Colonic Polyps:
The Harm of Overdiagnosis

In the United States, a lot of anxiety has been generated by the media and gastroenterology thought leaders over colonic polyps. Lay people and the primary care physician have been led to believe that any polyp is a threat and that advanced polyps (adenomas) are particularly worrisome. They accept the concern that missing any advanced adenoma by screening tests other than colonoscopy is not worth the risk, but is this concern justified? What are “advanced adenomas” and how likely are they to lead to death from colorectal cancer? Is finding an advanced adenoma important enough to justify population screening with colonoscopy? Some inquisitive clinicians and policy makers are wondering if polyps, even the advanced ones, are “sheep in wolves’ clothing.” Could they be a form of “overdiagnosis” thus labeling innocuous tumors as cancer and treating them as though they could be lethal when in fact most are not dangerous? The article below addresses these and other questions.

INTRODUCTION

In 2000, two articles published in The New England Journal of Medicine demonstrated the usefulness of optical colonoscopy as a screening test for colorectal cancer (CRC). Shortly thereafter, in the United States, several endoscopic societies and gastroenterology thought leaders proclaimed colonoscopy to be the best/preferred screening test and the media was quick to follow. Colonoscopy proponents have claimed that if patients are screened with a test other than colonoscopy, 25-65% of advanced neoplasms could be missed, depending on the other screening modality chosen.

The certainty of the recommendations from experts and the worry that advanced neoplasms would be missed have led to health policy decisions that have had important consequences in the U.S. Until 2001 all CRC screening tests recommended for Medicare coverage by the Centers for Medicaid and Medicare Services (CMS) were extensively evaluated to be sure they were appropriate and effective for Medicare beneficiaries aged 50 years or older. In 2001, CMS evaluation was bypassed and Medicare coverage of colonoscopy was mandated by Congress.

Since 2000, many gastroenterologists and their professional societies have promoted only one screening test as best, colonoscopy. A recent review of colorectal cancer screening by primary care physicians shows how effectively the message has been communicated.
Colonoscopy is now the most frequently recommended test and most physicians do not recommend the full menu of test options prescribed in national guidelines. This has led to the following consequences:

1. The number of people undergoing screening colonoscopy has greatly increased and doctors are struggling to keep up with demand.10

2. Some commercial insurance plans are spending more every year on colonoscopies than on cardiac bypass, hip and knee surgeries combined.11

3. Although screening rates for CRC have increased modestly since 2001, they continue to lag well behind those for other cancers.12

4. There has been a significant decline in the use of other effective screening tests particularly in the uninsured, underinsured and underserved population.13 Figures 1., 2.

5. Some gastroenterologists are spending up to 50% of their practice time simply performing colonoscopy.

Most advanced neoplasms are advanced adenomas and only a few are cancers. Lay people and primary care physicians accept the concern that missing any advanced neoplasm by screening tests other than colonoscopy is not worth the risk, but is this concern justified? What are advanced adenomas and how likely are they to lead to death from colorectal cancer? Is finding an advanced adenoma important enough to justify population screening with colonoscopy? Do colonoscopies find all advanced neoplasms?

Some clinicians and policy makers are wondering if polyps, even the advanced ones, are “sheep in wolves’ clothing.” Could they be a form of “over diagnosis” thus labeling innocuous tumors as cancer and treating them as though they could be lethal when in fact most are not dangerous?14 Barnett Kramer, M.D., Associate Director for disease prevention at the National Institute of Health (NIH), has declared over diagnosis pure unadulterated harm.15 Advanced neoplasia may be considered a convenient proxy for colorectal cancer, but its use as an outcome measure may be misleading in screening studies because the natural history of this lesion has not been fully established.16

In the paragraphs and illustrations below, the terms advanced neoplasm, advanced adenoma, polyp, adenoma, villous adenoma, tubulovillous adenoma, adenoma with dysplasia and serrated adenoma will be carefully defined and what is known about their risk for death from colorectal cancer discussed.

**Figure 1. CRC Screening Test Trends 2000-2008**

Colorectal Cancer Development: The Adenoma-Carcinoma Sequence

The relation between colorectal adenomas/polyps and colorectal cancer is less straightforward than often stated. Colorectal cancer arises in epithelial cells lining the interior of the large intestine. During the process of neoplasia, these cells gradually acquire cancer cell characteristics but, in most cases, this process never passes the precursor adenoma stage.

The concept of the polyp-cancer or adenoma-carcinoma sequence was first described by Morson and coworkers in 1975.17 However, hardly any longitudinal data about the actual progression risk of individual lesions exist. Nevertheless, the literature is full of firm statements that the adenoma-carcinoma sequence takes 10-20 years and that the risk of progression is determined by increasing size, villous histology and grade of dysplasia.

It is important to understand that this gap in the formal evidence available will not change because the optimal study for this purpose – i.e. leaving adenomas in situ and sampling them regularly for phenotypic
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and molecular features until they become malignant, is unethical. Once adenomas are detected, they are completely removed so that no neoplastic cells are left. As a consequence, only indirect data exist on the average duration of the adenoma-carcinoma sequence, and on the risk of progression of different adenoma phenotypes (e.g. size, histological type, polypoid, flat or serrated appearance).

Adenomas of the colon are quite common, occurring in 30 percent or more of individuals over 60 years of age and, with new high-resolution endoscopes, increasingly more small lesions are detected. It is essential for the clinician to understand that the majority of adenomas ‘never’ progress to cancer, i.e. certainly not within time frames covered by current annual FIT based screening programs. It has been estimated that only five percent of all adenomas actually progress to malignancy.18

Polyps

A colonic polyp is a term describing the gross appearance of a circumscribed lesion (tumor) that protrudes into the lumen of the colon. They are either pedunculated, consisting of a head and a stalk, or sessile, consisting of lesions without a clear stalk but still protruding into the lumen.

The term polyp does not provide any information about the pathological nature of the lesion, be it benign or malignant, epithelial or non-epithelial. Clinically, the most important issue is to identify those polyps most likely to progress to cancer and, in the GI literature, they are the ones designated as advanced adenomas. Advanced adenomas are defined as polyps 1 cm or greater or those with villous features or high-grade dysplasia. Evidence that this category of adenomas is the optimal target for screening is limited.19 The term “advanced adenoma” was introduced to increase statistical power in screening studies, and the risk of dying from colorectal cancer conferred by these lesions is much less than when actual cancer is present. Advanced neoplasms, as used in the clinical gastroenterology literature, are not late stage cancers. They are the term used to describe both advanced adenomas and all stages of cancers.

Adenomas

Adenomas (Figure 3) are benign neoplastic polyps derived from the colorectal epithelium. They show certain phenotypical characteristics, like increased proliferation, nuclear atypia and disturbed glandular architecture. By definition, adenomas do not show
invasion in surrounding tissue and cannot metastasize. Adenomas can, in a minority of cases, progress to carcinomas hence they are called pre-malignant.

**Histological Type of Adenomas (Figure 4)**
Adenomas are classified by their histological type. Adenomas that have crypts going down from the surface into the stroma of the polyp are called tubular adenomas. Other adenomas on the two-dimensional image under the microscope show leaf- or finger-like processes. These processes are called villi and these adenomas are called villous adenomas. Adenomas with a combination of both histological types are called tubulovillous.

**Adenomas Show Dysplasia (Figure 5)**
Dysplasia is the intermediate stage between normal and cancer and, in the colon, the most common form of dysplasia is an adenoma. Dysplasia is benign because there is not yet invasive growth. The morphologic changes of the neoplastic epithelium in adenomas affect the nuclei, cytoplasm and architecture of the crypts or glands (Figure 5). Nuclei first get elongated, enlarged, slightly hyperchromatic and crowded with some nuclear stratification, and crypts start branching. Further down the spectrum, a combination of features gives rise to an increased nuclear to cytoplasmic ratio. Changes in crypt architecture get more conspicuous and an increased number of mitoses can be found at all levels in the crypt. These changes are classified as low grade or high grade. Histopathologic grading in general is subjective and there are limitations to reproducibility.

**Malignant Polyps (Figure 6)**
Malignant polyp designates an adenomatous polyp with a focus of invasive carcinoma. A polyp consisting entirely of carcinoma, however, is called a polypoid carcinoma.

**Serrated Lesions Including Hyperplastic Polyps (Figure 7)**
In the recent polyp literature much attention has focused on serrated lesions of the large intestine. These are a heterogeneous group of lesions that share a phenotypic characteristic. The epithelial layer of these lesions under the microscope reveals a saw tooth or “serrated” pattern.

Ordinary and innocent hyperplastic polyps (Figure 7) are by far the most common serrated lesions. These

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hyperplastic polyps, especially in the rectum, are usually small (< 0.5 cm) and show a characteristic serrated or saw-tooth appearance of the upper part of the crypts with clear mucin production. The nuclei are smallest in the superficial part of the crypt and show no stratification or hyperchromatism, like nuclei in adenomas. A rare syndrome called hyperplastic polyposis, including a wide variation of phenotypes, with larger hyperplastic polyps and multiple hyperplastic polyps especially proximal to the sigmoid, is associated with an increased risk of colorectal cancer.

Less common variants include serrated adenomas, mixed adenomas and so called sessile serrated lesions. Serrated adenomas do have a serrated epithelium, but nuclear changes resemble those of adenomas (Figure 7), with enlargement, stratification and mitoses. In “ordinary” adenomas, but also adenocarcinomas, individual crypts with a serrated phenotype can occasionally be recognized under the microscope. When this is a very apparent feature, such adenomas are classified as mixed adenomas. In terms of management, serrated and mixed adenomas usually are dealt with like traditional adenomas.

The sessile serrated lesion is a particularly interesting entity. These lesions also have a serrated epithelium, but do not show nuclear atypia and hence no dysplasia and they mostly are flat or slightly elevated, but not polypoid. Typically crypts with a wider basis (“boot like”) can be recognized. These lesions have been associated with BRAF mutations and MSI colorectal cancer and are typically right sided and difficult to recognize. The frequency of these lesions in most series does not exceed 5%.

The pathology discussion above should give clinicians the security to look at most polyps (adenomas) as harmless and to be skeptical of the importance emphasized by some of a 25-65% miss rate in screening with tests other than colonoscopy. In the U.S. in 2011 the “colonoscopy is the best and/or preferred screening test option” remains in place even though there is emerging evidence that protection of the right colon from CRC by screening colonoscopy is significantly less than protection for the left colon.20-24 No randomized controlled trials have been completed showing colonoscopy every 10 years is a better screening test than the others recommended in the USPSTF Guidelines25 though two such trials have just begun. A decision analysis published with the

USPSTF guidelines did show that 4 screening strategies provided similar life-years gained: colonoscopy every 10 years, annual Hemoccult SENSA testing or fecal immunochemical testing, and sensitive FOBT every 2 to 3 years with 5-yearly sigmoidoscopy assuming equally high adherence.26 Recently published European Union CRC guidelines27 concluded that it was necessary to wait for the results of a randomized controlled trial before definite conclusions about the effectiveness of colonoscopy can be drawn.
Health policy decisions on which population screening test is best are difficult and should not be made as a result of over diagnosis of one of the main target lesions, the colonic polyp. These decisions will be more informed as more evidence becomes available. Until then, transparency and available evidence behooves gastroenterologists and their societies to encourage use of any and all of the evidence based recommended screening tests in the United States Preventive Services Task Force CRC guidelines. Much more screening will be done if primary care providers and the American public are not made to feel screening tests other than optical colonoscopy are ineffective. Of note, many European countries with national population based screening programs have after thorough evaluation of all evidence, reached the conclusion that fecal immunochemical testing, rather than colonoscopy is their best option for reducing death from colorectal cancer.27

References

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