

Seymour Katz, M.D., Series Editor

## Colonoscopic Surveillance and Burglar Alarms in IBD

by David B. Sachar

**D**ebates about the merits of colonoscopic surveillance for cancer in IBD tend to become embroiled in statistics: sensitivity, predictive values, risk assessments, cost-benefit analyses, etc. But what is it really all about? Fundamentally, it is nothing more than a decision about whether or not to buy something. The decision-making process about adopting a colonoscopic surveillance system, then, is essentially no different from deciding about buying an electronic surveillance system—i.e., a burglar alarm.

So what is the first question we ask ourselves when contemplating the purchase of a burglar alarm system at home? We ask ourselves, “**Do we really need it?**” In other words, how big is the risk? Well then, how big is the risk of developing a cancer in a long-standing case of colitis? That depends, of course, on who’s counting. Retrospective studies from tertiary referral centers tend to *overestimate* the risk on account of referral bias. Cohort studies from private practices tend to *underestimate* the risk if they fail to correct for short durations of follow-up, losses to follow-up, or removal from the population at risk by colectomy or mortality.

Nonetheless, the best statistics from population studies tend to agree that the incidence of colorectal cancer in extensive colitis, after the first 8–10 years of disease, is approximately 0.5%–1.0% per year (1–3). Most clinicians and epidemiologists alike, as well as patients, would consider this level of risk sufficient to take at least some protective action.

Once we have determined that there may be a need for some kind of burglar alarm, we then want to know

whether the particular product we’re considering will be worthwhile. Specifically, **if the alarm goes off, will anyone respond in time?** Having a bell go off won’t be of much use if the house is cleaned out and the burglars have escaped before the police arrive. Likewise, an “early-detection” system for cancer won’t help if the cancer is already incurable when first found.

Here again, though, the signals are favorable in support of the product. The prognosis of colitis-associated cancers when detected early seems to be every bit as good as cancers detected early in the general population (4). A surveillance system, therefore, should not be an exercise in futility.

Hence we come to our third question, a critical test of the efficacy of the system: **If someone tries to break in, will the alarm reliably go off?** If a cancer is brewing, how sure can we be that our surveillance program will pick it up? In statistical terms, this issue is nothing more than sensitivity. Once again, it depends on how we do the counting. It has been suggested, though, that thorough and aggressive sampling can yield sensitivities for dysplasia as high as 70%–85% (5). We might want more sensitive detectors in our houses, but as biological systems go, that’s not bad.

On the other hand, the biggest consumer concern about electronic surveillance systems might well be false alarms. Hence the question, **If the alarm goes off, can we be sure someone is really trying to break in?** People often phrase this issue as one of specificity, but actually that is not correct. *Specificity* is a concept with relatively limited application in clinical medicine; it can be construed as asking the question, “When no-one is trying to break in, how confident can I be that the

(continued on page 16)

---

David B. Sachar, M.D., FACP, MACG, Mount Sinai School of Medicine, New York, NY

(continued from page 14)

alarm will not go off?" The more precise statistical term for the practical question in bold type above is *positive predictive value*. In other words, if my surveillance biopsies show dysplasia, what is the likelihood that a cancer is actually present or will develop?

There is extensive literature pertaining to this issue, and it is subject to varying interpretations. If we boil it all down and state it in the simplest possible terms, though, it is not unreasonable to estimate that a finding of definite low-grade dysplasia in flat mucosa (not a fully-excisable polyp) carries about a 50% positive predictive value for synchronous or ultimate cancer development, while high-grade dysplasia carries as much as an 80% likelihood of present or future cancer (6–7). This is not an alarm that we can afford to ignore.

These first four questions will have moved us a long way toward our decision about acquiring a surveillance system, be it colonoscopic for cancer or electronic for burglary. But at this point, further more detailed questions will arise about the suitability of particular systems for our specific needs. For example, the next question might well pertain to the operating reliability of the system: **What happens if it breaks down?**

Certainly, there are several scenarios in which colonoscopic surveillance seems to be no longer feasible. Suppose there is a stricture I can't pass? Suppose there are too many pseudopolyps for me to be able to tell what's going on? It is at this point that a human element has to get introduced into the system. Burglar alarms that connect directly and automatically to police stations have more problems than those that are routed first through a staffed central monitoring station for evaluation. Likewise, operator skill and judgment enter the equation when colonoscopy is complicated by strictures or pseudopolyps. Options include pediatric scopes, dilation procedures, chromoendoscopy, intuitive selection of the most "suspicious" polyps, switching to backup systems (barium enema), or sending the cops just to be sure (colectomy). (8,9)

Question number six is perhaps the most practical and all-embracing: **What is the track record of the system?** Or as the old automobile advertisement used to say in a less politically correct generation: "Ask the man who owns one!" Among the published reports of surveillance program outcome (10,11), perhaps the most thorough and authoritative experience is that of

Lennard-Jones et al. in London (10). In a 30-year follow-up of 471 ulcerative colitis patients enrolled in surveillance, 5% developed colorectal cancer: 2% had Dukes A classification and all survived ("cancer cure"), 2% had Dukes B and also survived ("cancer control"), and 1% (4 patients) died of cancer ("system failure"). Given the facts that over a lifetime, 5% of a western population develops colorectal cancer and that 2.5% ultimately die of the disease, and considering that all 4 patients in the U.K. series were surveillance protocol violators, these figures represent a reasonably strong endorsement of the product under consideration—a regulated program of colonoscopic and clinical surveillance.

Next comes a question that is universal and unavoidable: **How much does it cost?** There are innumerable methods for calculating costs and cost-benefit ratios in medicine as in any other business. One reasonable and representative analysis has put the figure for colonoscopic surveillance, including all ancillary services and complications, at approximately \$100,000 per cancer detected or prevented (12). But this is not the whole story.

Skeptics will argue, correctly, that not every cancer detected and cured through surveillance is an *extra* life saved because 50% of cancers that are *not* found by surveillance are cured anyhow. Therefore, the cost per *extra* life saved by the program is actually double, or \$200,000. True enough, but we must remember that colorectal cancers detected in ulcerative colitis patients by colonoscopic surveillance are found on the average about 20 years *younger* than similar cancers arising in the general population. Hence, when considering the program cost *per year of life saved*, we come up with a figure of approximately \$5000, a tremendous bargain by any public health standards.

Once the preceding seven questions have been answered to some satisfaction, a few broader issues remain to be considered. Hence, the eighth question might well be, **Do I have any real choice in this matter?** As a case in point, some insurance companies have moved from offering discounted premiums for homes provided with any burglar alarms to refusing altogether to insure a home *unless* it has a specific approved alarm system. By the same token, the medical system has a

(continued on page 19)

(continued from page 16)

tendency to creep insidiously from recommendations to guidelines, from guidelines to standards, and from standards to mandates (13). The day may already be upon us when the mere occurrence of a colorectal cancer in a colitis patient who has not been on the strictest possible program of colonoscopic surveillance will be construed as *ipso facto* proof of negligence, irrespective of subtle interpretations of the evidence.

Related to this issue of varying interpretations of the scientific evidence is the question of whether the best science and the best statistics underlie our surveillance practice, **or are we merely buying a false sense of security?** What are we really buying with this system: a life-saving procedure or a bill of goods? Are we saving lives in a cost-effective manner, or are we just going through motions to make us feel better, to protect ourselves from legal liability, and to gain peace of mind? The arguments of skeptics are cogent and powerful (14), but the weight of answers to all the preceding questions seem to me to militate in favor of current practice, imperfect as it may still be.

This last phrase, then, leads to our last and most forward-looking question: **Is there anything better out there?** Surely there must be a better method of cancer prevention than relying on varying intensities of follow-up, varying skills of colonoscopists, varying numbers and spacing of biopsies, varying pathologic interpretations of dysplasia, and varying reactions of doctors and patients to the reported findings. Most certainly, there are many new and emerging technologies offering promise as better markers than dysplasia for cancer risk (15–17): DNA markers in stool; aneuploidy; p53, hMSH2, and other mutations; assays for sialyl Tn, sucrase-isomaltase, Ki-67 and other indicators; loss of beta-catenin; and numerous other approaches in animal models and human patients. The problem, of course, is that all these other systems are still in various degrees of testing; none is yet “on the market.” Ideally, chemoprevention might be an even better strategy—like remembering to lock your doors when you leave the house. The possible benefits of 5-aminosalicylate maintenance therapy have attracted much recent attention in this regard (18–20).

So once all is said and done, what do I do? Simply this: I have installed an electronic surveillance system to protect my home; I recommend a regular colono-

scopic surveillance program to protect my patients while I wait for something better to come along. ■

## References

- Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*, 2001;48:526-535.
- Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med*, 1990;323:1228-1233.
- Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut*, 1994;35:1590-1592.
- Sugita A, Greenstein AJ, Ribeiro MB, Sachar DB, Bodian C, Panday AK, Szporn A, Pozner J, Heimann T, Palmer M, et al. Survival with colorectal cancer in ulcerative colitis. A study of 102 cases. *Ann Surg*, 1993;218:189-195.
- Taylor BA, Pemberton JH, Carpenter HA, Levin KE, Schroeder KW, Welling DR, Spencer MP, Zinsmeister AR. Dysplasia in chronic ulcerative colitis: implications for colonoscopic surveillance. *Dis Colon Rectum*, 1992;35:950-956.
- Bernstein CN. Cancer surveillance in inflammatory bowel disease. *Curr Gastroenterol Rep*, 1999;1:496-504.
- Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology*, 2003;125:1311-1319.
- Friedman S, Rubin PH, Bodian C, Goldstein E, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's colitis. *Gastroenterology*, 2001;120:820-826.
- Saunders BP, Brown GJ, Lemann M, et al. Balloon dilation of ileocolonic strictures in Crohn's disease. *Endoscopy*, 2004;36:1001-1007.
- Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology*, 1994;107:934-944.
- Karlen P, Kornfeld D, Brostrom O, Lofberg R, Persson PG, Ekbom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. *Gut*, 1998;42:711-714.
- Provenzale D, Kowdley KV, Arora S, Wong JB. Prophylactic colectomy or surveillance for chronic ulcerative colitis? A decision analysis. *Gastroenterology*, 1995;109:1188-1196.
- Latov N. Evidence-based guidelines: not recommended. *J Am Phys Surg*, 2005;10:18-19.
- Axon A. Endoscopic surveillance in ulcerative colitis still does not work. *Gastroenterology*, 1995;109:1720.
- Brentnall TA. Molecular underpinnings of cancer in ulcerative colitis. *Curr Opin Gastroenterol*, 2003;19:64-68.
- Itzkowitz SH. Colon carcinogenesis in inflammatory bowel disease: applying molecular genetics to clinical practice. *J Clin Gastroenterol*, 2003;36(5 Suppl):S70-S74.
- Chambers WM, Warren BF, Jewell DP, Mortensen NJ. Cancer surveillance in ulcerative colitis. *Br J Surg*, 2005;92:928-936.
- Eaden J. Review article: the data supporting a role for aminosalicylates in the chemoprevention of colorectal cancer in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*, 2003;18 Suppl 2:15-21.
- Bernstein CN, Eaden J, Steinhart AH, Munkholm P, Gordon PH. Cancer prevention in inflammatory bowel disease and the chemoprophylactic potential of 5-aminosalicylic acid. *Inflamm Bowel Dis*, 2002;8:356-361.
- Itzkowitz SH, Present DH, Crohn's and Colitis Foundation of America Colon Cancer in IBD Study Group. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis*, 2005;11:314-321.