sonography		X	X	X	X			
Sigmoidoscopy		X	X	X	X	X	X	X
Spiral computed tomography	X							

^{*1} if there has been no preoperative total colonoscopy;

^{*2} if findings are unremarkable (no adenoma, no carcinoma), next colonoscopy in five years; UICC, Union Internationale Contre le Cancer (International Union Against Cancer); CEA, carcinoembryonic antigen

mucosal polyp or a sessile serrated adenoma, follow-up colonoscopy is mandatory after 3 years because of the potentially increased risk of developing cancer, regardless of the degree of intraepithelial neoplasia (level of evidence 4, strong consensus) (17).

After removing an adenoma which contains a pT1 carcinoma, one should proceed in accordance with the classification of early colorectal cancers into low-risk and high-risk adenomas. Thus, patients with well- to middle-differentiated adenocarcinomas (G1/G2) without lymphatic invasion who had R0 resection have a low risk of lymphogenic metastization (less than 1%). In contrast, there is a high risk of lymphogenic metastization (on average about 14%) in poorly differentiated and undifferentiated carcinomas (G3/G4), carcinomas with invasion of the lymphatic vessels, high tumor cell dissociation at the invasion front of pT1-carcinomas, and carcinomas that could not be removed in healthy tissue. While in high-risk cases surgery is inevitable, it should at least be taken into consideration in low-risk cases. The invasion depth of these pT1-carcinomas, the patient's age and, where applicable, co-morbidity are factors that enter into the decision. After complete (R0) resection of low-risk (pT1, low grade [G1,G2, L0]) carcinomas, local endoscopic follow-up is mandatory after 6 months and after 2 years (class of recommendation A, level of evidence 4, strong consensus) (17).

So-called hyperplastic polyposis is a singular case, presumed to increase the risk of developing colorectal cancer (17).

According to the consensus statement of the Swiss Society for Gastroenterology (Schweizerische Gesellschaft für Gastroenterologie) (24), follow-up colonoscopy after 3 years is also necessary in cases where there are one or more hyperplastic polyps above the rectum sigmoid, if the polyps are larger 1 cm or if there are more than 20 polyps. If the findings are unremarkable, a colonoscopy interval after five years is recommended. If the hyperplastic polyps are situated in the

rectosigmoid and ≤ 1 cm in size, no follow-up monitoring is necessary (24).

Regular follow-up examinations are indicated after surgical R0 resection of colorectal carcinomas of UICC stages II and III (class of recommendation B, level of evidence 1a, strong consensus) (25) (Table 3) (UICC, Union Internationale Contre le Cancer [International Union Against Cancer]).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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