



Update in Surveillance Recommendations in Individuals With Conventional Adenomas

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Abstract

Purpose of review Conventional adenomas, which are precursors to almost 70% of colorectal carcinomas, are found in more than one-third of screening colonoscopies. Surveillance recommendations, based on adenoma size, histology, and number, have evolved over the years and are currently reflective of index adenoma categorization as either low-risk (LRA) or high-risk (HRA). In this review, recent guideline recommendations as well as primary data that have helped to shape these recommendations are presented.

Recent findings Recent data have demonstrated that individuals with HRA on index exams may be at increased risk for CRC while those with LRA may have a minimal long-term risk

for CRC, similar to those adults with normal index exams. Furthermore, the quality of the index exams is important for minimizing CRC risk.

Summary While individuals with HRA may require close surveillance intervals of 3 years, those with LRA or normal exams may need longer such as 10-year follow-up.

Introduction

In the USA, colorectal cancer (CRC) is the fourth most common cancer in adults and the second leading cause of cancer death. About 1 in 22 men and 1 in 24 women will develop CRC in their lifetime. Despite an estimated 140,250 new cases and 50,630 deaths attributed to it in 2018, the incidence and mortality rate of CRC have been slowly but steadily decreasing over the past several decades, with a 22% decline in the latter seen from 1975 to 2000 [1, 2]. While risk factor reduction is contributing to this decline, the availability and acceptance of colon cancer screening have played a major role [2, 3].

Adenocarcinomas constitute over 95% of all colorectal cancers. The classical pathway (conventional adenoma-adenocarcinoma sequence) and a more recently described alternative pathway (serrated class lesions including sessile serrated adenoma/traditional serrated adenoma-adenocarcinoma sequence) represent the two main pathways of colorectal carcinogenesis [4, 5]. The management of conventional adenomatous polyps, believed to be precursors to almost 70% of carcinomas and detectable in greater than one-third of patients undergoing screening colonoscopy [6], will be the focus of this review.

Multiple modalities are available for CRC screening. Due to significant societal disparities in the performance and the cost, the United States Multi-Society Task Force (USMSTF) recently grouped such tests into three tiers, with tier 1 options including colonoscopy and annual fecal immunochemical test (FIT) being the preferred modalities [7]. Unlike with more inaccessible cancers, early detection and prevention of CRC can be achieved by screening with colonoscopy or flexible sigmoidoscopy [8].

Most sporadic CRC is believed to follow a slow stepwise polyp-to-cancer progression with adenomas recognized as precursors of CRC with malignant potential [9]. As such, the removal of these precancerous lesions is important in reducing the incidence and mortality of colorectal cancer [10]. Following their detection and removal, appropriate surveillance is important due to the risk of recurrent adenomatous polyps on follow-

up [11], with particular concern for metachronous advanced neoplasia (tubular adenoma [TA] ≥ 10 mm or adenoma with high-grade dysplasia (HGD) or with $> 25\%$ villous features) or CRC in those with high-risk lesions on index examination [11–15]. Conversely, over surveillance may be associated with unnecessary risk and cost.

Currently, recommendations call for protracted surveillance interval of 10 years in individuals with a normal exam or only distal small (< 10 mm) hyperplastic polyps (HP) and no family history of CRC [16], based on the premise that the adenoma-carcinoma sequence typically takes > 10 years in sporadic cancers. Data from several studies have demonstrated the low risk of metachronous advanced neoplasia after negative findings on index colonoscopy including that from the VA Cooperative Study (5.5-year interval) [17] and Lilly Colorectal Cancer Screening Program (5.3-year interval average) [18], supporting a screening interval longer than 5 years. Subsequently, the German colonoscopy screening program (11.9-year interval average) [19] and a more recent retrospective study by Ponugoti and Rex (9.7-year interval average) [20] showed a similarly low risk of advanced lesions at a longer-interval follow-up colonoscopy, supporting current recommendations for screening at 10-year intervals in average-risk individuals. Meanwhile, data from the Polyp Prevention Trial demonstrated no increased risk of adenoma (with or without advanced features) recurrence in those with coexisting hyperplastic and adenomatous polyps, regardless of HP location, within 3 years of follow-up evaluation [21].

For those patients with conventional adenomatous polyps on index colonoscopy, current guidelines categorize them into two separate groups: (1) low-risk adenomas (LRAs)—1–2 small TAs < 10 mm and (2) high-risk adenomas (HRAs)— ≥ 3 non-advanced adenomas or advanced adenomas [16]. Due to their increased risk of recurrent adenomatous polyps, closer surveillance colonoscopy is warranted.

In the next few sections, we will review the evidence behind current surveillance recommendations for these polyps and highlight new data that may shape future directions.

Most advanced finding on index examination = LRA (1–2 TAs < 10 mm)

In one of the earliest studies looking at the risk of interval neoplasia, Wayne et al. [22] showed 56% of patients following adenoma removal on index colonoscopy had further adenomas (i.e., metachronous lesions) on repeat examination at 1 year, leading to the recommendation for annual surveillance following polypectomy. However, subsequent data from the National Polyp Study demonstrated no significant difference in the proportion of advanced neoplasia (advanced adenoma or invasive cancer) detected at 1-year or 3-year follow-up following adenoma removal, allowing for prolonging of surveillance intervals to 3 years after adenoma removal [11]. A multivariate analysis from this study showed adenoma multiplicity (≥ 3) to be an independent risk factor for detection of advanced adenoma on follow-up colonoscopy, foreshadowing the eventual re-stratification of adenomas into high- and low-risk subgroups, with the latter possibly benefiting from prolonged surveillance intervals.

Over the last decade or so, numerous studies have established LRAs as being associated with a low risk for the development of metachronous advanced adenomas [17, 23–27]. Among these were the Polyp Prevention Trial [24], NCI Pooling Project [25], VA Cooperative Study [17], and PLCO Cancer Study [27], the data from which demonstrate a lower risk for interval advanced neoplasia in this LRA group in comparison with HRAs and a similar risk to that of a non-adenomatous group.

While these studies signify the low risk for metachronous advanced lesions, others have also highlighted the low risk of long-term CRC incidence in the LRA group. An early study by Atkin et al. looking at the long-term risk of CRC after rectosigmoid adenoma excision showed that patients with only a single, small TA with mild or moderate dysplasia were at no higher risk for CRC than the general population over a 14-year follow-up period (RR 0.4; 95% CI 0.0–1.3) [12]. Meanwhile, using data from the PLCO Cancer Study, Click et al. [6•] showed no significant increase in the risk of CRC between LRAs and a non-adenomatous group (RR 1.2; 95% CI 0.8–1.7) over a 12.9-year median follow-up. This landmark study provides data that will support lengthening surveillance intervals for LRA. It should be noted however that the authors point out the wide confidence intervals in the RR for the LRA. In addition, the individuals with LRA received more surveillance than individuals without adenomas. Thus, more data are needed to support longer intervals for LRA. A more recent meta-analysis by Dubé et al. [28] also showed a significantly lower risk of CRC (and CRC-related death) in this group in comparison with the general population at a median follow-up of 7.7 years (OR 0.68; 95% CI 0.44–0.99).

Examination of the literature reveals that LRAs do not confer an increased risk of metachronous advanced neoplasia. Data such as these have shaped the current USMSTF recommendation for 5–10-year surveillance interval in this group, with other clinical factors including quality of colonoscopy, family

history, physician judgment, and patient preference as keys influencing the timing of repeat examination [16, 29]. Yet despite this wealth of data, many endoscopists fail to adhere to these surveillance guidelines, a recognized quality indicator, as seen by the frequent recommendation for shorter surveillance intervals for individuals with LRAs despite no variability in detection of pathologically important lesions at an earlier time [30].

Aside from a meta-analysis by Dubé et al. showing a small albeit significantly increased risk of advanced adenoma development in individuals with LRAs—the clinical significance of which was questioned—the literature is supportive of the fact that LRAs do not confer a higher risk of metachronous advanced lesions or long-term colorectal cancer incidence. More recently accumulated data may also go as far in helping to categorize this group as lower than average risk in the future and lends support to a surveillance interval closer to 10 years for this population.

Most advanced finding on index examination = 3–10 non-advanced adenomas

An association between adenoma multiplicity and metachronous advanced adenomas has been demonstrated in multiple studies. In a meta-analysis, Saini et al. [23] examined the incidence of advanced adenomas at 3-year surveillance among HRA and LRA patients, showing an increased risk of recurrent advanced adenomas in patients with three or more non-advanced adenomas on index colonoscopy as compared with patients with LRAs (RR 2.52; 95% CI 1.07–5.97). Similarly, in the multivariate analyses of the data obtained in the NCI Pooling Project, Martinez et al. [13] showed an independent association between the number of prior adenomas and the risk of metachronous advanced neoplasia, with a linear increase in risk with each additional baseline adenoma. Adding to this, the VA Cooperative Study demonstrated a significantly increased risk of advanced neoplasia at 5 years in patients with 3 or more TAs < 10 mm at baseline in comparison with those without neoplasia at baseline (RR 5.01; 95% CI 2.10–11.96). This higher risk was also observed in comparison with those with 1–2 small TAs [17].

Findings from these studies, along with others suggesting an increased risk of missed lesions with polyp multiplicity on index colonoscopy [31–34], are reflected in the USMSTF recommendation for a 3-year interval colonoscopy for 3–10 non-advanced adenomas due to a level of risk similar to those with advanced neoplasia at baseline.

Not all studies, however, support the concept that ≥ 3 adenomas are a high-risk group. Click et al. [6•], in their prospective post hoc analysis of data from PLCO Cancer Screening trial, also examined the influence of multiplicity of non-advanced adenomas found during index colonoscopy on long-term risk of CRC incidence. No significant difference in cancer incidence was noted between those with ≥ 3 non-advanced adenomas in comparison with those with 1 to 2 non-advanced adenomas (RR 1.01; 95% CI 0.4–2.4) on index colonoscopy over a median period of 13.1 years. Unfortunately, wide confidence intervals prevent definite conclusions.

With improvements in colonoscopy and increased adenoma detection, in particular that of diminutive lesions (1–5 mm), arises the question as to whether these lesions confer the same risk of metachronous advanced neoplasia as small non-advanced polyps (6–9 mm). In a multicenter, retrospective cohort study, Moon et al. [35] evaluated the clinical significance of diminutive and small adenomas. After classifying index colonoscopy findings into five separate groups, data analysis demonstrated baseline advanced adenoma (HR 2.14; 95% CI 1.50–3.06) and 3–10 TAs (with ≥ 3 small adenomas) (HR 2.36; 95% CI 1.07–5.22) to be independent risk factors for the development of metachronous advanced neoplasia whereas 1–2 TAs, 3–10 diminutive TAs, and 3–10 TAs (with 1–2 small adenomas) were not significantly associated. More recently, Kim et al. [36] observed that having 3 or more small adenomas as opposed to 3 or more diminutive adenomas was associated with an increased risk for metachronous advanced adenomas when compared with the reference group of 1–2 non-advanced adenomas [36]. These findings challenge current guidelines suggesting multiplicity with non-advanced features is a representative of HRA and lends to the argument of stratifying multiplicity based on size. Perhaps those individuals with 3 or more diminutive adenomas could have another colonoscopy at 5 or more years after the index exam.

Most advanced finding on index examination = advanced adenoma (TA ≥ 10 mm or adenoma with HGD or with $> 25\%$ villous histologic features)

There is robust data attesting to a higher risk of metachronous advanced neoplasia among patients with advanced adenomas on index colonoscopy. Multivariate analysis of the NCI Pooling Project showed a significantly increased risk for interval advanced neoplasia in patients with baseline adenomas ≥ 10 mm (10–19 mm [OR 2.27; 95% CI 1.84–2.78], ≥ 20 mm [OR 2.99; 95% CI 2.24–4.00]); with villous or tubulovillous histology (OR 1.28; 95% CI 1.07–1.52); and with HGD (OR 1.77; 95% CI 1.41–2.22) [13]. The VA Cooperative Study showed a similarly increased risk of advanced neoplasia within 5.5 years among those with baseline advanced lesions in comparison with patients with no polyps (or LRAs). Compared with the 2.4% risk of interval advanced neoplasia in the non-adenomatous group, those with TAs > 10 mm, villous features, or high-grade dysplasia had a 15.5% (RR 6.40; 95% CI 2.74–14.94), 16.1% (RR 6.05; 95% CI 2.48–14.71), and 17.4% (RR 6.87; 95% CI 2.61–18.07) risk, respectively [17].

As can be inferred by a heightened risk of metachronous advanced lesions, the presence of advanced adenomas on index examination also confers an increased long-term risk of CRC incidence and mortality [6, 14, 15]. In their prospective post hoc analysis, Click et al. showed that in participants who underwent interval colonoscopy (9.0-year median length after index colonoscopy), there was a significantly higher rate of subsequent advanced adenoma removal (as well as all adenomas) in patients with baseline advanced adenomas in comparison with those with non-advanced or no adenomas (13.0% for advanced adenoma vs 7.6% for non-advanced adenoma [$p < 0.001$] vs 4.8% [$p < 0.001$] for no adenoma). Despite an increased subsequent colonoscopy

utilization (and interval adenoma removal), participants with index advanced adenomas remained at a significantly increased risk of CRC development (RR 2.6; 95% CI 1.9–3.7) and CRC death (RR 2.6; 95% CI 1.2–5.7) in comparison with those with no adenomas [6•].

Based on an increased short-term risk for metachronous advanced neoplasia and long-term risk for incident CRC, a 3-year surveillance interval colonoscopy is appropriate as per the current USMSTF guidelines for advanced adenomas on index examination [16]. More data has further added to the strength of these recommendations and future studies are unlikely to lead to significant change.

Consideration for quality index colonoscopies

The foundation of a successful screening colonoscopy program and associated surveillance recommendations is a high-quality index colonoscopy, which minimizes the risk of missed neoplastic lesions. Over the last several years, considerable data has emerged on the incidence of lesions missed on baseline colonoscopy and the risk of interval CRC, defined as cancer diagnosed between screening and post-screening surveillance examinations [37]. As part of the dietary Polyp Prevention Trial, Pabby et al. [38] demonstrated that 53.8% of interval cancers were either secondary to incompletely resected adenomas or to missed cancer on prior colonoscopy, meaning such cancers were potentially avoidable.

Unfortunately, many early studies on colorectal cancer screening with colonoscopy failed to comment on the quality of the index examinations. With the USMSTF implementation of colonoscopy quality benchmarks in the early 2000s [39, 40], recognition of the association between such quality indicators and the risk of interval cancer development was made evident. Quality measures such as withdrawal time and bowel preparation quality can impact adenoma detection significantly [30, 41–43]. Adenoma detection rate (ADR) has come to the forefront as the main metric for the determination of colonoscopy quality. It is now well recognized that higher ADRs are associated with lower CRC incidence and interval cancers [37, 44, 45]. Data from more than 260,000 colonoscopies demonstrated a 3% and 5% decrease in risk of interval and fatal interval CRC, respectively, with each 1% increase in ADR within the

Table 1. Surveillance intervals in individuals with baseline conventional adenomas

Baseline colonoscopy finding	Surveillance interval (current USMSTF recommendation) [16]	Future direction?
1–2 TAs ^a < 10 mm	5–10 years	10 years
3–10 TAs < 10 mm	3 years	3–10 years ^c
≥ 1 adenoma with HGD ^b	3 years	3 years
≥ 1 villous/ tubulovillous adenoma	3 years	3 years
≥ 1 TA ≥ 10 mm	3 years	3 years

Assuming high-quality index colonoscopy with complete removal of polyps
^aTA, tubular adenoma
^bHGD, high grade dysplasia
^cStratified by size (i.e., diminutive vs small adenomas)

observed range of 7.4 to 52.5% [44]. A more recent Polish prospective cohort study by Kaminski et al. [45] corroborates such findings. Data from the English Bowel Cancer Screening Program show that other technical quality indicators including cecal intubation rate, withdrawal time, bowel preparation quality, and endoscopist experience are additionally associated with increased adenoma detection, including right-sided and advanced lesions [46].

Not only is the quality of colonoscopy essential to screening efficacy but it may also influence surveillance recommendations when taken into account with other index examination findings including adenoma number, size, and histology. In a retrospective multicenter cohort study in the UK, Atkin et al. demonstrated that in an intermediate risk (1–2 adenomas ≥ 10 mm or 3–4 small adenomas) group of patients non-adherent with surveillance, suboptimal quality (incomplete or unknown completeness of exam, poor bowel preparation) of baseline examination (along with high-grade, large (> 20 mm) or proximal adenomas) was significantly associated with a higher rate of CRC incidence. In contrast, in patients without these features, CRC incidence was lower than that of the general population [47].

While these findings are unlikely to alter current USMSTF surveillance recommendations for adenomas ≥ 10 mm (an advanced adenoma), the assessment of the quality of index examination may allow for a refined re-stratification of at-risk colonoscopy subgroups.

Conclusion

Surveillance recommendations after screening colonoscopy have evolved from annual surveillance to up to 10-year intervals (see Table 1). Although the topic is beyond the scope of this review, it must be pointed out that the importance of serrated polyps in influencing CRC risk has been recognized in the past 15 years [48, 49]. New guidelines will have to account for the presence of synchronous serrated polyps which may influence the risk for metachronous adenomas [50•].

At present, there is robust data to support a 3-year surveillance interval for those with advanced lesions on index examination. The data guiding surveillance for LRAs and adenoma multiplicity however is a bit more tenuous, with the latter group benefiting from re-stratification based on size into diminutive and small adenomas. Further studies evaluating the risk of metachronous lesions by adenoma bulk (sum of baseline adenoma diameters), as described recently [51•], may also simplify risk stratification while obviating the need for histopathological assessment. More protracted surveillance intervals in these two cohorts will constrain procedure numbers and the associated aggregation of professional and related costs.

Compliance with Ethical Standards

Conflict of Interest

Rishabh Sachdev, Rahul Sao, John W. Birk, Joseph C. Anderson, and Joel Levine declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This analysis of data from the New Hampshire Colonoscopy Registry showed that the presence of index serrated polyps, especially sessile serrated polyps (SSP), can increase the risk for metachronous high-risk conventional adenomas (HRA), even greater than that for those with HRA alone. This paper also presented data that showed that large (> 1 cm) serrated polyps or SSPs predict metachronous large SPs but not HRA.

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examination predict risk of metachronous advanced neoplasia? *J Clin Gastroenterol*. 2018;52:628–34

This retrospective analysis of data from a chemoprevention trial demonstrated that a new risk stratification approach to surveillance, which involved adding adenoma size, performed as well as the conventional paradigm. Furthermore, this model did not require information about histology such as villous elements or high-grade dysplasia, which can be subject to variation in interpretation.

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