

Screening and surveillance for colorectal neoplasia: uncertainties of colonoscopic management

Joel S. Levine

University of Colorado Denver, School of Medicine, Aurora, CL, USA

Abstract: Over the past decade the use of screening and surveillance modalities has been associated with a small but significant decrease in the incidence of colorectal cancer and an increase in curability of lesions that are found. Although consensus-based international guidelines have stressed the variety of possible diagnostic options that can serve this purpose, in many countries colonoscopy with removal of all polyps has become the test of choice. The evidence-base for this choice is largely derivative rather than direct and prospective, and many uncertainties remain in its use as a primary screening modality. This review examines our current guidelines relative to risk stratifying the populations offered the test; the onset, interval, and discontinuation of testing; and the important role of operator variability in outcome.

Key words: colorectal cancer, colonoscopy, preventive health, screening

It is estimated that in the United States this year colorectal cancer (CRC) will be diagnosed in almost 150,000 people; of whom almost 50,000 will die, making CRC the second most common cause of cancer death in the country [1]. Cumulatively 1:20 in the population will get CRC during their lifetime. It is generally accepted that smaller growths, colonic adenomas, are the precursors of almost all sporadic CRCs and are among the most common human neoplasms, being found in over 40% of the population by age 60 [2].

The progression from normal mucosa to small tubular adenoma to larger adenomas and those with more advanced histologic features (villous histology and/or high grade dysplasia) to CRC, the adenoma-carcinoma sequence, has become the paradigm of our understanding and management of colonic adenomas. Within the past decade in the United States, in the absence of large randomized controlled prospective trials, removing polyps found at the time of screening colonoscopy performed every 10 years and the subsequent earlier surveillance of those in whom the polyps are found to be adenomas have become public health measures codified by the public and private payment for colonoscopy. The tangible value of this intervention on the health of the public will not be forthcoming for another decade.

An excellent recent review is available to understand current practice guidelines, and the multiple modalities that can

be employed in screening and surveillance to reduce the risk of CRC [3]. The focus of this review will be restricted to uncertainties that remain relative to one aspect of the current *clinical* paradigm, the use as reflected in consensus guidelines of colonoscopic screening and surveillance for adenomas and CRC.

Uncertainties relating to colonoscopic screening for CRC

Colonic adenomas usually do not cause symptoms and are most commonly found during endoscopic or radiologic imaging studies obtained because of unrelated symptoms or for CRC screening. Current guidelines [3] recommend that screening begin after age 50 in the absence of risk factors (CRC in a first degree family member; having risk factors for one of the familial polyposis syndromes; having ulcerative colitis or Crohn colitis >8–10 years) and with repeat screening in 10 years if the colonoscopy is negative. Although not all colonic polyps are adenomas (hyperplastic polyps account for about half of small recto-sigmoid polyps), and the majority of adenomas (>90%) do not progress to cancer, it is currently not possible during endoscopy to reliably identify the minority that will progress. Thus, the recommendation is that all colon polyps found during colonoscopy be removed.

How effective is colonoscopic screening?

Optimistic initial predictions, based on the effectiveness of flexible sigmoidoscopy and case controlled studies, that societal screening with colonoscopy could reduce the incidence of CRC by as much as 70–80% have been tempered by efficacy evaluations in practice and the variability of outcome of

Correspondence to:

Professor Joel S. Levine, MD, FACP, University of Colorado Denver, School of Medicine, Academic Office Building 1, 12631 E. 17th Avenue, Rm 7614, MS B-158, P.O. Box 6511, Aurora, CL, USA 80045, phone: 001-303-724-1858, fax: 001-303-724-1891, e-mail: joel.levine@uchsc.edu

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colonoscopy. It has been demonstrated that the detection rate for adenomas and cancer may vary as much as two-fold as a consequence of the adequacy of the bowel preparation [4], the inconsistency in technical performance based on training, and simple measures such as colonoscopy withdrawal time [5-8]. In practice therefore estimates of a 50–60% reduction in CRC, although still substantial, are more realistic.

Are there additional subgroups of patients that should be screened differently?

Guidelines do not currently address many important smaller subgroups of patients in whom epidemiological studies have demonstrated an increased risk of adenomas and CRC. As more patients have prolonged survival after receiving chemo/radiotherapy for cancer, or receive long term immune modulation for auto-immune diseases or organ transplantation, second malignancies, including CRC, become more common. Patients with acromegaly, particularly the sub-group with fasting hyperinsulinemia [9], are more likely to have adenomas. Reports of increased prevalence of CRC in patients with breast cancer, celiac disease, who smoke cigarettes [10], or are obese are also recognized. However, guidelines do not direct that screening should be done earlier or more frequently in these groups. In the absence of guidance management is highly variable and left to the evaluation of the individual patient by the referring physician. At a minimum, extra effort should be undertaken to assure that these patients get to screening at an appropriate time, perhaps using the immunologic tests for blood in stool more frequently, as a positive test leads to colonoscopy.

When should screening begin in patients whose relatives had “polyps”

There is epidemiologic evidence that a history of adenomas in a first degree relative can carry the same increased risk of developing CRC as does a history of CRC. The latter risk (doubling) has led to recommendations for earlier and more frequent colonoscopy. The risk of “polyps”, however, is limited to those with known “advanced adenomas” (adenomas that are large [≥ 1 cm] or contain any advanced histologic features [tubulovillous or villous histology, high grade dysplasia] or when the adenoma is detected at a younger age (<60 years) [11-13]. It has been recommended that first degree relatives of patients who have had colonic adenomas detected before age 60 should begin colonoscopic screening at age 40 [14] but this recommendation has not been validated in controlled trials. Thus if earlier, or more frequent, colonoscopy is desired by the patient or referring physician there is an obligation to obtain the original endoscopic and pathologic data from the family member to document the size and histology of the resected polyp. In its absence, we keep such patients in

a standard risk category beginning screening at age 50 and 10 years thereafter.

When should screening be started and stopped?

The age of 50 as the time to start screening is arbitrary, understanding that adenomas and CRC do occur uncommonly/rarely in the young. If enough 20 year olds are screened disease would be found, but the number needed to treat would be extraordinary. Colorectal cancer is predominantly a disease of the elderly and the yield of any intervention will always be greater the older the patient is at the time of screening. The guideline, appropriately, tries to balance the risk, benefit, and cost of the procedure. Such overt attempt at societal-based balancing of resources has not been commonly included in the discussions of the very elderly or infirm in the United States. Most consensus guidelines in the United States are mute as to what age screening should be discontinued. Recent analytic work weighing risks and benefits has suggested that screening colonoscopy should not be undertaken in the patient with a predicted life span of less than 5 years, a benchmark that is difficult for even the healthy patient >85 years old to achieve [15].

When should screening be repeated?

Recommendations to repeat screening at all, or in a defined period of time (10 years), after a negative screening study depend on assumptions of the time it takes to go from normal mucosa to cancer that have a weak evidence base. Recognizing that the yield of adenomas varies greatly among colonoscopists (see above), and that as much as 50% of metachronous cancer found within 5 years of a screening colonoscopy might be related to missed lesions on the initial screening [2], one could suggest earlier re-screening in average risk patients. However, the societal cost of such a recommendation (diverting resources from other worthy interventions that might improve other health outcomes) would be great. Thus, our current paradigm is being balanced against the willingness of the public to pay and the risk of the procedure. Alternative protocols that would use other screening modalities such as stool tests for blood or DNA mutations [1] to decide on the timing of subsequent colonoscopy (or replacing colonoscopy with computed tomography [CT] colonography) deserve study.

Uncertainties relating to colonoscopic surveillance for adenomas

Excising an adenoma eliminates the risk of CRC from that adenoma but the finding of colonic adenomas can be an indicator of an increased risk of subsequent adenomas and CRC for the patient. That risk is variable and related to the size, number, and histology of the polyps resected in the index colonoscopy. In the most recently published guidelines, that

are the current standard in the United States, surveillance recommendations (Tab.) are stratified based on the colonoscopic and pathologic findings of resected adenomas [3].

Patients with small (<1 cm) recto-sigmoid hyperplastic polyps are considered to have a normal colonoscopy and should continue to be screened; if colonoscopic screening is chosen a 10 year interval is recommended. Patients with high-risk adenomas (3–10 total adenomas or any advanced adenoma) are advised to have their next surveillance examination earlier (3 year interval) than those with only 1–2 small tubular adenomas (5–10 year interval depending on the clinician's judgement and the patient's preference). Earlier follow-up is recommended for patients with more than 10 adenomas (<3 year) and in those with large sessile adenomas that are removed piecemeal or when the polypectomy is incomplete (2–6 months) and more intensive surveillance is advised if the family history suggests a familial colon cancer syndrome.

Since expert endoscopists typically find one or more adenomas in more than 25% of men and 15% women undergoing colonoscopic screening, the cumulative burden of subsequent surveillance colonoscopy on the health care system is substantial. In 1999, it was estimated that the indication for 25% of the colonoscopies performed by gastroenterologists in the United States was for follow up of previous polyps and there has been a marked increase in endoscopic screening since that time [16]. Thus, the number of individuals found to have colonic adenomas and being advised to undergo regular colonoscopic surveillance is both substantial and increasing. This is compounded because in clinical practice surveillance colonoscopy is too often recommended at intervals shorter than needed. Over 50% of gastroenterologists and colorectal surgeons, and family physicians reported that they routinely recommend colonoscopy at more frequent intervals than the published guidelines at that time [17–18]. Excessive colonoscopic surveillance is expensive and diverts substantial endoscopic capacity away from screening efforts that would have a greater impact on colorectal cancer prevention. That this is occurring at a time when over 50% of patients with advanced adenomas and cancer are not returning for appropriate surveillance [19] magnifies the ineffectiveness of our current process of care.

How effective is colonoscopic surveillance?

If the adenoma is the major precursor of CRC and if patients with advanced adenomas have a high risk of developing subsequent adenomas, surveillance colonoscopy with removal of adenomas should substantially decrease CRC risk. Only indirect evidence is available, however, to assess the magnitude of the benefit of guideline recommended colonoscopic surveillance, and there have been no prospective controlled trials comparing this approach to any other follow-up method. Studies in the United States [20] and Europe [21] both reported an incidence rate of colorectal cancer that were 66–76% lower than registry-based estimates of rates in the

Table. Consensus guidelines for colonoscopic surveillance in United States

Colonoscopic findings	Recommended interval for next colonoscopy
Small hyperplastic polyps	10 years or other average risk screening option
1–2 low risk adenomas*	5–10 years
3–10 low risk adenomas or any high risk adenoma#	3 years
>10 adenomas	<3 years
Inadequately removed adenomas	2–6 months

* Low risk adenomas – <1 cm tubular adenomas
 # High risk adenomas – any large (>1cm), or histologically advanced (tubulovillous, villous or high grade dysplasia) adenoma

general population and 88–90% lower than historic controls with adenomas. In contrast, 2–4 fold higher CRC incidence rates have been reported in several other cohorts who have been under colonoscopic surveillance after polypectomy [22–24]. These higher rates translate into substantially lower estimates of CRC risk reduction, rates that are closer to that of the unscreened general population; raising the question as to whether surveillance provides any added benefit to that obtained from the screening colonoscopy. All of the estimates are uncertain, however, because of the lack of adequate control groups. Regardless of the precise magnitude of the benefit, prospective trials have established that colonoscopic polypectomy and surveillance is not a perfect preventive approach and patients need to be informed of its limitations as well as its benefits.

When should surveillance colonoscopy be stopped?

There are no controlled trials to guide decisions about when surveillance should be stopped. The risk and discomfort of colonoscopy (including the preparation and sedation) increases above the age of 80 (see above). Similarly, no guideline has questioned the value of continued surveillance after one or more negative colonoscopies in patients who initially had an adenoma. How many negative surveillance colonoscopies should lead to a return to routine screening for CRC? Our current practice is to return to routine screening after one negative surveillance exam in patients with fewer than 3 small adenomas, but to continue more intensive surveillance in the advanced adenoma and CRC follow up groups. As with screening we recommend that surveillance in individuals with an estimated life expectancy of less than 5 years be discontinued. Using CT colonography or stool analyses for blood or DNA mutations [3] to either replace or complement surveillance colonoscopy seems logical in low risk patients.

Are serrated adenomas or large hyperplastic polyps risk factors for subsequent CRC?

The role of some hyperplastic polyps and sessile serrated adenomas as precursors to CRC is uncertain. Sessile serrated adenomas share the serrated luminal border that is characteristic of hyperplastic polyps but also have unequivocal epithelial dysplasia. As serrated adenomas cannot be distinguished visually from flat adenomas, which have a strong association with dysplasia and CRC [25], they should all be removed when found. Although small left sided hyperplastic polyps are not thought to progress to CRC, recent clinical and molecular analyses suggest that large (≥ 1 cm) hyperplastic polyps and/or sessile serrated adenomas may be the precursors of a type of sporadic DNA microsatellite unstable CRC [26]. The natural history of these large hyperplastic polyps and sessile serrated adenomas is not well defined and appropriate surveillance intervals are not established. In the absence of data such patients are often followed as if they had adenomas [2].

SUMMARY

Evidence is slowly accruing that the public policies recommended by current guidelines are reducing the incidence and increasing the curability of CRC. Current clinical practice is to remove all colonic polyps at the time of screening colonoscopy and to recommend ongoing surveillance colonoscopy at intervals that depend on the number and types of adenoma found. This said, many uncertainties remain, particularly relating to the value, and intervals, of surveillance colonoscopy and the potential utility of imaging or stool tests to further refine current recommendations.

Although colonoscopic polypectomy and ongoing surveillance is expected to substantially decrease CRC incidence and mortality, it is far from perfect and the precise magnitude of the benefit is not known. Both the quality of colonoscopic performance and the adherence to surveillance guidelines is currently quite variable and improvements in both would be expected to substantially increase the clinical- and cost-effectiveness of colonoscopic polypectomy and surveillance.

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