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Post-Polypectomy Colonoscopy Surveillance

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1. Introduction

Surveillance is becoming common in the practice of colonoscopy because a large number of patients with colorectal polyps are now being discovered as a result of the increased use of colorectal cancer screening, and particularly because of the dramatic increase in screening colonoscopy. Although the term 'colorectal polyp' is not synonymous with colorectal adenoma, two-thirds of colorectal polyps are adenomas and most colorectal cancers arise from them. Therefore, removal of colorectal polyps using colonoscopic polypectomy has been shown to reduce the risk of future colorectal cancer (Winawer et al., 1993; Atkin et al., 2010).

A patient with one colorectal adenoma has a 30 to 50% likelihood of harboring a second synchronous adenoma elsewhere in the colon and rectum at that time, and they have a 30-50% likelihood of developing metachronous adenoma sometime in the future (Winawer et al., 2006; Arditi et al., 2009). Therefore, to minimize the risk for colorectal cancer in the future, patients with adenomas are usually placed into a post-polypectomy surveillance program.

Post-polypectomy surveillance refers to periodically examining the colon to detect and remove missed synchronous and new metachronous adenomas and cancers, by screening or other means, after the detection and removal of a precancerous lesion. Generally, it does not refer to the use of colonoscopy or other procedures to monitor for polyp or cancer recurrence following a diagnosis of colorectal cancer.

This chapter reviews the rationale, the recent literature and the current recommendations for post-polypectomy surveillance, with emphasizing the need to tailor surveillance strategies to the carefully considered individualized assessment of the risk factors as related to the characteristics of the baseline adenoma and those of the individual patient.

2. Risk of colorectal adenoma or cancer following polypectomy

The objective of post-polypectomy surveillance is to reduce the risk of the development of and death from a colorectal cancer by detecting and removing subsequent adenomas and cancers. The largest study on the risk of colorectal cancer after removal of adenoma in the colon or rectum was reported in 2010 from St. Mark's Hospital, London by Atkin et al. and the study involved using flexible sigmoidoscopy screening (Atkin et al., 2010). After 113,195 people were assigned to the control group and 57,237 people were assigned to the intervention group, they were followed for a median of 11.2 years. The incidence of colorectal cancer in the patients who underwent sigmoidoscopy was reduced by 23%

(hazard ratio: 0.77, 95% CI: 0.70-0.84) and mortality was reduced by 31% (hazard ratio: 0.69, CI: 0.59-0.82). On the per-protocol analyses, after adjusting for a self-selection bias for the patients who underwent sigmoidoscopy, the incidence of colorectal cancer in the people attending the screening was reduced by 33% (hazard ratio: 0.67, CI: 0.60-0.76) and the mortality was reduced by 43% (hazard ratio: 0.57, CI: 0.45-0.72). The relative colorectal cancer risk after polypectomy in all the previously published studies has ranged from 0.2 (range: 0.1–0.6) in the National Polyp Study to 1.3 (range: 0.6–2.3) in the Funen Adenoma follow-up Study (Winawer et al., 1993; Meagher and Stuart 1994; Citarda et al., 2001; Lund et al., 2001; Bertario et al., 2003; Loeve et al., 2005; Atkin et al., 2010). The difference can partially be explained by the inclusion or exclusion of patients with large sessile polyps and other factors too such as the patient characteristics at baseline, the duration of follow-up, the patient compliance and the quality of the initial colonoscopy and polypectomy. The risk of colorectal cancer for patients after polypectomy is lower than that in the general population.

2.1 Concept of the advanced adenoma as a surrogate marker of colorectal cancer

Based on the studies on the prevalence of adenoma from autopsy, the studies on follow-up colonoscopy after polypectomy and the lifetime cumulative incidence of colorectal cancer, it appears that only about 5% of colorectal adenomas undergo malignant transformation (Muto et al., 1975; Stryker et al., 1987; Vogelstein et al., 1988; Center et al., 2009; Hong et al., 2010). These follow-up experiences as well as the increasing information about the molecular genetics for the adenoma-carcinoma sequence are increasingly shifting the emphasis away from simply finding and harvesting large numbers of clinically insignificant adenomas toward strategies that focus on ways to reliably detect and resect the less common, but clinically much more dangerous advanced adenoma.

Colorectal carcinogenesis is a multistep process that occurs over many years and it results from the progressive accumulation of genetic and epigenetic alterations. An adenoma is a monoclonal derivative of a single epithelial stem cell that either inherits or acquires the first of these many genetic alterations. Each additional genetic "hit," which is probably caused by environmental carcinogenic factors, leads to a new clone of daughter cells with a growth advantage that allows the clone to take over the developing polyp. The reason most small simple tubular adenomas stay small and clinically benign is because they never develop the additional genetic alterations needed to make them advance (Vogelstein et al., 1988).

Observational studies also reported the different behavior of small tubular adenomas and advanced adenomas. Most previous studies of the natural history of small colorectal adenomas showed no increase in size, no changes that would have necessitated treatment within a couple of years and that malignant transformation is rare. Hoff et al. reported that 215 polyps less than 5 mm in diameter were left *in situ* in 112 persons for a 2 year follow-up period to ascertain their growth rate. At the end of the 2 years, 49% of the adenomas had increased in size and 14% had regressed. Although the total adenoma mass had increased by 36%, none had grown to a size greater than 5mm and none had developed high-grade dysplasia or cancer (Hoff et al., 1986). On the other hand, Eide reported that the risk of developing cancer in a 1cm sized adenoma was 3% per year in a Norwegian population (Eide 1986). Stryker et al. showed the considerable malignant potential of large adenomas. Before the availability of colonoscopy, 226 patients who had large (>l cm) polyps detected with a barium enema, but who refused their removal by surgery were followed for up to 20 years. Follow-up of these untreated patients showed that 37% of the polyps enlarged, 21 invasive cancers developed at a polyp site and 11 cancers developed at another site. The

cumulative risk of cancer at 5, l0 and 20 years was 2.5, 8 and 24%, respectively (Stryker et al., 1987).

Based on a large volume of high-quality scientific evidence published during the past decade, the concept of the advanced adenoma as a surrogate biological indicator of the cancer risk has been established (Winawer and Zauber 2002). Although colorectal cancer would be a more ideal outcome measure, the advanced adenoma was adopted as an early outcome measure of efficacy because a much longer period of time would be required for conclusions to be drawn if cancer was used as the outcome measure.

The recent guidelines for surveillance after polypectomy have adopted the concept of advanced adenoma and the guidelines have introduced the concept of risk stratification of patients at the time of polypectomy into those who are more likely or less likely to develop subsequent serious neoplasia (Bond 2000; Davila et al., 2006; Winawer et al., 2006; Sung et al., 2008; Arditi et al., 2009; Schmiegel et al., 2009; Cairns et al., 2010). However, a uniform definition of an advanced adenoma has not yet been clearly established, but most definitions include that advanced adenoma is an adenoma with high-grade dysplasia or an adenoma that is >10 mm in size or it has a villous component (≥25%), and advanced neoplasia is advanced adenoma and invasive cancer. A synchronous adenoma is an adenoma that is diagnosed at the same time as that of an index colorectal neoplasm. Thirty to fifty percent of colons with one adenoma will contain at least one other synchronous adenoma. A metachronous adenoma is an adenoma that is diagnosed at least 3 to 6 months after the diagnosis of a previous adenoma.

2.2 Colonoscopy is the procedure of choice for post-polypectomy surveillance

Colonoscopy is the preferred modality for post-polypectomy surveillance. It offers the advantages of complete visualization of the entire colon, detection and removal of polyps, and diagnostic sampling of cancers. An early controlled, single-blinded study that compared the accuracy between colonoscopy and a double contrast barium enema performed in the same patients demonstrated a sensitivity of double-contrast barium enema and colonoscopy for detecting polyps of 67% and 94%, respectively (Durdey et al., 1987; Winawer et al., 2000).

Computed tomography (CT) colonography is now being studied for the surveillance of patients with colorectal cancer or polyps. CT colonography has already been shown to be more accurate than a double-contrast barium enema for detecting polyps as well as having similar or more accuracy than colonoscopy for detecting large (≥ 1cm) polypoid adenomas, although the accuracy rapidly drops for medium-sized and small polyps (Kim et al. 2007; Benson et al., 2010). However, a major limitation of CT colonography compared with conventional colonoscopy is that, as with a barium enema, this modality has only diagnostically usefulness. Whenever a suspicious lesion or clinically significant neoplasia is found, the patient must undergo a subsequent colonoscopy to confirm and resect the lesion. Considering a patient with one colorectal adenoma has a 30-50% likelihood of developing new metachronous adenoma, the need to do two expensive tests would make such surveillance costly and inconvenient.

3. Quality of baseline colonoscopy

The quality of the baseline colonoscopy is important to clearly visualize synchronous and to predict the risk for subsequent neoplasia. To assess the quality of colonoscopy, several direct

and indirect quality measures have been proposed, including the bowel preparation status and other parameters for the performance of colonoscopy, and the parameters include the cecal intubation rate, the withdrawal time and the adenoma detection rate. Until now, there is a lack of objective data related to any of these measures to assess the most important outcome of screening colonoscopy, which is the subsequent incidence of advanced adenoma or colorectal cancer. However, the US Multi-Society Task Force defined a high-quality colonoscopy as a colonoscopy that reaches the cecum, it has little fecal residue and it has a minimum time of withdrawal from the cecum of 6–10 minutes (Rex et al., 2002). With the current recommendations suggesting that the postpolypectomy surveillance colonoscopy intervals should lengthen to improve the efficacy of the utilization of resources, the need for high-quality colonoscopy is of paramount importance.

3.1 Bowel preparation

Even small amounts of fecal material can obscure colorectal adenomas, advanced adenoma and cancers. In a retrospective evaluation of more than 5,000 colonoscopies performed over a 3.5-year period, Leaper et al. identified 17 patients with a missed colorectal cancer. Poor bowel preparation was noted in 6 of these patients, which suggested that the cleansing quality may have an impact on the diagnostic yield during a colonoscopy.(Leaper et al., 2004) In a larger retrospective study, Harewood et al. analyzed the impact of the adequacy of bowel-preparation on the detection of polypoid lesions for approximately 93,000 colonoscopies recorded in the Clinical Outcome Research Initiative database. Suspected neoplasms were identified in 26,490 colonoscopies (29%) overall, with higher detection rates for those cases with adequate preparation (rated excellent or good by the endoscopist) versus those cases with inadequate preparation (fair or poor) (29% vs. 26%, respectively, P<.0001). Although significant lesions (a polyp >9 mm or a mass lesion) were detected in approximately 7% of the colonoscopies, regardless of preparation quality (P = .82), lesions ≤ 9 mm were more likely to be detected when the bowel preparation was adequate versus inadequate (22% vs. 19%, respectively P<.0001) (Harewood et al., 2003). Although the risk of advanced neoplasia increases with polyp size, high-grade dysplasia and carcinoma can occur in adenomas of any size. High-grade dysplasia was reported in 0.9 to 3.4% of the adenomas ≤5 mm and in 3.6 to 12.5% of the adenomas 5 or 6 mm to 10 mm in size.

In addition, a prospective study by Froehlich et al. reported that the detection of neoplasia, including polyps of any size as well as large lesions (>10 mm), was associated with the quality of bowel preparation; polyps were detected in 29% of the patients with high-quality cleansing versus 24% of the patients with low-quality cleansing (P<.007). Identifying polyps of any size significantly depended on the cleansing quality (intermediate-quality vs. low-quality preparation: OR: 1.73, 95% CI: 1.28-2.36; high-quality vs. low-quality preparation: OR: 1.46, 95% CI: 1.11-1.93). For polyps ≥ 10 mm in size, the OR was 1.83 (95% CI: 1.11-3.05) for intermediate-quality cleansing and 1.72 (95% CI: 1.11-2.67) for high-quality cleansing, respectively (Froehlich et al., 2005). Furthermore, flat and depressed lesions are rarer than protruding lesions, but they more frequently contain advanced neoplasia, including invasive carcinoma. Parra-Blanco et al. reported that the number of flat lesions detected in patients with inadequate bowel preparation was significantly lower than that in patients with adequate bowel preparation (9 vs. 28, respectively, P = .002) (Parra-Blanco et al., 2006).

3.2 Adenoma detection rate

In one of the most important studies of the past year, Kaminski et al. demonstrated that the adenoma detection rate for individual endoscopists, which is the most commonly proposed

proxy for quality in colorectal cancer screening, is indeed an independent predictor of the risk for subsequent colorectal cancer after screening colonoscopy. Among 45,026 patients who were enrolled in a national screening colonoscopy program, 42 interval colorectal cancers were identified by a search of national and regional cancer registries in Poland. Most patients with cancer had no family history of colorectal cancer (83.3%) and no polyps identified on the screening examination (92.9%). Only one cancer (2.4%) was attributed to incomplete polyp resection at the time of the screening procedure. The 186 contributing endoscopists had a median adenoma detection rate of 12.2%. The 42 interval cancers occurred after procedures by 32 endoscopists, with three endoscopists contributing three cases each and four contributing two cases each. A strong association between the adenoma detection rates and the subsequent identification of interval cancers was noted (P=0.008), with significant hazard ratios for those endoscopists with adenoma detection rates of less than 11%, 11–14.9%, and 15–19.9%, as compared with those endoscopists with adenoma detection rates over 20% (P = 0.02 for all comparisons). The adenoma detection rate is an independent predictor of the risk of interval colorectal cancer after screening colonoscopy (Kaminski et al., 2010).

3.3 Withdrawal time

Numerous published series have assessed correlations between the proportion of patients with identified polyps or adenomas and the colonoscopic withdrawal time. Barclay et al compared the rates of detecting neoplastic lesions among 12 gastroenterologists who had mean colonoscopic withdrawal times of less than 6 minutes with the rates of those gastroenterologists who had mean withdrawal times of 6 minutes or more. There were large differences among the gastroenterologists in the adenoma detection rates (9.4% to 32.7%) and in their withdrawal times of the colonoscope from the cecum to the anus (range: 3.1 to 16.8 minutes). As compared with the colonoscopists with mean withdrawal times of less than 6 minutes, those colonoscopists with mean withdrawal times of 6 minutes or more had higher rates of detecting any neoplasia (28.3% vs. 11.8%, respectively P<0.001) and advanced neoplasia (6.4% vs. 2.6%, respectively, P=0.005) (Barclay et al., 2006). Furthermore, most series have also shown significant associations between the speed of withdrawal and the polyp or adenoma detection rates, and some series have shown associations between the speed of withdrawal and the detection of high-risk lesions, based on size or histology.

3.4 Cecal intubation

Cecal intubation is defined as insertion of the colonoscope tip into the cecal caput so that the medial wall of the cecum proximal to the ileocecal valve can be fully inspected. The targets for successful cecal intubation rates are 90% for all colonoscopies and 95% for screening colonoscopies. However, because almost all the previous studies excluded the colonoscopy with incomplete cecal intubation from analysis, there is very scare information about the effect of incomplete colonoscopy on the detection of advanced neoplasia with surveillance colonoscopy. In the Funen adenoma follow-up study by Jorgensen and colleagues, the 53 patients with incomplete initial colonoscopy had at least 1 complete colonoscopy during surveillance; advanced neoplasia was detected in 6 of these patients. The area of new advanced neoplasia had been covered by the initially incomplete colonoscopy in three of the six patients, and later the area was covered in four of the six, before advanced neoplasia was detected. Newly detected advanced neoplasia was associated with incomplete colonoscopy at the initial examination (OR: 2.5; 95% CI: 1.0-6.3) (Jorgensen et al., 1995).

3.5 Completeness of polypectomy

In the absence of magnifying endoscopy combined with dye spraying, it is often not possible to determine the histological type of a polyp by endoscopic inspection. Diminutive polyps (<5 mm) may be indistinguishable from hyperplastic polyp and adenomas. In addition, the unusual large hyperplastic polyp may mimic an adenoma. For this reason, all polyps should be considered for removal. Magnifying endoscopy is likely to become increasingly available and an endoscopic diagnosis may reduce the requirement to remove minute polyps in patients with multiple lesions. Diminutive polyps may be too numerous to be completely cleared. In subjects with multiple small polyps, a sample of at least three should be biopsied for histological study. The cancer risk is related to the number of adenomas, so the documentation of the polyp type has prognostic value and surveillance implications. Hot biopsy and electrocoagulation have been used to eradicate diminutive polyps, but destruction of the specimen makes it difficult to histologically review it, and hot biopsy and electrocoagulation may leave residual polyp behind. Cold snare polypectomy is an effective alternative and it does not compromise the histology(Deenadayalu and Rex 2005).

Lesions less than 2 cm in diameter can readily be transected with one application of the snare with submucosal injection. Inclusion of a small portion of normal mucosal adjacent to the confines of the polyp does not pose a problem, providing that this portion of normal mucosa is also resting on the submucosal fluid-filled bleb. However, sessile polyps greater than 2cm in diameter may require piecemeal removal, but this will make histological evaluation difficult or it may be impossible to completely remove them in a piecemeal fashion. Residual neoplastic tissue has been reported in up to one-third of cases after piecemeal resection of sessile polyps greater than 2cm in diameter. The area may be tattooed with sterile India ink to facilitate follow-up evaluation. Tattooing will also identify the site for subsequent surgical resection. A repeat clearing colonoscopy to insure complete polypectomy is essential after piecemeal resection of large sessile polyps. Such polyps often contain appreciable amounts of villous tissue with a high malignant potential and they tend to recur locally after colonosoopic resection even in cases where the initial polypcctomy appeared to be complete. A repeat clearing colonoscopy should be performed in 3-6 months to confirm that the resection was complete (Winawer et al., 2006; Cairns et al., 2010). In order to decrease the incidence of recurrent polyp at the polypectomy site, the base and edges of the polyp can be treated with a thermal modality. Although many endoscopists treat small residual fragments of adenoma following removal of large polyps with a thermal modality, this has not been studied for any device except the argon plasma coagulator (Zlatanic et al., 1999). If polyp tissue persists after two or three examinations, then patients with low surgical morbidity should usually be referred for surgical resection. When patients are found to have these large sessile polyps, they need to be educated at the time of the initial diagnosis about the importance of complying with the entire course of management and follow-up. Most experienced colonoscopists have witnessed tragic cases in which a patient was partially treated by piecemeal snare polypectomy and was then lost to follow-up, and the patient returned later with an advanced cancer at the polyp site.

4. Predictors of subsequent advanced adenomas

The increased risk of recurrent adenomas after polypectomy is the result of lesions missed during the initial colonoscopy as well as a true increased risk of developing de-novo neoplastic lesions due to environmental and genetic risk factors that are particular to the

patient. In other words, the characteristics of initial adenoma and the patient serve as a marker for an increased risk of colorectal neoplasia. Although multiple studies have tried to identify the risk factors for metachronous neoplasia at the time of surveillance, the studies differed with respect to the classification levels of the risk factors and on the definition of advanced neoplasia. In addition, the studies also covered different periods of follow-up evaluation and they used different measures of effect such as ORs, relative risks, hazard ratios and standardized incidence ratios. To clarify these issues, Martinez and colleagues published the pooled analysis using individual data from 8 prospective studies (The Antioxidant Polyp Prevention Study, National Polyp Study, Calcium Polyp Prevention Study, Wheat Bran Fiber study, Veterans Affairs Cooperative Study, Aspirin Folate Trial and Ursodeoxycholic Acid study) that included 9167 men and women aged 22 to 80 with previously resected colorectal adenomas to quantify their risk of developing subsequent advanced adenoma or cancer, as well as to identify factors associated with the development of advanced colorectal neoplasia during surveillance (Martinez et al., 2009).

4.1 Characteristics of baseline adenomas

4.1.1 Multiplicity

Multiplicity at baseline has been shown to predict subsequent detection of advanced adenomas. The pooled analysis of prospective studies showed that the number of adenomas at baseline was related to an increased risk (OR: 1.32, 95% CI: 1.25–1.40) for advanced adenomas at the time of surveillance. Of the randomized controlled trials, with excluding the studies included in the pooled analysis, Funen's adenoma follow-up study and the European fiber and calcium study showed that multiplicity conferred an increased risk for advanced neoplasia at the time of surveillance. The Erlangen Registry of Colorectal Polyps by Nusko and colleagues showed that individuals with 2 or more adenomas at baseline were more likely than those with 1 adenomas at baseline to have an adenoma detected at the time of surveillance (OR: 1.54, 95% CI: 1.12–2.12).

The observational prospective cohort studies also showed that multiplicity was a risk factor for subsequent advanced adenomas and cancer. Noshirwani and colleagues reported that the number of adenomas at baseline was related to an increased risk (OR: 1.25, 95% CI: 1.13–1.38) for advanced adenomas at surveillance in a cohort from the Cleveland Clinic. However, the Study of Colonoscopy Utilization described by Pinsky and Bertario et al. failed to show a significant association between baseline multiplicity and the detection of advanced adenoma at the time of follow-up evaluation.

Study	Number of index adenoma	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Jorgensen (The Funen Adenoma Follow-up Study) 1995	1	not mentioned		1
	2	not mentioned		1.3 (0.6-3.0)
	≥3	not mentioned		3.0 (1.2-7.1)
Noshirwani (Cleveland Clinic Foundation Adenoma Registry) 2000	per 1 increase	697	63	1.25 (1.13-1.38)

Nusko (Erlangen Registry of Colorectal Polyps) 2002	1	not mentioned		1
	≥ 2	not mentioned		1.54 (1.12–2.12)
Bertario 2003	1	736	7	1
	≥ 2	350	7	2.0(0.7–5.8)
Bonithon-Kopp (European Fiber-Calcium Intervention trial) 2004	1	360	18	1
	2	109	8	1.4 (0.59–3.51)
	≥ 3	83	15	3.6 (1.64–7.89)
Martinez (Pooled anaylsis) 2009	1	5465	497	1
	2	2054	271	1.39 (1.17–1.66)
	3	890	146	1.85 (1.46–2.34)
	4	326	68	2.41 (1.71–3.40)
	≥5	377	94	3.87 (2.76–5.42)
Pinsky (Study of Colonoscopy Utilization) 2009	1–2 small tubular adenoma	not mentioned		1
	≥ 3 small tubular adenoma	not mentioned		1.5 (0.8–2.6)
The below studies were included in the pooled analysis (Martinez et al. 2009)				
Winawer (National Polyp Study) 1993	1	541	6	1
	2	200	4	1.5 (0.4-5.6)
	≥ 3	197	18	6.9 (2.6-18.3)
van Stolk (Antixoidant Polyp Prevention Trial) 1998	1 or 2	393	13	1
	≥ 3	84	5	1.13 (0.40–3.18)
Martinez (Wheat bran fiber trial) 2001	1	742	86	1
	2	284	28	0.76 (0.43–1.36)
	≥3	261	32	1.01 (0.54–2.10)

Table 1. Multiplicity of adenoma as a risk factor for advanced neoplasia at surveillance

4.1.2 Size

An adenoma size larger than 1 cm also was shown to predict metachronous advanced adenomas in a pooled analysis of prospective studies by Martinez (OR, 1.68; 95% CI, 1.39-2.02). However, other randomized controlled trials, including Funen's adenoma follow-up study and the European fiber and calcium study, did not find adenoma size at baseline to be an independent predictor of advanced neoplasia at the time of surveillance. Adenoma size was important in the prospective observational cohort studies that assessed advanced neoplasia. Noshirwani's study, the Erlangen Registry of Colorectal Polyps and the Study of Colonoscopy Utilization showed that a baseline adenoma of 1 cm or larger, as compared with a baseline adenoma 1cm or smaller, conferred an OR of 3.68 (95% CI: 2.01-6.76), 1.81 (95% CI: 1.42-2.31) and 1.5 (95% CI: 1.03–2.3), respectively, for subsequent advanced neoplasia. Bertario found that patients with adenomas larger than 2 cm, as compared with adenomas 2 cm or smaller, at baseline had a hazard ratio of 4.0 (95% CI: 1.1–14.4) for the development of follow-up advanced adenomas.

Study	Size of index adenoma (mm)	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Jorgensen (The Funen Adenoma Follow-up Study) 1995	≤5	not mentioned		1
	6-10	not mentioned		1.2 (0.5-2.9)
	>10	not mentioned		1.2 (0.5-2.9)
Noshirwani (Cleveland Clinic Foundation Adenoma Registry) 2000	< 10	not mentioned		1
	≥ 10	not mentioned		3.68 (2.01-6.76)
Nusko (Erlangen Registry of Colorectal Polyps) 2002	≤10	not mentioned		1
	> 10	not mentioned		1.81 (1.42–2.31)
Bertario 2003	≤10	700	6	1
	10-20	256	4	1.9 (0.5–6.6)
	> 20	107	4	4.0 (1.1–14.4)
Bonithon-Kopp (European Fiber-Calcium Intervention trial) 2004	<10	243	19	1
	≥ 10	309	22	1.06 (0.54–2.06)
Martinez (Pooled anaylsis) 2009	<5	2540	209	1
	5-10	3115	287	1.17 (0.95–1.42)
	10-20	2487	415	2.27 (1.84–2.78)
	≥ 20	672	138	2.99 (2.24–4.00)
	pooled	not mentioned		1.56 (1.39-1.74)
Pinsky (Study of Colonoscopy Utilization) 2009	<10	not mentioned		1
	≥10 TA	not mentioned		1.5 (1.03–2.3)
The below studies were included in the pooled analysis (Martinez et al. 2009)				
Winawer (National Polyp Study) 1993	≤ 5	228	3	1
	6-10	354	8	1.3 (0.3-5.2)
	> 10	356	17	2.2 (0.6-7.8)
van Stolk (Antixoidant Polyp Prevention Trial) 1998	< 10	258	11	1
	≥ 10	219	7	0.49 (0.16–1.51)
Martinez (Wheat bran fiber trial) 2001	< 5	395	36	1
	6–10	543	52	0.88 (0.52–2.14)
	10	349	58	2.27 (1.25–4.14)

Table 2. Size of adenoma as a risk factor for advanced neoplasia at the time of surveillance

4.1.3 Histology

The histologic type of adenoma at baseline also was shown to predict metachronous advanced adenomas in a pooled analysis of prospective studies by Martinez (OR: 1.40, 95% CI: 1.17-1.68). However, in the randomized trials, the histologic type of adenoma at baseline

was not a significant predictor of advanced neoplasia. In the observational cohorts, villous or tubulovillous adenoma was a significant predictor of advanced neoplasia in the Study of Colonoscopy Utilization, but not in the study by Norshirwani.

Study	Histology of adenoma at the index polyp	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Jorgensen (The Funen Adenoma Follow-up Study) 1995	Tubular	not mentioned		1
	Tubulovillous	not mentioned		1.2 (0.6-2.7)
Noshirwani (Cleveland Clinic Foundation Adenoma Registry) 2000	Tubular	not mentioned		1
	Others	not mentioned		1.37 (0.72-2.62)
Bertario 2003	Tubular	772	10	1
	Tubulovillous	205	3	1.5 (0.4–5.6)
	Villous	80	1	1.2 (0.2–10.2)
Bonithon-Kopp (European Fiber-Calcium Intervention trial) 2004	Tubular	455	31	1
	Tubulovillous/villous	97	10	1.67 (0.76–3.67)
Martinez (Pooled anaylsis) 2009	Tubular	7268	749	1
	Tubulovillous/villous	1899	336	1.28 (1.07–1.52)
Pinsky (Study of Colonoscopy Utilization) 2009	Tubular	not mentioned		1
	Tubulovillous/villous	not mentioned		2.2 (1.5–3.1)
The below studies were included in the pooled analysis (Martinez et al. 2009)				
Martinez (Wheat bran fiber trial) 2001	Tubular	842	92	1
	Tubulovillous	317	41	1.10 (0.64–1.87)
	Villous	59	9	0.41 (0.15–1.13)
	Unspecified/incipient	69	4	0.47 (0.09–2.62)
Lieberman (VA Cooperative Study Group 380) 2007	No neoplasia	298	7	1
	Villous adenoma	81	13	6.05 (2.48-14.71)

Table 3. Tubulovillous/villous adenoma as a risk factor for advanced neoplasia at the time of surveillance

4.1.4 Degree of dysplasia

By definition, all adenomas have some level of dysplasia. In the past, dysplasia has been classified as mild, moderate, severe or carcinoma in situ. Currently, severe dysplasia or carcinoma in situ is considered the equivalent of high-grade dysplasia and mild or moderate

dysplasia is considered the equivalent of low-grade dysplasia. High-grade dysplasia at baseline was not a significant predictor of advanced neoplasia in the pooled analysis of prospective studies (OR: 1.08, 95% CI: 0.82-1.41) and randomized controlled studies. However, high-grade dysplasia is related to a larger adenoma size and villous component at baseline. Although the VA Cooperative Study by Lieberman and colleagues was included in the pooled analysis, the VA Cooperative Study determined that 10.9% of the patients with high-grade dysplasia in adenomas of any size at baseline had advanced neoplasia over the 5-year surveillance period, as compared with 0.6% in those with tubular adenomas less than 1.0 cm in size and that lacked high-grade dysplasia.

Study	Degree of atypia of the index polyp	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Jorgensen (The Funen Adenoma Follow-up Study) 1995	Mild	not mentioned		1
	Moderate	not mentioned		1.0 (0.4-2.2)
	Severe	not mentioned		2.1 (0.6-7.1)
Bertario 2003	Low/moderate	1050	11	1
	Severe	36	1	3.3 (0.7–15.5)
Bonithon-Kopp (European Fiber-Calcium Intervention trial) 2004	Mild	308	17	1
	Moderate/Severe	244	24	1.86 (0.96–3.64)
Martinez (Pooled anaylsis) 2009	Low grade dysplasia	6485	719	1
	High grade dysplasia	683	118	1.05 (0.81–1.35)
The below studies were included in the pooled analysis (Martinez et al. 2009)				
Lieberman (VA Cooperative Study Group 380) 2007	no neoplasia	298	7	1
	High grade Dysplasia	46	8	6.87 (2.61-18.07)
	CRC	23	8	13.56 (5.54–33.18)

Table 4. High-grade dysplasia of adenoma as a risk factor for advanced neoplasia at the time of surveillance

4.1.5 Location

The pooled analysis by Martinez reported that a proximal adenoma at baseline was associated with an increased risk for subsequent advanced adenomas. The OR was 1.68 (95% CI: 1.39–2.02) for any proximal adenomas at baseline vs distal adenomas only at baseline. Similarly, Bonithon-Kopp reported an OR of 2.63 (95% CI: 1.31–5.3) for subsequent advanced neoplasia for patients with a proximal location of baseline adenomas compared with no proximal location of baseline adenomas. In the observational cohort study of

Pinsky, the risk of metachronous neoplasia at surveillance was significant higher for patients with adenomas on the proximal colon only at baseline than for patients with adenomas on the distal colon only.

Study	Location of index adenoma	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Bertario 2003	Right colon	317	2	0.7 (0.1–7.6)
	Left colon	641	11	2.0 (0.3–16.1)
	Rectum	128	1	1
Bonithon-Kopp (European Fiber-Calcium Intervention trial) 2004	No distal location	50	2	1
	Distal location	502	39	3.37 (0.74–15.3)
	No proximal location	438	23	1
	Proximal location	114	18	2.63 (1.31–5.3)
Martinez (Pooled anaylsis) 2009	Distal	4434	395	1
	Proximal only	2620	330	Any proximal: 1.68 (1.43–1.98)
	Both	1754	325	
Pinsky (Study of Colonoscopy Utilization) 2009	Distal colon only	not mentioned		1
	Proximal colon only	not mentioned		1.8 (1.1–2.7)
The below studies were included in the pooled analysis (Martinez et al. 2009)				
Martinez (Wheat bran fiber trial) 2001	Distal colon	701	68	1
	Proximal colon	349	44	1.65 (1.02–2.67)
	Both	234	33	2.69 (1.34–5.42)

Table 5. Location of adenoma as a risk factor for advanced neoplasia at the time of surveillance

4.1.6 Shape of adenoma

The flat adenoma may be a more aggressive pathway in colorectal carcinogenesis. However, O'Brien reclassified the histopathologically sessile adenomas from the National Polyp Study cohort as flat (defined as an adenoma thickness ≤1.3 mm and <2× the normal mucosa thickness) or polypoid and O'Brien compared between the initial and surveillance pathology. Flat adenomas identified in the National Polyp Study cohort at baseline were not associated with a higher risk for advanced adenomas at the time of surveillance.

4.1.7 Serrated polyps

Recent studies have shown that, aside from classic adenomas, serrated polyps (sessile serrated adenomas, mixed mucosal polyps and traditional serrated adenomas) are of special significance. These lesions are also associated with an elevated risk of malignant degeneration via the so called serrated cancer development pathway (Hiraoka et al., 2010; Leggett et al., 2010; Lu et al., 2011). However, in contrast, after the removal of singular hyperplastic polyps, no special follow-up examination is required (Imperiale et al., 2008).

4.2 Patient's characteristics

4.2.1 Age

Pooled analysis and several prospective observational studies by Bertario and Yamaji reported an increasing risk for subsequent neoplasia with increasing age. However, age was frequently used as a control variable in the analyses without an explicit risk factor presented for the age effect.

Study	Age at the time of polypectomy (years)	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Jorgensen (The Funen Adenoma Follow-up Study) 1995	≤60	not mentioned		1
	>60	not mentioned		1.5 (0.8-3.0)
Noshirwani (Cleveland Clinic Foundation Adenoma Registry) 2000	per 10-year increase	not mentioned		1.10 (0.82-1.45)
Bertario 2003	<60	503	5	1
	60–69	339	5	2.1 (0.6–7.5)
	≥70	244	4	4.1 (1.0–16.0)
Yammaji 2004	< 40	154	6	1
	40-49	804	52	2.3 (0.7–7.6)
	50-59	2397	213	3.6 (1.1–12)
	≥ 60	62	12	5.5 (1.6–19)
Martinez (Pooled anaylsis) 2009	< 40	154	6	0.41 (0.18–0.94)
	40-49	804	52	0.67 (0.48–0.93)
	50-59	2397	213	1
	60-69	3676	460	1.39 (1.16–1.68)
	70-79	2074	328	1.72 (1.40–2.11)
	≥ 80	62	12	2.70 (1.31–5.57)
	< 40	154	6	0.41 (0.18–0.94)
Laiyemo 2009, USA	≤65	not mentioned		1
	> 65	not mentioned		1.3 (0.7–2.5)

Table 6. Age at the time of polypectomy as a risk factor for advanced neoplasia at the time of surveillance

4.2.2 Gender

Gender was also frequently used as a control variable in the analyses without an explicit risk factor presented for the gender effect. The pooled analysis and the observational study by Bertario reported an increased risk for males for advanced neoplasia at the time of surveillance.

Study	Gender	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Jorgensen (The Funen Adenoma Follow-up Study) 1995	Female	not mentioned		1
	Male	not mentioned		1.1 (0.6-2.5)
Noshirwani (Cleveland Clinic Foundation Adenoma Registry) 2000	Female	not mentioned		1
	Male	not mentioned		1.48 (0.74-2.93)
Bertario 2003, Italy	Female	487	2	1
	Male	599	12	6.5 (1.4–29.9)
Yammaji 2004, Japan	Female	not mentioned		1
	Male	not mentioned		0.9 (0.5–1.5)
Martinez (Pooled anaylsis) 2009	Female	2642	267	1
	Male	6525	815	1.40 (1.19–1.65)
Laiyemo (Continued Follow-Up Study of the Polyp Prevention Trial) 2009	Female	not mentioned		1
	Male	not mentioned		2.0 (0.9–4.6)
Pinsky (Study of Colonoscopy Utilization) 2009	Female	not mentioned		1
	Male	not mentioned		1.2 (0.9–1.8)

Table 7. Gender as a risk factor for advanced neoplasia at the time of surveillance

4.2.3 Family history of colorectal cancer in first degree relatives

A family history of colorectal cancer in first degree relatives is an established risk factor for the development of colorectal cancer. However, few studies have specifically addressed the relationship between a family history and metachronous advanced adenomas in postpolypectomy patients. The Erlangen Registry of Colorectal Polyps reported that a parental history of colorectal cancer is associated with subsequent advanced neoplasia, but the pooled analysis, Bertario's study and the Continued Follow-Up Study of the Polyp Prevention Trial by Laiyemo did not find a significant association between the subsequent advanced neoplasia and a family history of colorectal cancer in first degree relatives.

4.2.4 History of previous polyps

Both the pooled analysis and Bonithon-Kopp study noted that a history of polyps before the baseline adenoma was associated with an increased risk for advanced neoplasia at the time of surveillance. Although it is not always possible to determine whether prior polyps are adenomatous polyps, the presence of prior polyps can be considered as an additional risk factor.

Study	Family history of colorectal cancer	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Nusko (Erlangen Registry of Colorectal Polyps) 2002	No	not mentioned		1
	Yes	not mentioned		2.32 (1.77–3.04)
Bertario 2003, Italy	No	787	10	1
	Yes	299	4	1.3 (0.4–4.1)
Martinez (Pooled anaylsis) 2009	No	6547	759	1
	Yes	2089	255	1.17 (0.99–1.38)
Laiyemo (Continued Follow-Up Study of the Polyp Prevention Trial) 2009	No	not mentioned		1
	Yes	not mentioned		1.0 (0.5–2.0)

Table 8. A family history of colorectal cancer in first degree relatives as a risk factor for advanced neoplasia at the time of surveillance

Study	History of previous polyp	Total patients (N)	Patients with Metachronous Advanced Neoplasia (N)	Adjusted OR/RR/HR (95% CI)
Bonithon-Kopp (European Fiber-Calcium Intervention trial) 2004	No	468	29	not mentioned
	Yes	84	12	
Martinez (Pooled anaylsis) 2009	No	6941	722	1
	Yes	2057	329	1.76 (1.48–2.09)

Table 9. A history of previous polyp as a risk factor for advanced neoplasia at the time of surveillance

4.2.5 Race

The pooled analysis of prospective studies by Martinez reported that the race of patients with polyp removal was associated with a different risk for subsequent advanced neoplasia. Compared to the white race, the black race showed an increased risk for subsequent advanced neoplasia (OR: 1.08, 95% CI: 0.79–1.47), whereas other races showed a tendency for a decreased risk for subsequent advanced neoplasia (OR: 0.83, 95% CI: 0.60–1.16).

5. Risk stratification for the metachronous advanced adenoma risk

The totality of evidence suggests that multiplicity (3 or more adenomas), size (1 cm or more), villous features, high-grade dysplasia, a proximal location and a history of previous polyp are the predictors of future advanced neoplasia. Race, age, gender and a family

history of colorectal cancer also may predict metachronous advanced neoplasia, but this has not been well studied. Analysis of the relative importance of each of these predictors is complicated by their interrelationships.

The current guidelines from the major organizations, including the US Multi-Society Task Force on Colorectal Cancer (USMTF), the American College of Gastroenterology (ACG), the American Society of Gastrointestinal Endoscopy (ASGE), and the British Society of Gastroenterology (BSG), have accepted the risk stratification listed in Table 10 (Bond 2000; Davila et al., 2006; Winawer et al., 2006; Cairns et al., 2010).

There is a consensus among many of the studies that the group at a lower risk for subsequent advanced neoplasia has only 1 or 2 tubular adenomas that are less than 1 cm in size and low-grade dysplasia and they are located only in the distal colon. In the colonoscopy based studies, the patients have been followed-up for only 5–6 years after colonoscopic polypectomy to assess their subsequent risk for neoplasia.

Term	Definition
Low risk group	All of the following: 1 or 2 adenomas Size < 1 cm Tubular histology No high-grade dysplasia
High risk group	Any of the following: Multiple adenomas (≥ 3) Size ≥ 1 cm Villous or tubulovillous histology High-grade dysplasia
Higher risk group	Any of the following: >10 small adenomas Piecemeal resection of large sessile adenoma

Table 10. Risk stratification for subsequent advanced neoplasia

6. Post-polypectomy surveillance interval

Based on risk stratification, the major organisations have suggested the post-polypectomy colonoscopy surveillance interval (Table11). All the guidelines rely on periodic colonoscopy as the primary method of surveillance. The surveillance interval is based on the risk of metachronous advanced neoplasia as predicted by the findings on initial colonoscopy. Most of the guidelines recommend repeat colonoscopy in 5–10 years for low-risk patients (only one or two small adenomas, <1 cm in size); for such patients, the BSG advises either repeat colonoscopy in 5 years or no surveillance at all (the patients can continue average-risk screening). For the patients at high risk (advanced neoplasm or 3–10 small adenomas), colonoscopy should be repeated in 3 years, with subsequent colonoscopies every 5 years if the preceding colonoscopy was negative. In most of the guidelines, an advanced neoplasm is defined as a villous or tubulovillous adenoma, an adenoma with intermediate-grade or high-grade dysplasia, or a tubular adenoma 1 cm in size or larger. The USMTF guidelines specify that the colonoscopy intervals can be extended to 10 years if the preceding colonoscopy did not show adenomas. In patients with numerous (>10) adenomas but there

was no overt adenomatous polyposis syndrome, colonoscopy should be repeated in less than 3 years, with the exact interval to be determined by the endoscopist. For patients with large sessile adenomas that are difficult to completely remove in one session, a repeat colonoscopy after a short interval (2–6 months) is recommended. Subsequent intervals are customized according to the level of suspicion for residual adenomatous tissue at the polypectomy site. If a sessile polyp is very extensive or it has high-grade dysplastic features, then surgical resection should be considered. After it is certain that all adenomatous tissue has been removed, surveillance with 3–5 year intervals can be resumed.

	Organization	First surveillance interval	Second surveillance interval if surveillance colonoscopy shows no adenomas
Low risk group			
1–2 tubular adenomas, <1cm and lowe-grade dysplasia	USMTF	5–10 years	-
	ACG	5 years*	5 years
	ASGE	No earlier than 5 years	No earlier than 5 years
	BSG	5 years or no surveillance	No surveillance
High risk group			
3-10 adenomas, ≥ 1 cm, tubulovillous /villous adenoma or High-grade dysplasia	USMTF	3 years	5 years
	ACG	3 years†	5 years
	ASGE	3 years	No earlier than 5 years
	BSG	3 years‡	3 years§
Higher risk group			
>10 small adenomas	USMTF	<3 years	
	ACG	-	-
	ASGE	<3 years	5 years
	BSG	1 year¶	3 years‡
Large sessile adenoma	USMTF	2–6 months	Customised
	ACG	3–6 months	-
	ASGE	2–6 months	Customised
	BSG	3 month	1 year‖

Abbreviation: US Multi-Society Task Force on Colorectal Cancer, USMTF; American College of Gastroenterology, ACG; American Society of Gastrointestinal Endoscopy, ASGE; British Society of Gastroenterology, BSG.

*The ACG guidelines note that selected low-risk patients might not need surveillance at all, but they do not further elaborate. †The ACG guidelines consider patients with 1–2 small adenomas and a positive family history in a first-degree relative to be at intermediate risk. ‡The BSG guidelines define intermediate-risk patients as those with 3–4 small adenomas or at least one adenoma ≥1 cm in size. §The BSG guidelines recommend ceasing surveillance if two consecutive follow-up colonoscopies are negative. ¶The BSG guidelines define high risk patients as those with ≥5 adenomas or ≥3 adenomas with at least one of which is ≥1 cm in size. ‖The BSG guidelines recommend repeating colonoscopy in 1 year after confirmation of complete removal, and then every 3 years.

Table 11. Summary of the post-polypectomy guidelines

Over the past few decades, the recommended intervals between surveillance colonoscopies have been extended, on the basis of accumulating data that showed longer surveillance intervals are safe. For example, the National Polyp Study showed no difference in the adenoma risk between patients who had repeat colonoscopy at 1 year versus those who had colonoscopy at 3 years, while the Funen Adenoma Study showed no statistically significant difference in the adenoma recurrence rates at 4 years colonoscopy compared with 2 years colonoscopy. Depending on the patient's and physician's preference, surveillance may be discontinued if the life expectancy is under 10 years (USMTF) or if the patient is over 75 years old (BSG). For most guidelines, the surveillance recommendations are relaxed after one or two negative follow-up colonoscopies. However, the ACG considers those patients with a history of adenomas to be at a lifelong risk for metachronous lesions and the ACG recommends colonoscopies at least every 5 years indefinitely. It is important to note that these surveillance interval recommendations are based on the assumption that the baseline colonoscopy is of high quality with good bowel preparation, thorough removal of polyps has been done, there is an adequate examination time and complete visualization of all colonic mucosa up to and including the caecum.

Surveys have shown that the patients' compliance with physicians' recommendations for surveillance is high (up to 85%), and particularly in the presence of multiple or larger polyps (Klabunde et al., 2003; Mysliwiec et al., 2004; Kang et al., 2006). Also, patients are often interested in chemopreventive measures such as antioxidants, fiber, and calcium or other dietary supplements, although the efficacy of all these agents has not been unequivocally shown. The effect of surveillance colonoscopy on the quality of life has not been directly studied, although patients probably derive benefit if we extrapolate the results from quality-of-life studies on screening colonoscopy. Unfortunately, many clinicians do not adhere to the surveillance guidelines and they often do colonoscopies more frequently than is recommended. This over-surveillance is probably due to concerns about missed lesions or interval cancers, which can occur even in patients who are under close surveillance. Improved adherence to guidelines could be achieved by the use of reminder devices and algorithms for continuous improvement. Other screening measures, such as the use of interval testing of faecal occult blood, might also allow practitioners to feel more comfortable with longer surveillance intervals (Bampton et al., 2005).

7. Conclusion

Identifying the high risk subjects is important, as is ensuring that the subjects accept and comply with the recommended surveillance program. Two important factors, in addition to the individual patient factors, have a profound effect on the cancer risk: these are the quality of performing the examination, and ensuring complete removal of large sessile lesions. In addition to the potentially therapeutic value of polyp removal, colonoscopy is an opportunity to identify a small, high risk group of patients who require careful surveillance to prevent the development of cancer. It is also an opportunity to identify a much larger group of patients who can be informed with some confidence that their cancer risk is low. The overall effectiveness of an adenoma surveillance program for preventing colorectal cancer depends on each colonoscopy being undertaken slowly, carefully and thoroughly with a fail-safe system in place for recalling the higher risk patients

Further research will help define the best surveillance intervals, as well as the role of technical innovations such as CT colonography, chromoendoscopy and narrow-band imaging.

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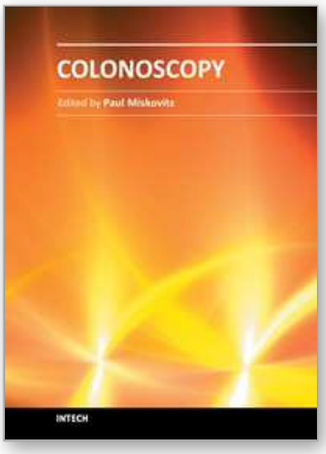

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To publish a book on colonoscopy suitable for an international medical audience, drawing upon the expertise and talents of many outstanding world-wide clinicians, is a daunting task. New developments in videocolonoscope instruments, procedural technique, patient selection and preparation, and moderate sedation and monitoring are being made and reported daily in both the medical and the lay press. Just as over the last several decades colonoscopy has largely supplanted the use of barium enema x-ray study of the colon, new developments in gastrointestinal imaging such as computerized tomographic colonography and video transmitted capsule study of the colonic lumen and new discoveries in cellular and molecular biology that may facilitate the early detection of colon cancer, colon polyps and other gastrointestinal pathology threaten to relegate the role of screening colonoscopy to the side lines of medical practice. This book draws on the talents of renowned physicians who convey a sense of the history, the present state-of-the art and ongoing confronting issues, and the predicted future of this discipline.

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