Risk and surveillance of individuals with colorectal polyps

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Since colorectal adenomas are very probably the precursors of colorectal cancer, their detection and removal should result in a decrease in the incidence and mortality from colorectal cancer. Individuals who harbour an adenoma have a 30–50% probability of having additional adenomas at that time, and a 30% probability of having additional adenomas later. Adenomas are prevalent in countries where colorectal cancer is prevalent, about two-thirds of them being tubular and the rest tubulovillous or villous.

The initial management of patients with an adenoma consists in searching by colonoscopy the entire colon and removing all additional polyps. Surgical resection is required wherever there is invasive cancer with adverse histological factors. Follow-up in most patients can be after 2–4 years, earlier follow-up being reserved for patients with numerous polyps or with a polyp that had been removed piecemeal.

The results of ongoing trials should provide firm guidelines for follow-up and could also be used in mathematical modelling to examine alternative strategies and to help understand the evolving patterns of appearance of new polyps. Finally, a deeper understanding of the biology and inherited and acquired genetics will help identify individuals at risk for adenomas initially and at follow-up. Nutritional factors may also provide a basis for prevention of adenomas in high-risk countries. Many of these issues are being addressed in current research.

Introduction

Interest in colorectal adenomas stems from their relationship to colorectal cancer (*1*). The idea that the majority of colorectal cancers evolve from benign adenomas has been discussed in the literature for more than 50 years and is widely accepted. The evidence includes epidemiological data correlating adenoma and carcinoma prevalences, the association of adenomas and carcinomas in patients, and the frequent finding of contiguous benign adenoma in a colorectal cancer. Support for the adenoma–carcinoma sequence is also found in inherited colorectal cancer syndromes, both familial polyposis and the cancer family syndrome (*1–4*). Recent findings on *ras* gene mutations and chromosome deletions provide additional biological evidence of this association (*5–7*).

The development of colorectal cancer probably evolves through a sequence of stages—beginning with environmental carcinogens acting on a genetically susceptible mucosa and resulting in a hyperproliferative state, followed by a series of oncogene mutations and chromosome deletions. This leads to a precursor adenoma, successive stages of dysplasia, and then invasive cancer (*5*). The etiology of colorectal adenomas and colorectal cancer has been reviewed in detail (*8, 9*). Adenomas are extremely prevalent in western countries, being observed in autopsy studies in 30–40% of persons aged over 60, but are rare in some areas such as Africa (*10, 11*). They are strongly age-related and predominant in males (*2*).

Polyps and adenomas

Through the wider application of stool-blood testing, flexible sigmoidoscopy and colonoscopy, individuals who harbour polyps are now being identified with increasing frequency.

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Polyps are growths into the lumen of the bowel and may be classified as neoplastic or non-neoplastic (*10*). Non-neoplastic polyps have no malignant potential and include hyperplastic polyps, hamartomas, benign lymphoid polyps, inflammatory polyps, and normal mucosa. Neoplastic polyps are adenomas and are potentially malignant. These are classified into three types: tubular, tubulovillous, and villous adenomas having varying degrees of villous features.

- Tubular adenomas contain a normal lamina propria and straight or branched tubules of dysplastic epithelium.
- Villous adenomas contain elongated non-branching folia or crypts of dysplastic epithelium.

Only a portion of colonic polyps that are detected are true adenomas. In the United States National Polyp Study, adenomas accounted for 68% of the polyps removed by colonoscopy in the initial examination (*12*). The remaining polyps were overgrowths of normal mucosa and other miscellaneous non-neoplastic polyps (22%) as well as hyperplastic polyps (11%). Adenomas discovered in autopsy studies are small (< 1 cm), mostly tubular, and uniformly distributed throughout the colon (*11, 12*). In clinical studies based on symptomatic patients such as the St. Marks Study and the National Polyp Study, the adenomas tend to be larger, have a more varied histology, and 2 out of 3 are distal to the splenic flexure (*3, 12*). All adenomas have at least mild dysplasia, by definition, and a proportion have moderate or severe dysplasia, carcinoma-in-situ, or invasive cancer (*3, 12*). The terms low-grade and high-grade dysplasia are used by some investigators instead of moderate and severe dysplasia. Carcinoma-in-situ has no clinical significance and has been included in severe or high-grade dysplasia in order to avoid clinical overreaction to the diagnosis of carcinoma-in-situ in an adenoma (*13*).

The most common type of adenoma is tubular (68%), which has less premalignant potential than those with villous features. Villous features are more common with increasing size. Approximately 5% of the adenomas have high-grade dysplasia or carcinoma-in-situ, and 2.5% have invasive cancer at the time of presentation. Carcinoma-in-situ and high-grade dysplasia are not influenced by sex but are related to age and also to multiplicity of the adenoma. Individuals presenting with an adenoma have 40–50% likelihood of having additional adenomas at the same time (synchronous) (*10, 12, 14*).

Patients who have had an adenoma removed from their colon have an increased risk of developing a subsequent adenoma. Prior to fibreoptic colonoscopy, the reported rate of recurrence ranged from 20% to 50%. Although patients enrolled in the original studies did not have an examination of the entire colonic mucosa to exclude synchronous lesions, investigations performed with colonoscopy have confirmed the previous observations. In the pre-endoscopy era, Henry et al. (*15*) and Kirsner et al. (*16*) reported recurrent adenomas in 30–41% of patients over the 5–9 years of follow-up. Since the advent of colonoscopy, Macrae & Williams followed up 330 patients after polypectomy for an average of 3.6 years and found adenomas in 37% (*17*); Aubert et al. reported an identical incidence in a 10-year follow-up of 123 patients (*18*). Waye & Braunfeld (*19*) reported that 56% of 227 patients had adenomas at their first annual colonoscopy following removal of the index adenomas. Fowler & Hedberg (*20*) reported that adenomas recurred in 60% of 383 polypectomy patients followed for four years. Matek and co-workers presented similar follow-up data and reviewed many of the studies reported in the literature, all of which had significant recurrence rates (*21*).

The National Polyp Study has also generated data on adenomas after complete clearing of all synchronous adenomas in a cohort that had not had any prior intervention. In this population, it was noted that adenomas recurred at a rate of 29–35%, depending on the interval from their initial colonoscopy. Adenomas tended to be small, mostly tubular, with only mild dysplasia, and uniformly distributed throughout the colon as compared to the distal distribution of larger adenomas with varied histology seen at initial diagnosis (*12*). This agrees with other reports (*17, 19–22*).

Management

Initial management

The management of patients with colorectal polyps can be divided into initial management and follow-up (*10, 13*). After detection, the index polyp should be removed completely to eliminate all neoplastic tissue and the entire specimen should be submitted for microscopic examination to detect the foci of malignancy and adequately classify the lesions histologically. Polypectomy of larger polyps can be accomplished with the cautery snare, while small sessile polyps may be biopsied and ablated with the "hot-biopsy" forceps. Pedunculated polyps and sessile polyps with a small attachment to the colon wall can be removed completely with one application of the cautery snare.

If a sessile polyp with a wide-based attachment is not completely removed at the initial polypectomy, additional endoscopy may be required to remove the rest of the tumour. Endoscopic excision of a polyp may not be possible when it is located in an inaccessible site, or if the polyp is larger than 2 cm in

diameter and sessile, especially with a broad area of implantation into the colonic wall. If complete endoscopic resection cannot be performed, surgical resection may be required. This, however, is necessary in only a very small proportion of cases. Since the frequency of additional (synchronous) adenomas in patients with a demonstrated adenoma at the time of diagnosis is approximately 40–50%, the initial management of a patient with an identified adenoma should include total colonoscopy with removal of all polyps. This policy may be modified, however, in the presence of significant medical problems.

Classification of the removed polyp. After endoscopic resection, every effort must be made to retrieve the entire specimen for examination and classification. It is important to record both clinical and anatomical features such as the number of polyps and their size, gross morphology (pedunculated or sessile), and their locations. An attempt should be made to identify the base of the polyp. Contraction of the muscularis mucosae may cause a specimen to curl into a ball, making subsequent identification of the resection site extremely difficult. To avoid this, sessile polyps should be placed flat on a piece of cardboard, thick paper, Gelfoam, or a frosted glass slide before insertion into the fixative. Polyps that are pedunculated or have a small site of attachment to the colon wall may be marked with indian ink at the line of resection (*10, 11, 14*).

Histological classification of polyps is made according to WHO criteria. Multiple histological sections are examined from stepwise slides of the entire polyp. In each adenoma, the degree of dysplasia should be recorded as mild, moderate, and severe or, alternatively, as low grade or high grade. The diagnosis of carcinoma-in-situ should be included in the category of severe or high-grade dysplasia for clinical reporting, the term "carcinoma-in-situ" being used for research studies only. Intramucosal or focal carcinoma are terms best not used, or used with caution, because of the same potential for clinical misinterpretation. Invasive cancer in an adenoma should be reported in terms of depth of invasion, involvement of stalk or cautery line, lymphatic or vascular space involvement, degree of differentiation, and volume of adenoma replaced. Pseudo-invasion with adenoma misplaced into the stalk or submucosa should not be interpreted as true invasive carcinoma. The report should include whether the excision appears to be complete (*10, 11, 14*).

Patients with carcinoma in an adenoma

The occurrence of carcinoma within an adenoma is not unusual. Most cancers within adenomas are in the category of high-grade dysplasia. Their presence increases with age and when there are multiple adenomas, as well as with increasing size and increasing villous histology. This finding has no clinical significance (*2, 3, 12, 23*). Invasive cancer has been reported in less than 1% to more than 8% of adenomas, but more often where there is villous change and increasing size. Lymph-node metastases and invasion of the bowel wall have been reported in up to 25% of the patients with invasive cancer, although most studies report the frequency of such findings as less than 10%. However, when the histology is favourable and there has been complete excision of the polyp, the probability of having residual or metastatic cancer is considerably less than 1%. This is equal to or less than the risk for surgery with bowel resection in average-risk patients (*24–31*). The following guidelines can be used for patients with invasive cancer within an adenoma. Adenomas with severe or high-grade dysplasia or carcinoma-in-situ, i.e., histological features of carcinoma limited to the mucosa and not penetrating the muscularis mucosae, are not considered to have metastatic potential. Surveillance of this group of patients, who have had the adenoma completely resected, should follow the protocol for other adenomas.

An adenoma is considered to have invasive carcinoma when malignant cells have penetrated the muscularis mucosae. When invasive carcinoma occurs in an adenoma, further clinical decisions are based on the presence or absence of "favourable criteria" which are: well-differentiated or moderately well-differentiated carcinoma, absence of malignant cells at the resection margin and absence of vascular or lymphatic invasion. If the adenoma with invasive carcinoma is sessile, a surgical resection, with dissection of regional lymph nodes, is recommended. This may be avoided if the cautery line is definitely clear. Patients with pedunculated adenomas with invasive carcinoma should undergo similar surgery if the cancer extends to the line of cautery, the carcinoma is poorly differentiated, or lymphatic or vascular invasion is demonstrated on histologic sectioning. The almost total replacement of an adenoma with invasive cancer may also require surgery.

There is considerable controversy about the necessity for additional surgery following endoscopic removal of a sessile adenoma with a small focus of well-differentiated or moderately differentiated carcinoma that has invaded the muscularis mucosae, but does not involve vascular or lymphatic spaces or the line of resection. At present, there are insufficient data on the metastatic potential of such lesions, and no general guidelines can be given. However, there is growing conservative opinion for a non-operative approach to these patients. Thus, there is agreement that a patient with invasive carcinoma in an adeno-

ma who meets the usual criteria for surgical resection may be spared surgery when there are medical problems that make the patient a poor surgical risk. If the lesion is low in the rectum and surgery is indicated, a local deep excision is usually adequate. Abdominal perineal resection is generally not done for malignant adenomas (*10, 24, 31*).

There has been interest in recent years in certain types of polyps such as the small polyps and hyperplastic polyps. Small polyps are so classified when they are approximately 5–6 mm in size or less. In recent years, studies by Waye (*32*) and Tedesco (*33*) have demonstrated that these are adenomas in about 60% of the cases. The National Polyp Study has demonstrated that small polyps that are adenomas have all the features of the larger adenomas but to a lesser degree quantitatively. Hyperplastic polyps have no malignant potential but seem to arise in the colon of individuals who harbour true adenomas. These polyps are primarily located in the rectosigmoid, but whether their presence in the rectosigmoid implies the presence of adenomas more proximally is as yet unsettled (*34*). The data indicating the predictive value of the hyperplastic polyp for more proximal adenomas are based on small sample sizes and without true controls; larger studies with good controls have not confirmed this finding (*35*).

Recommendations and guidelines

Follow-up recommendations

Colonoscopy is the preferred method of follow-up examination after removal of an initial adenoma. Sigmoidoscopy with a high-quality double-contrast barium enema, however, is a possible acceptable alternative in the absence of good colonoscopy. Annual fecal occult-blood tests have been used in the follow-up period when the surveillance intervals were longer than one year (*3*), but this is of questionable value.

The objective of a surveillance programme is to prevent the development of colorectal cancer. The recurrence rate of adenomas in patients after initial polypectomy is high enough to justify periodic follow-up. Ideally, all synchronous adenomas are removed at the time of the initial polypectomy. The frequency of missed synchronous lesions, however, has been suggested to be 5–10%. A proper surveillance scheme should, therefore, offer the opportunity of finding these missed lesions and new metachronous adenomas, but must be designed to protect the patient from the risk and cost of unnecessary examinations and an overloading of medical resources. Several studies have been investigating follow-up strategies in these patients.

The endoscopist must be confident that a "clean colon", free of adenomas, should be established before instituting long-term follow-up. Frequently, repeated examinations may be indicated after incomplete or piecemeal removal of some large or sessile lesions, for patients with numerous polyps, or after a technically unsatisfactory examination. Following apparently complete removal of a pedunculated malignant polyp, judged on combined endoscopic and histological grounds, most endoscopists perform repeat examination at 3–6 months and 1 year before reverting to general follow-up.

Data on which to base general follow-up intervals are incomplete except that six-monthly examinations are too frequent. Current information suggests that after establishing a clean colon, there can usually be an interval of 1–3 years before repeat examination. Some centres present predictive evidence of an increased risk in patients with multiple adenomas and recommend a follow-up examination every two years in those with two or more adenomas but every four years in those with a single adenoma (*21*). The likelihood of prolonging life expectancy by continued colonic surveillance becomes small in old age, but individual considerations such as ill-health or predictive factors (such as very numerous polyps) will affect the age at which follow-up is discontinued, usually around 75–80 years (*13*).

Finally, the approach to patients with adenomas will change dramatically over the next few years as we begin better to understand the biology of the adenomas. Progress in inherited genetics may provide a basis for identifying those individuals who harbour adenomas with significant pathology and whose adenomas are likely to progress and recur. Oncogene and surface antigen expression as well as other characteristics of adenomas will assume a more important role as a basis for the management of these high-risk patients (*5, 36–38*).

Research recommendations

(1) There is a need for demonstration of a reduction in incidence and mortality from colorectal cancer by periodic intervention using colonoscopy to remove adenomas.
(2) The most cost-effective intervals for follow-up surveillance in post-polypectomy patients need to be demonstrated by completion of current ongoing trials.
(3) The relative value of colonoscopy, barium enema, and stool-blood testing needs to be compared in the follow-up of patients after polypectomy.
(4) There should be improved methods for identification of individuals harbouring adenomas, or at risk for developing adenomas.

(5) Predictive factors for recurrent adenomas (biochemical, biological, pathological, and family history) would be of importance in separating risk groups of individuals for varying follow-up strategies after polyps have been removed.
(6) A standardized nomenclature for reporting of clinical, endoscopic and pathological studies related to polyps should be developed.
(7) Studies need to be done on the malignant polyp, to ascertain the need for surgical resection following polypectomy.
(8) Dietary assessment and family history should be obtained in well characterized cohorts of patients with polyps in order to understand their interrelationships in terms of etiology.
(9) The patient with polyps should be used more extensively to study the biology of carcinoma of the colon. Blood and tissue phenotypic abnormalities should be clearly examined in these patients and correlated with the occurrence, progression and recurrence of disease.
(10) Patients with polyps should be used more extensively to study effects of nutritional intervention. Parallel studies with phenotypic markers should be done and familial factors should be controlled for.
(11) The benefit of polypectomy and follow-up surveillance should be correlated with age, pathology, family history and diet.
(12) The use of mathematical modelling based on data from polypectomy patient groups may help to answer many of the currently unsolved questions.
(13) Adenoma tissue should be used for study of chromosome, oncogene and other cellular abnormalities in order to help elucidate the genetic basis of "sporadic" adenomas and hence "sporadic" colorectal cancer.

Practical guidelines

(1) When a polyp has been identified it should be removed for histological examination. Small polyps found in the rectosigmoid on flexible sigmoidoscopy can be biopsied.
(2) Histology of the polyp should be assessed to classify the polyp according to the criteria of the World Health Organization.
(3) Patients with an adenoma should have the entire colon examined for additional polyps by colonoscopy and all polyps should be removed and studied histologically. If colonoscopy is unavailable, flexible sigmoidoscopy and double-contrast barium enema can be performed as an alternative.
(4) Family history should be obtained in all patients with adenomas to determine if screening of the family is indicated.
(5) Adenomas with severe (high-grade) dysplasia need no additional surgery. The term carcinoma-in-situ should be dropped for routine clinical use since it can be misleading. Adenomas that are sessile with invasive cancer to the cautery line usually need surgical resection. Adenomas that are pedunculated with cancer that is poorly differentiated, involves lymphatic or vascular spaces, or extends to the cautery line may require surgery, but each case must be judged individually.
(6) Rectal malignant adenomas requiring surgery can often be managed by local excision.
(7) All patients with adenomas should have complete excision initially.
(8) All patients with adenomas need a follow-up programme. In most patients, this can be with colonoscopy every 1–3 years. Some patients will require alternative individual follow-up, e.g., those with invasive cancer, large sessile adenomas, or a large number of adenomas.

Résumé

Les polypes recto-coliques: risque et surveillance

L'intérêt porté aux polypes recto-coliques vient de ce qu'ils précèdent souvent un cancer du côlon et du rectum. Ces polyadénomes sont extrêmement fréquents dans les pays où ce type de cancer est courant. L'évolution de ces cancers se fait probablement par une série d'étapes, commençant par l'action d'agents de l'environnement sur une muqueuse génétiquement sensible au stade hyperprolifératif et passant par un stade adénomateux avant d'atteindre le stade du cancer invasif. C'est un processus lent qui prend en moyenne au moins 10 ans.

Les polyadénomes sont constitués pour environ deux tiers de polypes recto-coliques, le reste étant principalement formé d'excroissances muqueuses normales et de polypes hyperplasiques. Ces derniers n'ont aucun potentiel néoplasique et ne sont pas considérés comme cancéreux. On classe ces polyadénomes en formes tubulaires, tubulo-villeuses, ou villeuses, selon l'importance des végétations. Tous les polyadénomes présentent au moins une légère dysplasie et certains d'entre eux (5%) une forte dysplasie. Ces derniers comprennent les cancers in-situ, terme qu'il faut éviter d'employer en clinique car sans aucune signification pour le malade. Les

polyadénomes avec cancer invasif (3%) sont appelés polyadénomes malins.

La probabilité que le malade chez qui l'on décèle un polyadénome en présente plusieurs autres au même moment (synchrones) est de 30 à 50% et la probabilité pour que l'on en découvre d'autres (métachrones) à la colonoscopie est d'environ 30%. On n'a pas encore défini la proportion respective des polyadénomes métachrones récents et de ceux passés inaperçus.

La prise en charge des sujets présentant des polypes se fait en deux temps: prise en charge initiale et suivi. Dans une première étape, on débarrassera le côlon de tous les autres polypes trouvés. Plusieurs colonoscopies peuvent être nécessaires pour éliminer un important polype sessile, vérifier que l'exérèse est complète et s'assurer de l'absence de toute récurrence. L'examen histologique après orientation, fixation et coupe convenable est indispensable. Les indications de la résection chirurgicale après ablation d'un polype présentant une dégénérescence maligne sont les suivantes: cancer invasif dans un polyadénome sessile ou extension à la base d'implantation, accompagnée d'une faible différenciation cellulaire et de l'extension aux espaces lymphatiques ou vasculaires dans un polype pédiculé. Si l'exérèse chirurgicale est indiquée pour un polype rectal, l'excision locale est généralement suffisante.

Une fois le colon débarrassé de tous les polypes, la colonoscopie est la meilleure méthode de suivi. Si l'on ne peut disposer d'une colonoscopie de bonne qualité, on pourra employer la sigmoïdoscopie souple et le lavement baryté en double contraste. L'objectif d'un programme de surveillance est d'éviter les décès par cancer du côlon. Des essais sont en cours pour évaluer l'intervalle optimal entre deux contrôles. A l'heure actuelle, on recommande des examens de contrôle précoces après exérèse de nombreux polypes ou exérèse d'un polype important en plusieurs fois. Chez la plupart des sujets, un examen 2 à 4 ans après résection de tous les polypes rectocoliques est semble-t-il suffisant.

Il reste de nombreuses questions à résoudre, notamment celles de l'intervalle entre deux contrôles, de la nécessité d'une résection chirurgicale, de son coût/efficacité et de l'observance des malades vis-à-vis des possibilités offertes. Il est probable que dans les quelques années à venir, nous aurons une meilleure compréhension de la biologie de la séquence polyadénome-adénocarcinome, ce qui nous permettra d'identifier dès la prise en charge initiale et au cours du suivi les sujets présentant le plus grand risque de cancérisation. Les progrès dans le domaine de l'hérédité seront particulièrement importants à cet égard. En outre, la connaissance des interactions existant entre les facteurs nutritionnels et les facteurs génétiques pourrait nous fournir des méthodes de prévention applicables dès la prise en charge initiale des polyadénomes et lors du suivi. On pense que la prévention des polypes et leur élimination précoce devraient permettre de diminuer l'incidence et la mortalité liée au cancer du côlon, mais cela reste à démontrer.

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