

A nurse-led model at public academic hospitals maintains high adherence to colorectal cancer surveillance guidelines

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The known Adherence to surveillance colonoscopy guidelines is often poor. Unnecessarily frequent colonoscopies increase costs, waiting lists, and the risk of adverse outcomes, but delayed surveillance can increase the risk of colorectal cancer.

The new Nurse-initiated recommendations in public academic hospitals for colonoscopy surveillance intervals were 97% compliant with Australian guidelines, compared with 83% for physician-led recall recommendations in private, non-academic hospitals. About one-quarter of colonoscopies were undertaken ahead of schedule, usually because of patient symptoms or faecal occult blood test results.

The implications Nurse coordinators can help ensure adherence to guideline recommendations about colorectal cancer surveillance and thereby reduce endoscopy workloads.

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide.¹ Early diagnosis has a major impact on survival, and can be achieved by screening with faecal occult blood tests (FOBT) or colonoscopy.^{2,3} A family or personal history of colorectal neoplasia can increase a person's risk of CRC as much as fourfold,^{4,5} and such individuals are advised to undergo regular surveillance colonoscopy. Screening and surveillance guidelines aim to optimise the effectiveness of CRC prevention, with surveillance intervals generally ranging between one and 5 years.^{6,7}

Audits have often indicated that practice deviates from the guideline recommendations. Performing colonoscopies too frequently increases costs and the risk of complications, but delays can increase the risk of CRC.⁸ As many as 89% of patients receive inappropriate surveillance, in most cases colonoscopy before the recommended date.^{8,9} Improved compliance with guidelines would significantly reduce costs, as at least one-quarter of colonoscopy resources are consumed by surveillance procedures.¹⁰

A number of studies have investigated approaches for improving adherence to guidelines. The introduction of surveillance registries in the United States increased the proportion of people with an adenomatous polyp who were offered colonoscopy in the recommended timeframe from 44% to 85%;¹¹ a notification system similarly improved adherence to colonoscopy follow-up from 23% to 45%.¹² In the Southern Co-operative Program for the Prevention of Colorectal Cancer (SCOOP) in South Australia, facilitation by a nurse coordinator increased the proportion of decisions that matched guidelines for post-polypectomy surveillance in the short term from 37% to 96%.^{13,14}

SCOOP was established in 1999 to improve surveillance rates in accordance with the Australian National Health and Medical

Abstract

Objective: To examine the compliance of colorectal cancer surveillance decisions for individuals at greater risk with current evidence-based guidelines and to determine whether compliance differs between surveillance models.

Design: Prospective auditing of compliance of surveillance decisions with evidence-based guidelines (NHMRC) in two decision-making models: nurse coordinator-led decision making in public academic hospitals and physician-led decision making in private non-academic hospitals.

Setting: Selected South Australian hospitals participating in the Southern Co-operative Program for the Prevention of Colorectal Cancer (SCOOP).

Main outcome measures: Proportions of recall recommendations that matched NHMRC guideline recommendations (March–May 2015); numbers of surveillance colonoscopies undertaken more than 6 months ahead of schedule (January–December 2015); proportions of significant neoplasia findings during the 15 years of SCOOP operation (2000–2015).

Results: For the nurse-led/public academic hospital model, the recall interval recommendation following 398 of 410 colonoscopies (97%) with findings covered by NHMRC guidelines corresponded to the guideline recommendations; for the physician-led/private non-academic hospital model, this applied to 257 of 310 colonoscopies (83%) ($P < 0.001$). During 2015, 27% of colonoscopies in public academic hospitals (mean, 27 months; SD, 13 months) and 20% of those in private non-academic hospitals (mean, 23 months; SD, 12 months) were performed more than 6 months earlier than scheduled, in most cases because of patient-related factors (symptoms, faecal occult blood test results). The ratio of the numbers of high risk adenomas to cancers increased from 6.6:1 during 2001–2005 to 16:1 during 2011–2015.

Conclusion: The nurse-led/public academic hospital model for decisions about colorectal cancer surveillance intervals achieves a high degree of compliance with guideline recommendations, which should relieve burdening of colonoscopy resources.

Research Council (NHMRC) guidelines on CRC prevention. SCOOP is based on a consensus best practice guideline for the surveillance of people at increased risk of CRC: those with a personal history of colonic neoplasia, or a family history that includes either one primary degree relative with CRC diagnosed before the age of 55, or two primary degree relatives or one primary and one secondary degree relative (on the same side of the family) with CRC diagnosed at any age.⁶ With the expansion of the program, two systems are now used: at public academic hospitals, nurse coordinators review the data for each patient and make a recommendation based on NHMRC guidelines, which is then confirmed

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by a physician; in private non-academic hospitals, specialist physicians manage the entire process, with assistance from printed guidelines (paper-based decision aid) to determine the appropriate surveillance interval. Many of the physicians involved work in both hospital types.

Colonoscopies may be performed more frequently than recommended by guidelines because of incomplete adherence by physicians to the guidelines, or because the patient has developed symptoms that require investigation earlier than the scheduled surveillance colonoscopy. Audits of colonoscopy procedures do not always specify the cause of non-compliance with recall timings. The aims of our audit were to examine the compliance of surveillance decisions in SCOOP with current evidence-based guidelines and to determine whether compliance differs between surveillance models. Secondary aims were to determine actual compliance (ie, reasons for procedures not being performed at the scheduled time) and pathology outcomes.

Methods

The Southern Co-operative Program for the Prevention of Colorectal Cancer (SCOOP)

Within the SCOOP framework, decision-making processes regarding surveillance recommendations differ between hospital types. In public academic hospitals, a nurse coordinator reviews medical reports and notes for all patients undergoing colonoscopy for a family history of CRC, personal history of neoplasia, and current polyp histology details, and makes a written recommendation about follow-up based on NHMRC guidelines.⁶ If the guidelines do not provide definitive surveillance advice for a particular case, local policies govern the most frequent scenarios, including 3-year recall for sessile serrated adenomas less than 10 mm in diameter and without dysplasia, and one-year recall for large sessile serrated adenomas with dysplasia. The recommendation is forwarded to the responsible specialist physician (a gastroenterologist or colorectal surgeon); after it is accepted, the patient is entered into the recall database, and they and their general practitioner are informed by letter of the histology result and the planned surveillance interval. If there is any conflict between the recommendations of the nurse and the specialist, the recommendation of the specialist is adopted. In private non-academic hospitals, patients are enrolled in SCOOP by their gastroenterologist, who is required to complete a colonoscopy request form that details current guideline recommendations according to histology and family history. On the basis of these details, the specialist recommends an appropriate surveillance interval, and the planned future surveillance dates are entered into the same recall database as that used by the public hospitals.

Eligible enrolees aged 50–74 years have interval FOBTs as previously described.¹⁵ We have found that interval FOBT provides a significant additional yield (ie, detects additional pathology),¹⁶ and lesions are detected significantly sooner in participants in the interval FOBT program than in non-participants.¹⁵ All positive test results lead to the scheduled surveillance colonoscopy being brought forward for diagnostic purposes.

Compliance of surveillance recommendation with NHMRC guidelines

Compliance of surveillance decisions with evidence-based guidelines is assessed by prospective auditing. The results of audits at the start of the program and after 5 years have been published.^{13,14} In this article we report an audit of compliance conducted during

March–May 2015 in which we assessed outcomes for the two different models of interval recommendation. The audits were conducted at Adelaide hospitals that have had full implementation of SCOOP for more than 10 years: two public hospitals (the Repatriation General Hospital; Flinders Medical Centre) and four private hospitals with gastroenterologists through the South Australian Group of Specialists (Flinders Private Hospital; the Tennyson Centre, Kurrultra Park; Wakefield Clinic; the Western Hospital).

Actual practice outcome and reasons for earlier than planned colonoscopy

The scheduled and actual dates of all surveillance colonoscopies during the calendar year 2015 were assessed. Colonoscopies performed more than 6 months before the scheduled date were deemed early procedures.¹⁷ Numbers of and reasons for early procedures were assessed. The numbers of early procedures according to original recall interval (3 years or less *v* more than 3 years) were compared.

Pathology findings from surveillance colonoscopies

As a measure of the long term outcomes of SCOOP, surveillance outcomes (invasive CRC and high risk adenomas) during the period 2000–2015 were assessed. High risk adenomas were defined by at least one of the following features: high grade dysplasia; size ≥ 10 mm; $> 20\%$ villous pathology; presence of three or more small tubular adenomas. As most CRCs develop from adenomas and because adherence to guidelines and effective removal of adenomas should reduce the number that progress to cancer, the ratio of high risk adenomas to CRCs by 5-year interval during the period 2000–2015 was calculated.

Data analysis

Outcomes for the two program styles were compared in χ^2 tests. Descriptive data were compared in unpaired *t* tests; age data (non-parametric distribution) were compared in Mann–Whitney tests. $P < 0.05$ was deemed statistically significant. Analyses were performed in GraphPad Prism 6 (GraphPad Software).

Ethics approval

The study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (reference, 422.13).

Results

Compliance of surveillance recommendations with guidelines

In the two public academic hospitals with nurse-led decision making, 422 colonoscopies were completed during the 3-month audit. Patients were aged 19.9–84.2 years (median, 61.8 years; interquartile range [IQR], 53.4–68.0 years); 199 (47%) were men. The findings of 410 colonoscopies were covered by the NHMRC guidelines, with recall recommendations ranging from 3 to 60 months; in 398 cases (97.1%), the recommendations made matched those of the guidelines. Of the 12 cases (2.9%) in which they did not (there was a discrepancy of at least 6 months), seven patients were given shorter surveillance intervals by the proceduralist (one each of 12 instead of 36 months and 24 instead of 36 months; five of 36 instead of 60 months), and five longer surveillance intervals (four of 24 instead of 12 months; one of 36 instead of 12 months). For a further 12 cases, the colonoscopy

1 Findings from 12 colonoscopy procedures (of 422 in total, March–May 2015) for which the NHMRC guidelines did not include a recommendation regarding the surveillance interval

Colonoscopy outcome	Number
Mucosa-associated lymphoid tissue	1
Human papillomavirus infection of the anal canal	1
Repeat investigations for an area of suspicious mucosa	1
Normal findings, but at elevated risk (immunosuppressive therapeutic agents)	1
Annual recurrence of an adenoma on polypectomy scar	1
Large proximal hyperplastic polyp	1
Incomplete excision of adenoma (< 10 mm)	6

outcomes were not covered by the guidelines for recall timing (Box 1).

In the four private non-academic hospitals using the physician-led surveillance model, 310 colonoscopies were completed during the 3-month audit, the recall recommendations for 257 of which (83%) matched the guidelines. The compliance by proceduralists ranged between 32% and 93%; the overall compliance of 83% (257 of 310) was significantly different from that for the public academic hospitals using nurse guidance for recall intervals ($P < 0.001$).

Actual practice and reasons for early colonoscopies

At the public academic hospitals with nurse-led decision making, 27% of colonoscopies were performed earlier than planned during 2015, compared with 20% for the private non-academic hospital, physician-led model (Box 2). The magnitude of the advance in procedure date was greater for the nurse-led decision-making model (mean, 27.4 months; standard deviation [SD], 12.9 months; private non-academic hospital physician-led model: mean, 22.9 months; SD, 11.5 months; $P < 0.001$). There were no differences in the median age of patients undergoing early colonoscopy in the two models, but the proportion of early procedures that were undertaken in men was higher in the nurse-led decision-making model (61% v 41%) (Box 2). Reasons for early procedures were similar in the two models, the most frequent being symptoms or positive FOBT results (Box 2). In both models, a higher proportion

of patients with a recall recommendation of greater than 3 years had an early procedure than of those with a shorter recall interval (nurse-led decision-making model: 173 of 414 [41.8%] v 63 of 470 [13.4%]; physician-led model: 168 of 522 [32.2%] v 85 of 757 [11.2%]).

Pathological findings from surveillance colonoscopies

The ratio of high risk adenomas to CRCs in patients enrolled in SCOOP was 6.6:1 during 2001–2005, 12.0:1 during 2006–2010, and 16.1:1 during 2011–2015. The proportion of high risk adenomas detected increased significantly, from 10.5% to 14.5% ($P < 0.001$) and that of detected cancers decreased significantly, from 1.6% to 0.9% ($P = 0.016$); 37.9% of colonoscopies were in patients tested during all three 5-year intervals.

Discussion

SCOOP has been operating for more than 15 years. Its expansion and implementation in hospitals with differing resource levels led us to investigate different approaches to maintaining compliance with surveillance guidelines. While the nurse-led model in public academic hospitals achieved greater compliance, the physician-led model with paper-based decision tools in private non-academic hospitals achieved 83% compliance. About one-quarter of procedures were undertaken earlier than initially recommended because of positive FOBT results or symptoms; this proportion is smaller than previously reported.^{8,9} The proportion of colonoscopies resulting in diagnoses of cancer declined between 2001 and 2015, indicating the success of ongoing surveillance.¹⁸

As most CRCs develop by the adenoma to carcinoma or serrated pathways, appropriately timed surveillance provides the opportunity to remove precursor lesions prior to disease progression.¹⁹ The American National Polyp Study accordingly found a reduction of up to 90% in the incidence of CRC in patients undergoing colonoscopic surveillance.²⁰ We similarly found that the ratio of high risk adenomas to CRCs increased during the period in which SCOOP operated, consistent with adenomas being removed before they progressed to cancer.

An early procedure may reflect an inappropriate initial recommendation by the specialist, or be motivated by patient-related factors. Prior to the introduction of the SCOOP nurse-led model in public academic hospitals in 2000, adherence to guidelines was 46%, but by 2002 had increased to 96%.¹³ This level of guideline adherence has been maintained 15 years later, evidence of the long

2 Numbers of and reasons for surveillance colonoscopies performed before the recommended interval, January–December 2015

	Public academic hospitals with nurse-led model	Private non-academic hospitals with physician-led model	P
Colonoscopy performed at least 6 months early			
Early colonoscopies	236 of 884 (27%)	253 of 1279 (20%)	< 0.001
Age (years), median (IQR)	65.9 (59.4–72.7)	66.6 (58.1–70.4)	0.19
Sex (men)	145 of 236 (61%)	104 of 253 (41%)	< 0.001
Reasons for early procedure			
Symptoms	86 of 236 (36%)	94 of 253 (37%)	0.87
Positive FOBT result	124 of 236 (52%)	124 of 253 (49%)	0.44
Other	26 of 236 (11%)	35 of 253 (14%)	0.35

FOBT = faecal occult blood test; IQR = interquartile range. ♦

term sustainability of the model. Adherence was higher for the nurse-led/public academic hospital model than for the physician-led/private non-academic hospitals approach. Factors other than the two models may have contributed to the difference, such as hospital type, but most gastroenterologists relevant to this audit performed colonoscopies at both public and private hospitals. Further, all patients were enrolled and alerted through the same recall database, and in both models clerical and nursing staff from each hospital attend regular meetings for ensuring quality of service. Indeed, these features may have resulted in the physician-led model achieving better adherence to guidelines than reported by previous studies.^{8,9}

It is important to assess both surveillance recommendations and actual practice to determine how best to relieve demand on endoscopy resources. In this audit, one-quarter of colonoscopies were performed early despite appropriate recommendations. Although compliance with guidelines was greater in the nurse-led/public academic hospital model, the proportion of colonoscopies performed earlier than scheduled in this model was larger than in the physician-led/private non-academic hospital model. As moving procedures forward was driven by patient-related factors, the difference cannot be attributed to differences between the two models.

In Italy, inappropriate recommendations were made for 37% of all colonoscopies; when a low risk adenoma was detected, 67% of recommendations were inappropriate.²¹ In Australia, 41–81% of recommendations concurred with guidelines.^{22,23} Audits of actual practice have found that up to 76% of procedures in Australia⁹ and 48% of those in the Netherlands⁸ are performed early. Not all early procedures are inappropriate; we have previously reported an increased yield of advanced neoplasia at early colonoscopies triggered by positive FOBT results.¹⁵ Gastroenterologists may also apply extra knowledge to alter surveillance recommendations in individual cases, as for 2.9% of our audited cases in the nurse-led academic hospital model. Published guidelines guide best practice at the population level, but a specialist may decide that they are not applicable to an individual presenting with features not covered by their recommendations.

One limitation of the current study was that we defined early procedures as those undertaken at least 6 months earlier than

intended, consistent with a recent Canadian study;¹⁷ it would, however, be useful to apply shorter cut-offs for shorter recall periods (eg, 3 months for one-year recommendations, as applied in another study⁸). A further limitation was that we did not examine reasons for specialists deviating from guideline recommendations. The relatively good adherence to guidelines in the physician-led model may reflect long term experience and learning. The paper-based decision aid in the physician-led model at private non-academic hospitals should be tested separately to further assess its usefulness in encouraging compliance with guidelines.

Our results may have implications for both early and late surveillance colonoscopy, but we focused on procedures undertaken ahead of schedule, as procedures performed too frequently can increase risks to patients, are expensive, and lengthen waiting lists. Australian studies have found the risk of bowel perforation during colonoscopy to be 0.10–0.13%.^{24,25} Early colonoscopies were more frequent in patients with an original surveillance interval of greater than 3 years. An Italian study found increased frequency of surveillance resulted in about 6700 more colonoscopies than expected, accounting for more than one-third of all of colonoscopies recommended in 2013.²¹ We have previously reported that adherence to national guidelines could reduce the annual number of post-polypectomy colonoscopies by 26%.¹⁴

In conclusion, our audit found that the strategies implemented by SCOOP ensure compliance with national surveillance guidelines of greater than 80%, with a nurse-led model in public academic hospitals achieving 97% adherence. Continuous monitoring of and education about colonoscopy surveillance intervals for patients at elevated risk of CRC promotes adherence to recall guidelines and efficient use of limited endoscopy resources.

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- 1 Australian Institute of Health and Welfare. Health system expenditure on cancer and other neoplasms in Australia: 2008–09. Canberra: AIHW, 2014.
- 2 Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer* 2015; 121: 3221–3229.
- 3 Barzi A, Lenz HJ, Quinn DI, et al. Comparative effectiveness of screening strategies for colorectal cancer. *Cancer* 2017; 123: 1516–1527.
- 4 Ait Ouakrim D, Lockett T, Boussioutas A, et al. Screening participation for people at increased risk of colorectal cancer due to family history: a systematic review and meta-analysis. *Fam Cancer* 2013; 12: 459–472.
- 5 Cottet V, Jooste V, Fournel I, et al. Long-term risk of colorectal cancer after adenoma removal: a population-based cohort study. *Gut* 2012; 61: 1180–1186.
- 6 Cancer Council Australia Colonoscopy Surveillance Working Party. Clinical practice guidelines for surveillance colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease. Dec 2011. https://wiki.cancer.org.au/australiawiki/images/8/80/Colonoscopy_Surveillance_Guidelines_FINAL_version_NHMRC_approved_Dec2011.pdf (viewed Feb 2018).
- 7 Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy surveillance after colorectal cancer resection: recommendations of the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2016; 150: 758–768.e711.
- 8 van Heijningen EM, Lansdorp-Vogelaar I, Steyerberg EW, et al. Adherence to surveillance guidelines after removal of colorectal adenomas: a large, community-based study. *Gut* 2015; 64: 1584–1592.
- 9 Baraty B, Wang H, Zhou D, et al. Non adherence to NHMRC post polypectomy surveillance intervals in an Australian tertiary institution [abstract: Australian Gastroenterology Week, Adelaide, 10–12 October 2016]. *J Gastroenterol Hepatol* 2016; 31(Suppl 2): 10.
- 10 Viiala CH, Tang KW, Lawrance IC, et al. Waiting times for colonoscopy and colorectal cancer diagnosis. *Med J Aust* 2007; 186: 282–285. <https://www.mja.com.au/journal/2007/186/6/waiting-times-colonoscopy-and-colorectal-cancer-diagnosis>
- 11 Alvarado GR, Basel AP, Hatzigeorgiou C, et al. Effect of a polyp tracking and notification program on colon adenoma surveillance and compliance to guideline recommendations. *Mil Med* 2016; 181: 920–925.
- 12 Leffler DA, Neeman N, Rabb JM, et al. An alerting system improves adherence to follow-up recommendations from colonoscopy examinations. *Gastroenterology* 2011; 140: 1166–1173.e1–3.
- 13 Bampton PA, Sandford JJ, Young GP. Applying evidence-based guidelines improves use of colonoscopy resources in patients with a moderate risk of colorectal neoplasia. *Med J Aust* 2002; 176: 155–157. <https://www.mja.com.au/journal/2002/176/4/applying-evidence-based-guidelines-improves-use-colonoscopy-resources-patients>
- 14 Bampton PA, Sandford JJ, Young GP. Achieving long-term compliance with colonoscopic surveillance guidelines for patients at increased risk of colorectal cancer in Australia. *Int J Clin Pract* 2007; 61: 510–513.

- 15 Lane JM, Chow E, Young GP, et al. Interval fecal immunochemical testing in a colonoscopic surveillance program speeds detection of colorectal neoplasia. *Gastroenterology* 2010; 139: 1918-1926.
- 16 Bampton PA, Sandford JJ, Cole SR, et al. Interval faecal occult blood testing in a colonoscopy based screening programme detects additional pathology. *Gut* 2005; 54: 803-806.
- 17 Schreuders E, Sint Nicolaas J, de Jonge V, et al. The appropriateness of surveillance colonoscopy intervals after polypectomy. *Can J Gastroenterol* 2013; 27: 33-38.
- 18 Atkin W, Wooldrage K, Brenner A, et al. Adenoma surveillance and colorectal cancer incidence: a retrospective, multicentre, cohort study. *Lancet Oncol* 2017; 18: 823-834.
- 19 Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007; 50: 113-130.
- 20 Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; 329: 1977-1981.
- 21 Zorzi M, Senore C, Turrin A, et al. Appropriateness of endoscopic surveillance recommendations in organised colorectal cancer screening programmes based on the faecal immunochemical test. *Gut* 2016; 65: 1822-1828.
- 22 Bobridge A, Bampton P, Cole S, et al. The psychological impact of participating in colorectal cancer screening by faecal immuno-chemical testing — the Australian experience. *Br J Cancer* 2014; 111: 970-975.
- 23 Yusoff IF, Hoffman NE, Ee HC. Colonoscopic surveillance for family history of colorectal cancer: are NHMRC guidelines being followed? *Med J Aust* 2002; 176: 151-154. <https://www.mja.com.au/journal/2002/176/4/colonoscopic-surveillance-family-history-colorectal-cancer-are-nhmrc-guidelines>
- 24 Azzopardi J, DeWitt DE. Quality and safety issues in procedural rural practice: a prospective evaluation of current quality and safety guidelines in 3000 colonoscopies. *Rural Remote Health* 2012; 12: 1949.
- 25 Viiala CH, Zimmerman M, Cullen DJ, Hoffman NE. Complication rates of colonoscopy in an Australian teaching hospital environment. *Intern Med J* 2003; 33: 355-359. ■