COLORECTAL CANCER SCREENING

Surveillance guidelines after removal of colorectal adenomatous polyps

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Most colon cancers are assumed to have a premalignant adenomatous polyp phase, therefore colonoscopic detection and polypectomy provides the opportunity for cancer prevention. Some patients who have undergone colonoscopy and have had adenomas removed are at increased risk of developing colorectal cancer (CRC) in the future, and therefore might benefit from colonoscopic surveillance. However, it is important to appreciate that colonoscopy is an invasive and costly procedure with some associated morbidity. It is also an under-resourced procedure in the UK, with a serious lack of fully trained endoscopists. Around one third of the population will develop an adenoma by age 60. Most adenomas are asymptomatic and remain undiagnosed. If colorectal screening is introduced this situation will change dramatically. There are few data on the benefits of colonoscopic surveillance in preventing colorectal cancer after a baseline clearing colonoscopy. It is therefore important that this practice is applied judiciously, balancing the risks and benefits in each individual case. Using published evidence, this guideline recommends appropriate surveillance after adenoma removal. The decision to perform each follow up colonoscopy should also depend on the patient's wishes, the presence of comorbidity, the patient's age, and the presence of other risk factors.

EXECUTIVE SUMMARY

Risk of colorectal cancer and adenomas with advanced pathology (≥1 cm or severely dysplastic) (see fig 1)

Risk can be stratified according to findings at baseline and refined at each subsequent surveillance examination. **(Recommendation Grade B)**

Low risk

Patients with only 1–2, small (<1 cm) adenomas.

Recommendation: no follow up or five yearly until one negative examination.

Intermediate risk

Patients with 3–4 small adenomas or at least one >1 cm

Recommendation: three yearly until two consecutive negative examinations.

High risk

If either of the following are detected at any single examination (at baseline or follow up):

≥5 adenomas or ≥3 adenomas at least one of which is ≥1 cm.

Recommendation: An extra examination should be undertaken at 12 months before returning to three yearly surveillance

Stopping surveillance due to comorbidity or age

The cut off age for stopping surveillance is usually 75 years, but should also depend upon patient wishes and comorbidity. **(Recommendation Grade C)**

Incomplete examinations

Patients with failed colonoscopies, for whatever reason, should undergo repeat colonoscopy or an alternative complete colon examination. These guidelines are based on accurate detection of adenomas; otherwise risk status will be underestimated.

Large sessile lesions

Large sessile adenomas removed piecemeal should be re-examined at three months. Small areas of residual polyp can be retreated endoscopically, with a further check for complete eradication in three months. If extensive residual polyp is seen, open surgical resection needs to be considered. If there is complete healing of the polypectomy site, then there should be a sigmoidoscopy or colonoscopy at one year before returning to three yearly surveillance. India ink tattooing aids recognition of the polypectomy site at follow up.

THE NATURAL HISTORY OF COLONIC POLYPS

The concept that most cancers arise from pre-existing adenomas is now widely accepted, based on epidemiological, clinical, postmortem, and molecular biological studies. Synchronous adenomas and cancers are a common finding as are adenomas with a focus of malignancy.[1 2] Adenomas are diagnosed on average 10 years earlier than CRCs, providing temporal evidence for the adenoma-carcinoma sequence.[3] Genetic changes have been identified that seem to promote the growth of adenomas and their malignant transformation.[4] Postmortem[5 6] and screening colonoscopy[7] studies estimate the prevalence of colonic adenomas to be 30%–40% at age 60 years, however the lifetime cumulative incidence of CRC is 5.5% therefore many colonic adenomas do not progress to cancer. Small adenomas are rarely malignant, however the malignant potential increases with increasing size.[8] The development of invasive cancer from a small (<10 mm) adenoma is unlikely in less than five years.[9] A barium enema study, before the colonoscopy era, of large polyps (≥1 cm), left in situ, has shown the cumulative risk of malignancy at 5, 10, and 20 years to be 2.5%, 8%, and 24%.[10] The exception to this slow progression may be flat or depressed adenomas, which may progress more rapidly than polypoid adenomas to cancer. Small flat cancers have been reported to account for 10%–30% of CRC in Japan,[11 12] but are still an uncommon finding in the West.[13 14] Flat adenomas and cancers are easy to miss during conventional endoscopy and the true incidence in the West has yet to be determined.

EVIDENCE THAT COLONOSCOPIC POLYPECTOMY PREVENTS CANCER

Although there is no direct evidence that endoscopic polypectomy reduces cancer mortality, there is a wealth of observational evidence demonstrating a likely benefit. The USA National Polyp Study[15] observed a 70%–90% lower than expected incidence of CRC in patients undergoing colonoscopic surveillance compared with three reference populations. Several studies have shown reductions in incidence and mortality rates of distal colorectal cancer after sigmoidoscopy screening of the order of 60–80%.[16–20] A single screening endoscopy seems to confer protection of 6–10 years.

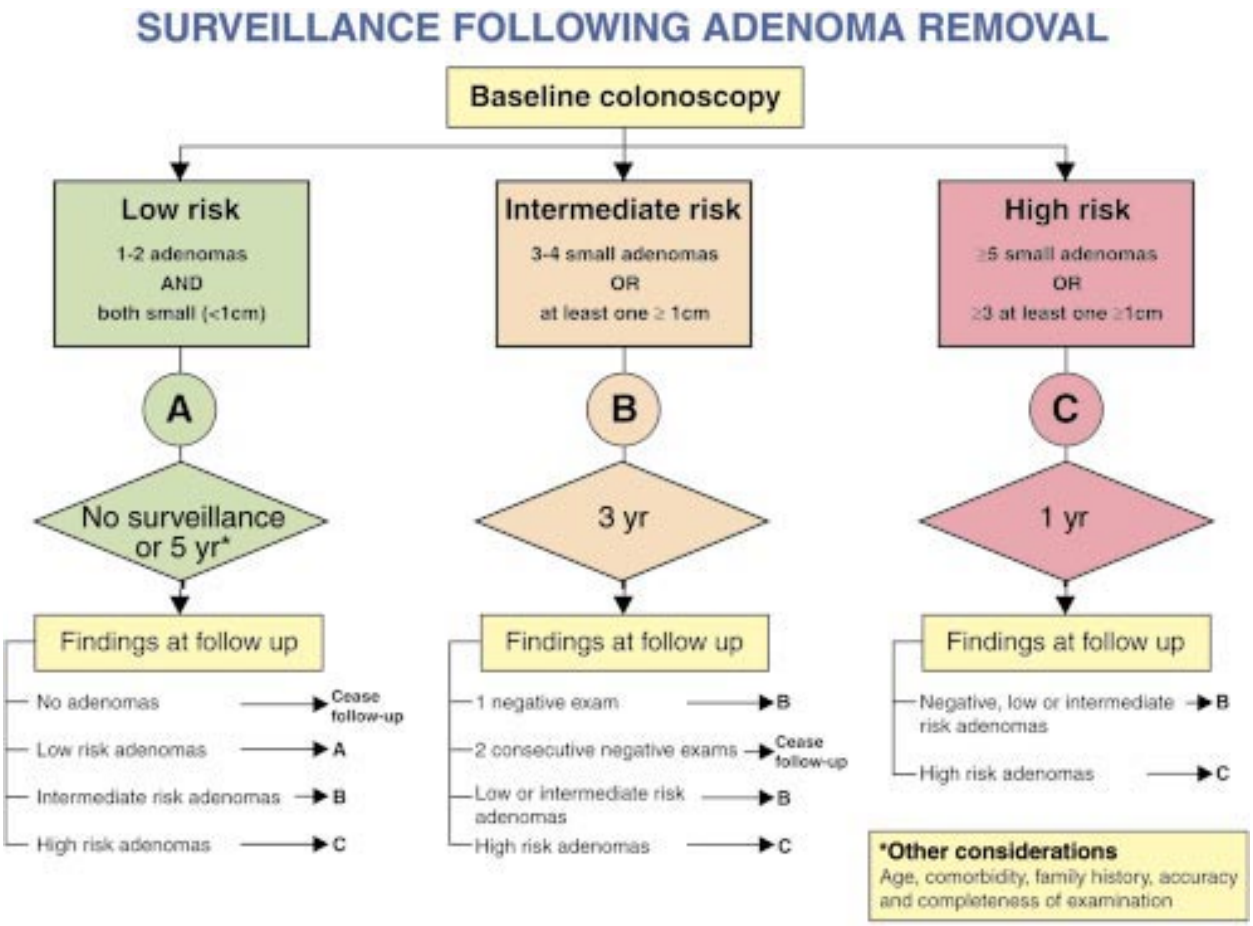

Figure 1 Surveillance after adenoma removal.

There have been no randomised trials examining the benefit of colonoscopy surveillance after adenoma detection. Independent studies undertaken on the US National Polyp Study dataset[21] showed that the observed reduction in incidence of colorectal cancer could be accounted for entirely by the initial colonoscopic polypectomy. Thus this study does not provide evidence that colonoscopic surveillance reduces risk further than achieved by the initial clearing colonoscopy.

COLONOSCOPY AND POLYPECTOMY

Colonoscopy provides detailed views of most of the colonic surface and is currently the gold standard examination for the detection and removal of colonic polyps. It has greater sensitivity than barium enema for both polyps and cancer[22] and permits simultaneous excision of polyps, thereby having the advantage of being both diagnostic and therapeutic. Passage of the colonoscope to the caecum, careful inspection of the mucosal surface during withdrawal, and safe removal of colonic polyps are the main aims of colonoscopy. Colonoscopy with or without polypectomy is, however, an invasive procedure requiring bowel preparation, considerable cooperation from the patient, and has a small risk of major complication, either from perforation (0.06% to 2.0 % overall) or major haemorrhage after polypectomy (0.4%–2.7%).[23–27] For this reason surveillance colonoscopy should be targeted at those who will most benefit and where possible should be performed by fully trained endoscopists.

SENSITIVITY OF COLONOSCOPY FOR POLYP DETECTION

In approximately 20% of patients colonoscopy is technically difficult for a variety of anatomical reasons.[28] Although near 100% total colonoscopy rates are seen at expert centres,[28 29] total colonoscopy rates nationally are only 75% (personal communication Dr Epstein, BSG audit). Even expert colonoscopists, using careful examination technique may miss some polyps and even some early cancers.[30 31] The miss rate is greatest for small polyps (25%) and varies according to examination technique.[32]

EVIDENCE TO SUPPORT THE GUIDELINES

Rationale for colonoscopic surveillance after adenoma detection

Patients who have adenomas *completely* excised from the rectum and distal sigmoid colon via the rigid sigmoidoscope have on average a twofold increased risk of developing colon cancer, but have no increased risk of developing rectal cancer.[17] The residual risk of colorectal cancer after removal of adenomas at colonoscopy is not known. It is possible that most patients are at very low risk after an initial colonoscopy with polypectomy of all detected lesions.

The rationale for colonoscopic surveillance has always been based on the high detection rate of colorectal adenomas at follow up (30%–50%) after a complete clearance colonoscopy.[33–37] However, the main object of colonoscopic surveillance is the prevention of subsequent colorectal cancer rather than the detection and removal of adenomas, most of which will not become malignant. Adenomas with advanced pathology (≥1 cm, with villous elements or severe dysplasia) have a much higher malignant potential[9] and the object of screening is to ensure that such lesions are detected before they become invasive.

The US National Polyp Study[34] was a randomised comparison of different surveillance intervals in 1418 patients with newly diagnosed adenomas removed at colonoscopy. In this

study, the cumulative detection rate of advanced adenomas or cancer was 3% in the groups having either one or two examinations within three years. The Funen Adenoma Follow-up Study[36] found that the incidence of advanced neoplasia was higher in patients examined at four compared with two years (8.6% *v* 5.2%) although the difference was not significant. However, on balance, the authors concluded that the more than 50% reduction in the number of examinations and the probable reduction in complications might justify the longer interval.

These results suggest that the first follow up colonoscopy can be safely left until three years for most patients with adenomas unless they fall into the low or high risk groups defined below.

Stratification of risk for development of advanced neoplasia

Several studies have shown that subsequent risk of developing advanced neoplasia is related to the characteristics of previously removed adenomas and that colonoscopic surveillance intervals can vary accordingly.

Low risk group

Four studies[38–41] identified a low risk group in which follow up colonoscopy can be safely delayed at least five years. All but one[41] of these studies agree that having only one to two adenomas confers low risk but disagree on the importance of size and histology.

The longer term risk of developing colorectal cancer also seems to be low for such patients. No increased incidence of cancer was observed in 751 patients after removal of small (1 cm or less) colorectal polyps,[42] most of which were unexamined histologically. A similar study from St Mark's Hospital,[17] in which all removed polyps were examined histologically, found that patients from whom only small (<1 cm) tubular adenomas were removed had no increased risk of developing colon cancer long term. Risk of rectal cancer was profoundly decreased compared with the unexamined population.

Thus it seems that whether the outcome is an advanced adenoma or cancer, future risk is low among patients with one to two small adenomas. There is uncertainty as to the role of histology as a predictor of future risk. Histological subtyping of adenomas is subjective and the reproducibility is poor. The WHO criteria[43] for the presence of tubulovillous or villous histology stipulates the finding of villous elements in more than 20% of the specimen. Sampling errors in small biopsies exacerbate difficulties in interpretation.

Available results suggest that the benefits compared with the risks of surveillance colonoscopy are likely to be small in patients with only one to two small adenomas, and that follow up colonoscopy, if undertaken at all, should be delayed at least five years.

The reason we suggest surveillance at all for this group is that there is no routine screening programme to otherwise assess them in follow up. If a screening programme is introduced, it will identify many people with one to two, small adenomas, and it will not be feasible or appropriate to routinely offer them surveillance as they can be managed adequately by continued population screening.

High risk group

It has been shown consistently that patients with three or more adenomas are a high risk group for the development of advanced adenomas and cancer, particularly if one of the adenomas is also large (≥1 cm).

In the National Polyp Study,[34] 9% of patients with three or more adenomas and 5% of those with a large adenoma removed at baseline developed an advanced adenoma by their first follow up examination, compared with only 1% in those with a single adenoma. An analysis of 697 patients in the Cleveland Clinic Foundation Adenoma Registry[40] showed that, compared with one to two small adenomas, risk is increased fivefold after removal of multiple (four or more), small adenomas and 10-fold after removal of multiple adenomas at least one of which is larger than 1 cm. The high recurrence rate of advanced neoplasia found at follow up after removal of multiple adenomas might result from a higher miss rate combined with a potential for such adenomas to be more advanced. In a study[44] in which a second colonoscopy was performed by different examiner immediately after the first, 17% of patients with one adenoma, 29% with two adenomas, and 42% with three or more adenomas at the first colonoscopy were found to have a missed lesion. No large adenomas were missed, but another similar study[31] found that 6% of large lesions were missed.

There have been two studies of the long term risk of colorectal cancer after removal of distal large polyps. Risk was increased threefold (compared with the general population) in patients from whom large polyps were removed and by fivefold in those from whom both multiple (>1) and large polyps[45] were removed. In the study from St Mark's Hospital[17] risk was increased fourfold after removal of large adenomas or those with a villous component and sevenfold if there were also multiple adenomas.

Although not entirely consistent, the data suggest that an additional colonoscopy at 12 months is warranted in people found at a single colonoscopy to have five or more, small adenomas or three or more adenomas, at least one of which is large.

EFFECT OF FAMILY HISTORY OF COLORECTAL CANCER ON RISK IN PATIENTS WITH ADENOMAS

Several studies have suggested that the prevalence of adenomas on baseline colonoscopy is increased in patients with a family history.[7 46] The National Polyp Study[47] found that the subsequent risk of advanced adenomas was increased in people with a family history. However, these data are published only in abstract form. The risk of recurrence of advanced adenomas in 1287 participants in a trial of wheat bran fibre was unaffected by inclusion of family history in a multivariate model after adjustment for adenoma characteristics at baseline.

There is no evidence to suggest that recommendations should differ for patients with a family history who are found to have an adenoma unless it is suspected that they have one of the dominantly inherited syndromes.

SIGNIFICANCE OF A NORMAL SURVEILLANCE COLONOSCOPY

Khoury[48] undertook a retrospective examination of 389 patients who had undergone follow up colonoscopy at one year intervals after resection of colorectal cancer. The adenoma detection rate at follow up was 10% at one year if the prior colonoscopy was negative and 40% if the prior colonoscopy was positive. If multiple adenomas were found at the prior examination, 70% of colonoscopies were positive. Similarly in patients with a history of adenomas, a normal follow up colonoscopy was associated with a lower incidence of subsequent adenomas at the next colonoscopy.[49] Risk of advanced adenomas was reported by the National Polyp Study[50] to be higher after detection of adenomas at the first follow up, although no data were published.

None of the studies to date has provided evidence to inform guidelines on the degree of protection afforded by a single negative follow up examination in patients with "high risk" adenomas at baseline. One study[51] has shown that a negative result at first follow up examination in patients with multiple adenomas initially does not preclude the subsequent development of new adenomas. Thus, until data to the contrary are available, it must be assumed that patients with "high risk" adenomas remain at increased risk despite a single negative follow up examination. After two consecutive negative examinations there can be greater confidence that adenomas have not been missed and that subsequent risk is decreased.

This suggests that surveillance can cease following a single negative follow up colonoscopy in lower risk patients, but that two negative examinations are required for higher risk patients.

STOPPING SURVEILLANCE

The cut off age for stopping surveillance is usually quoted as 75 years as the remaining life expectancy is likely to be less than the average time required for new adenomas to become malignant. After this age, it is unlikely that the benefits of surveillance will outweigh the potential risks of the procedure. However, this should not preclude further surveillance in a fit and motivated person who has a tendency to produce multiple or advanced adenomas at follow up.

The risks and benefits of adenoma surveillance need to be balanced at all ages, particularly in patients who have significant comorbidity.

The decision to undertake each colonoscopy examination at follow up should depend not only on the number and type of adenomas, but also on the patient's age and wishes, and the presence of significant comorbidity. The patient status should be established prior to attendance for each examination possibly by questionnaire.

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