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Abstract

Colonoscopic surveillance in patients with a personal or family history of colorectal carcinoma or colonic polyps represents a significant workload for endoscopy services. Effective colonoscopic surveillance relies on quality endoscopic examination and appropriate surveillance interval. This review will discuss quality in colonoscopy and review guidelines for surveillance.

Introduction

Colonoscopic surveillance aims to fully visualise the colonic and rectal mucosa for abnormalities. Identification and treatment of colorectal adenomas prevents progression to carcinoma. Colonoscopic identification of primary carcinomas and early recurrences allows treatment with curative intent. In inflammatory bowel disease (IBD), the identification of dysplasia at colonoscopy allows treatment prior to the development of invasive carcinoma. Colonoscopy can also allow clinicians to stratify patients who require more intensive colonoscopic surveillance.

Colonoscopic surveillance represents a significant workload for colorectal units, comprising 23% of all colonoscopies in a series at an Australian tertiary centre.[1] Guidelines exist to optimise patient outcomes whilst limiting the financial burden to the health system.

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This review will discuss the use of colonoscopy for surveillance in patients with a personal and/or family history of colorectal carcinoma (CRC) and in patients with colonic polyps.

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Quality in Colonoscopy

Colonoscopic surveillance relies on thorough examination of the colorectal mucosa. There is considerable variability in the performance of colonoscopy among individual clinicians. This is demonstrated by the variance in the adenoma-detection rate (ADR), ranging from 7 to 52%.[2] ADR is defined as the fraction of patients who had one or more adenomas detected at screening colonoscopy. A target ADR of ≥25% is outlined in guidelines published by the American Society for Gastrointestinal Endoscopy/American College of Gastroenterology Task Force on Quality in Endoscopy.[3] It has been shown that protection from colorectal cancer is lower if the colonoscopy is performed by an endoscopist with an ADR of less than 20%,[4] and each 1% increase in ADR corresponded to a 3% reduction in cancer risk.[2]

The ADR is inversely related to the development of interval cancer, including advanced and fatal cancers.[2] Interval cancer is defined as a colorectal malignancy arising more than 6 months following "clear" surveillance colonoscopy but prior to the patient's next scheduled endoscopy. The finding of interval cancer suggests that an adenoma may have been missed at the preceding examination, and it can be used as a measure of poor

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quality of baseline colonoscopic examination. Patients undergoing surveillance by high ADR endoscopists are more likely to have adenomas identified and removed, and consequently are subject to earlier repeat examination, providing further adenoma protection when compared to patients undergoing endoscopy by low ADR clinicians.

Colonoscope withdrawal time can also be used as a surrogate marker for quality of examination, with longer withdrawal times associated with a higher ADR.[5] Protocol driven withdrawal times of at least 8 minutes are associated with a higher rate of neoplasia detection.[6]

Caecal intubation rate is an indicator of complete colonoscopic examination. Screening colonoscopy is protective for CRC in the right colon, with a 65% reduction in risk of death from right sided colon cancer.[7] Guidelines suggest a caecal intubation rate of e90% is a performance target and that caecal intubation should be documented photographically in all cases.[3]

Adequate examination of the colorectal mucosa at colonoscopy requires satisfactory bowel preparation. Poor bowel preparation at colonoscopy is associated with longer procedure duration, incomplete colonoscopy, and lower detection rates of adenoma and carcinoma.[8] There is no consensus on the optimal preparation for colonoscopy. Choice of regime needs to be individualised based on patient health, comorbidities, as well as agent cost and tolerability.[9] Giving half of the bowel preparation

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on the day of colonoscopy ("split-dosing") results in higher quality examination and increased adenoma detection.[9] This involves patients taking the second dose of bowel preparation within 3-8 hours of the colonoscopy and having a reduced 2-hour fast prior to colonoscopy.

There are multiple other factors that can compromise the quality of colonoscopic examination, including; patient factors,[10] such as tumour biology; technical factors,[11] in the form of low quality endoscopic equipment; and system factors,[10] in the form of financial incentives and time pressure.

Processes to improve quality in colonoscopy

In Australia, accreditation of training in colonoscopy is overseen by the Conjoint Committee for Recognition of Training in Gastrointestinal Endoscopy (CCRTGE), a national body comprising representatives of the Gastroenterological Society of Australia (GESA), Royal Australasian College of Physicians (RACP) and the Royal Australasian College of Surgeons (RACS). Training consists of supervised practice and a logbook with a minimum number of procedures and threshold caecal intubation rate, prior to applying for certification.[12] Whilst this system has improved training and allowed certification of existing practitioners through a grandfather clause, not all clinicians practicing and teaching colonoscopy have certification from the committee.[12] The National Bowel Cancer Screening Program (NBCSP) has recommended that the conjoint

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committee certification be compulsory for clinicians making Medicare benefit claims for NBCSP colonoscopies.[13]

Following training in colonoscopy there is currently no mandated national program of quality assurance, or re-accreditation. In 2016, GESA introduced the voluntary colonoscopy recertification program, funded by the National Bowel Cancer Screening Program. This voluntary triennial recertification program incorporates formal recertification based around an online logbook and increased training and education opportunities for colonoscopists. Criteria for re-certification includes: 150 colonoscopies over 3 years, 95% caecal/terminal ileal intubation rate, adenoma detection rate of at least 25%, and completion of a "no-fail" online cognitive review.[14]

Guidelines

Guidelines (such as the local Cancer Council Australia guidelines for colonoscopic surveillance) assume uniform performance in colonoscopy, and do not take into account aforementioned factors that influence quality of examination.

Guideline intervals are based on the risk of development of a metachronous lesion. Risk stratification is dependent upon adenoma size and number, the nature of adenoma resection, duration and history of IBD and colorectal cancer. It is also worth considering that guidelines exist within health systems with resource limitations, which may influence surveillance recommendations.

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Adherence to guidelines for surveillance colonoscopy is poor, with an Australian series showing that only 23% of CRC surveillance cases receive colonoscopic surveillance according to the Cancer Council Australia guidelines.[15]

Family history of Colorectal Carcinoma

An average Australian in 2017 is estimated to have a risk of 1 in 13 of developing colorectal cancer by their 85th birthday.[16] Patients with a family history are at increased risk compared to the general population, accounting for approximately 15-20% of CRC..[17] This can represent chance; common environmental factors within families (i.e. smoking, diet); an inherited predisposition to colorectal cancer without evidence of genetic mutation/known syndrome; or the presence of an inherited colorectal cancer syndrome. (I.e. familial adenomatous polyposis [FAP] or Hereditary Non Polyposis Colorectal Cancer [HNPCC])

How much does a positive family history increase the risk of CRC?

A meta-analysis by Johns et al revealed that the presence of one first degree relative with CRC conferred a relative risk (RR) for CRC of 2.25 (95% CI 2.00-2.53), which increased to 4.25 (95% CI 4.25) if there was more than one relative with a history of CRC. Of note, even a history of colorectal adenoma in a relative increases the risk of CRC with a RR of 1.99 (95% CI 1.55-2.55).[18] It is worth noting that the relative risk

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conferred by a family history of bowel cancer decreases with age, and trends toward the population risk by age 70.[19]

Management of the patient with a family history of colorectal cancer

The decision for surveillance colonoscopy depends on the patient's individual risk assessment. A risk assessment require a thorough family history that will assess specifically for relatives with colorectal cancer or polyps, detailing their age of diagnosis, site of malignancy and the presence of synchronous/metachronous bowel cancer. It is also important to include history of HNPCC related malignancy (endometrial, ovarian, small bowel, renal pelvis, ureter, biliary tract or brain cancer). Following thorough history – patients can be stratified into three groups as per the Cancer Council Australia guidelines[17] as shown in Table 1.

Average risk individuals have only one first or second degree relative with CRC diagnosed age e 55 and can be managed with 2 yearly FOBT (and *consider* 5 yearly flexible sigmoidoscopy) from age 50. Intermediate risk individuals have relatives with CRC diagnosed at age < 55, or 2 relatives (same side of family) with CRC at any age, necessitating screening colonoscopy every 5 years from age 50, or at an age 10 years younger than the age of the diagnosis of the youngest relative with CRC. Patients at high risk of CRC have multiple family members with CRC with high-risk features (as outlined in Table 1). Such a family history should raise concern for the presence of a colorectal

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cancer syndrome (discussed below) and these patients should be referred for genetic counselling and an individualised screening recommendation.[20]

Could it be an inherited CRC syndrome?

Familial Adenomatous Polyposis (FAP) is an autosomal dominant inherited polyposis syndrome characterised by numerous (>100) colonic adenomatous polyps and extra-intestinal manifestations. Untreated, patients inevitably develop colorectal cancer at a mean age of 40. Attenuated FAP describes a variant in which there are fewer (<100) polyps, with carcinoma developing at a later age. Patients are diagnosed by flexible sigmoidoscopy, which occurs from a young age in known kindred, and/or by genetic testing for the *APC* mutation on chromosome 5. Management of the colon consists of intensive surveillance with flexible sigmoidoscopy, Initially yearly from age 12-15 until age 30-35 after which interval can be extended to 3 yearly if no adenomas or genetic mutation has been identified.[20] Affected individuals undergo prophylactic colectomy/proctocolectomy at an age dictated by individual risk based on genotype and polyp burden.[21]

MUTYH-associated polyposis (MAP) is an autosomal recessive inherited polyposis syndrome caused by biallelic mutations in the base excision repair gene, MUTYH. Affected individuals have a phenotype that is similar to FAP with multiple colorectal polyps, however family history reveals a lack of polyposis in the preceding and

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following generations. Affected individuals are managed as per FAP, and families require genetic counselling.[20]

Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is an autosomal dominant syndrome characterised by a germline mutation in the DNA mismatch repair (MMR) genes. Suspect HNPCC when CRC develops at a young age and when there is high levels of microsatellite instability (MSI) in tumour DNA. Affected individuals have a 70% lifetime risk of CRC also can also have extra-intestinal manifestations. Management consists of genetic counselling and consideration of testing for germline mutations in the MMR genes. Family members are screened with 2-yearly colonoscopy from age 25 (or 5 years earlier that the age of diagnosis of youngest family member with CRC), and should a CRC be diagnosed, consideration should be given to extended colectomy to reduce future risk of metachronous CRC.[20]

Evidence for screening colonoscopy in patients with a family history of CRC:

Nishihara et al used data from two prospective cohort studies over 22 years to assess long-term colorectal cancer incidence and mortality after lower endoscopy.[22] They demonstrated that colonoscopy and sigmoidoscopy were associated with a reduction in colorectal cancer and colorectal-cancer mortality. For patients with a family history they found that screening colonoscopy reduced the risk of CRC within 5 years (HR 0.44 [95%CI 0.30-0.66]), validating the use of colonoscopy in this population. Furthermore

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this risk rose after 5 years (HR 0.91 [95%CI 0.55-1.52]) validating 5 years as an acceptable interval for screening in this population.

Polyps

A polyp is any protuberance into the lumen of the colon. They can be divided into non-neoplastic and neoplastic. Non-neoplastic polyps include hyperplastic, mucosal, submucosal, hamartomatus and pseudopolyps. They will not be discussed within the scope of this article. Neoplastic polyps include adenomatous polyps and serrated polyps.

Adenomatous polyps

Adenomatous polyps are the most common type of colonic polyp, which are by definition dysplastic and consequently have malignant potential. Most colorectal cancers arise from an adenoma that becomes dysplastic through the adenoma-carcinoma sequence in which there is a stepwise pattern of progressive mutational activation of oncogenes and inactivation of tumour suppressor genes.[23] Whilst approximately 40% of the Western population will develop colonic adenomas, only 3% will progress to cancer. There is no reliable criteria to predict adenoma progression or recurrence[23] and thus management relies on endoscopic treatment and subsequent surveillance.

Factors affecting the risk of developing carcinoma from adenomatous polyps include pathology (villous lesions, high grade dysplasia), size (>1cm), number and genetic predisposition (polyposis syndromes).

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Surveillance after polypectomy for adenomatous polyps

Colonoscopic management of polyps has been shown to decrease colon cancer incidence by 67-90%.[24] The multicentre National Polyp Study demonstrated that colonoscopic polypectomy confers a 53% reduction in mortality from colorectal cancer.[25]

Interval of surveillance depends on the above risk factors given they dictate the risk of progression to carcinoma. Features that indicate highest risk of future adenoma/interval carcinoma are high-grade dysplasia, villous morphology and polyps >1cm in size. The Cancer Council Australia guidelines provide direction on appropriate surveillance intervals based on the risk as shown in Table 2.

Rationale for follow up intervals*:*

For low risk lesions, patients that subsequently undergo a negative colonoscopy return to a baseline risk and consequently do not require ongoing intense surveillance.[26] The US national polyp study showed no difference in detection rates of advanced or any adenoma in follow up colonoscopies randomised to either one or three years.[24]

When to stop surveillance*?*

The Cancer Council Australia guidelines suggest there is no benefit to continue colonoscopic surveillance for polyps beyond 75 years of age, given the lead time for progression from adenoma to carcinoma is the same as the life expectancy at this age.[27] Such recommendations need to be considered within the context of a patient's general

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health and individualised risk profile. It may be appropriate to consider colonoscopic surveillance beyond age 75 in healthy individuals who are at a high risk of CRC on the basis of a personal or family history of CRC, or in the presence of an inherited CRC syndrome.

Serrated polyps

Sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas also have malignant potential. However, these lesions progress to carcinoma by the serrated polyposis pathway, undergoing early mutations in BRAF or KRAS and being distinct from malignant transformation in adenomas.[28] The sessile nature of these lesions means they can be difficult to identify at colonoscopy. The presence of a mucus cap can herald an underlying SSA/P. Other clues include a rim of debris, contour alteration or interruption in the mucosal vascular pattern.[29] Serrated lesions are thought to precede and account for 20-30% of all CRC, and likely account for a higher proportion of right colon cancer given the right-sided predominance of SSA/P.[30] SSA/P are associated with interval cancer, as they are difficult to identify at colonoscopy, often incompletely excised and can be rapidly progressive (particularly those with cytological dysplasia) in the interval between examinations.[31] SSA/P with cytological dysplasia represents progression towards carcinoma, and should be considered as a significant risk (similar in risk profile to adenomas with high grade dysplasia).[30]

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Serrated polyposis syndrome(SPS) is characterised by multiple serrated polyps, and the diagnosis can be made according to WHO criteria (as outlined in Supplementary Table S1).[32] No genetic mutation has been identified to account for SPS. The exact risk of CRC in SPS in unknown. Guidelines suggest yearly colonoscopy to clear all serrated lesions, and suggest that extended colectomy should be considered in the case of CRC in a patient with SPS.[30]

Surveillance for serrated lesions

A consensus statement formulated by an expert panel in Cleveland in 2010, provides guidelines for the follow up of serrated lesions, stratifying surveillance interval by lesion histology, size, number and location..[30] (As outlined in Supplementary Table S1)

These guidelines suggest complete removal of all serrated lesions with the exception of diminutive sigmoid and rectal lesions. Identification and resection of serrated lesions can be difficult given their size and shape. This group suggests that narrow band imaging and chromoendoscopy can enhance identification and resection of serrated lesions.[30]

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Previous Colorectal Cancer

Colonoscopic surveillance aims to identify recurrence of the primary cancer at an earlier stage to allow curative treatment, and to identify metachronous colorectal neoplasms.[33] Patients who underwent curative treatment (including those who underwent metastasectomy with curative intent) are eligible for colonoscopic surveillance.

A large study by Sargent et al, pooled individual patient data for 20,800 patients from 18 trials and identified recurrence in 35% of colorectal cancer patients, with over 90% developing in the first 5 years. The annual recurrence rate drops to 1.5% per year after 5 years and to 0.5% per year after 8 years.[34] A further series has shown that locoregional recurrence occurs in up to 11.5%, with most in the first three years post operatively.[35]

An Australian tertiary series identified a rate of 1.7% of metachronous carcinoma on surveillance colonoscopy, occurring on average 3 years after surgery.[1]

Effectiveness of colonoscopic surveillance

There is controversy as to the effectiveness of colonoscopic surveillance following resection of colorectal carcinoma. With the current available evidence it can be difficult to determine the effectiveness of colonoscopy as a single modality as studies include it as a component of a surveillance regime. There is data to support its use in identifying metachronous carcinomas and adenomas, however it is less effective in

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detecting recurrence of primary tumours. Rulyak et al found that one colonoscopy within a year of diagnosis improved overall survival with a hazard ratio of 0.58 (95%CI 0.44-0.75). Most abnormalities were found on initial follow up colonoscopy and the majority were metachronous tumours with far fewer episodes of recurrence at the anastomosis.[36]

Colonoscopy is not as efficient in detecting recurrent CRC. A meta analysis by Renehan failed to show that annual or more frequent colonoscopies provide any survival benefit with respect to the primary tumour.[37] This likely represents the low rate of intraluminal recurrence and the low rate of subsequent curative resection for recurrence identified on colonoscopy.[33]

Guidelines for Colonoscopic Surveillance in CRC:

Multiple guidelines exist for colonoscopic follow up after treatment for CRC and these are compared in Table 3. The Cancer Council Australia guidelines outline that clinicians should consider the patients' *individual* risk. In particular they outline patients who are high risk in whom more frequent colonoscopic examination should be considered, including patients diagnosed with CRC under the age of 40; with suspected HNPCC; with serrated polyposis syndrome and BRAF mutations; and synchronous cancers. These patients should undergo colonoscopy at one year then second or third yearly depending on their risk profile.[27]

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Conclusion

Colonoscopic surveillance is a valuable tool for patients at increased risk of colonic polyps and carcinoma. Efficacy relies on quality examination and appropriate surveillance intervals. Endoscopists should ensure that outcomes of colonoscopy are audited, rates of adenoma detection and interval cancer are within accepted ranges, and that patients undergo follow up examination at an appropriate interval.

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Table 1:Guidelines for patients with a Family history of CRC
(Adapted from Cancer Council guidelines)

Category 1 Average risk and slightly above average risk **98% of the population**	Category 2 Moderately increased risk **1-2% of the population**	Category 3 Potentially high risk **<1% population**

• One 1° or 2° relative with CRC e 55
• Two relatives diagnosed with CRC e 55 on *different* sides of the family.
	• One 1° relative with CRC < 55
	• Two 1° or one 1° and one 2° relatives on *same* side of family with CRC (any age)
		• e Three 1° relatives or a combination of 1° and 2° relatives on the *same* side of family with CRC.
		• e Two 1° or 2° relatives on the *same* side of the family with CRC, plus any high risk features:
		  ○ Multiple CRC in a family member
		  ○ CRC before age 50
		  ○ A family member who has/had an HNPCC-related cancer
		• Any 1° or 2° relative with a large number of colonic adenomas (suspected FAP).
		• Any relative with a known gene mutation that confers a high risk of CRC.

Recommendation • FOBT every 2 years from age 50 • *In addition* it is acceptable to offer flexible sigmoidoscopy	**Recommendation** • Colonoscopy 5 yearly from age 50 or 10 years younger than the age of diagnosis of CRC in family	**Recommendation** • Referral to familial cancer service for genetic counselling and testing • Colonoscopy ○ FAP: Colonoscopy or Flex. Sigmoidoscopy starting at age 12-15 until prophylactic colectomy

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every 5 years	• Consider FOBT in intervening years	○ HNPCC: Every 1-2 years from age 25 or 5 years younger than youngest diagnosis in family

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Table 2: Polyp follow up recommendations
(Based on Cancer Council Australia Guidelines)

	Low Risk	High risk	Incomplete excision/piecemeal excision	Greater than 5 polyps
Polyp characteristics	1-2 <10mm tubular adenomas (And no high risk features)	three or more adenomas, e 10mm, or with tubulovillous, or villous histology, or high grade dysplasia	Any	Any
Follow up Colonoscopy	5 year colonoscopy	3 yearly colonoscopies	3-6 months	12 Months
Subsequent colonoscopy	10 year colonoscopy or 2 yearly FOBT		12 months to ensure complete removal	(Note if >10 polyps consider earlier and consider polyposis syndrome)

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Table 3: Comparison of guidelines for surveillance following treatment for CRC

	Perioperative colonoscopy (If not done preoperatively)	Follow up Colonoscopy	Rectal Surveillance
Cancer Council Australia[27]	3-6 months	First: 1 year If normal: 5 years If advanced adenoma on 1 year scope or on peri-op scope: 3 years	6 monthly assessment of the rectum for 2-3 years with: DRE, rigid proctoscopy, flex. proctoscopy, or rectal endoscopic US.
NZ Guidelines[38]	Within 12 months	3-5 yearly ongoing	3, 6 months, 1 and 2 year assessment with proctoscopy, sigmoidoscopy or DRE
American Gastroenterology Association[33]	3-6 months	First: 1 year If normal: 3 year interval If normal: 5 year interval	Consider proctoscopy (rigid or flexible) or endoanal US at 3-6 monthly for the first 2-3 years
UK NICE[39]	No recommendation	First: 1 year If normal: 5 years	No recommendation

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