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ORIGINAL RESEARCH—CLINICAL

Clinicopathological Correlates of Dysplastic Sessile Serrated Lesion: A Prospective Cohort Study With a High Detection Rate

Mehul Lamba,[1] Ian Brown,[2,3] Mark Bettington,[3] Kimberley Ryan,[1] Katherine Hanigan,[1] Kay Lasenby,[1] Alicia Dixon,[1] Florian Grimpen,[1] Chun Gan,[1] Nicholas Tutticci,[1] Mark Appleyard,[1] and Barbara Leggett[1,4]

[1]*Department of Gastroenterology and Hepatology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia;* [2]*Department of Pathology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia;* [3]*Envoi Specialists Pathologists, Brisbane, Queensland, Australia; and* [4]*The School of Medicine, University of Queensland, Brisbane, Australia*

BACKGROUND AND AIMS: Sessile serrated lesions (SSLs) develop colorectal cancer (CRC), through a critical intermediary stage of SSL with dysplasia (SSLd). In this prospective observational study, we aimed to assess clinicopathological correlates of SSLd in the setting of a high lesion-detection rate. **METHODS:** Patients diagnosed with SSL and SSLd from February 2018 until January 2020 were prospectively recruited, and SSLd specimens were re-evaluated by 2 expert pathologists in a blinded manner. Associations were analyzed using multivariate logistic regression models. **RESULTS:** A total of 6425 patients underwent 7423 colonoscopies, and 2671 SSLs were resected from 1047 patients. The overall SSL detection rate per colonoscopy was 15.9%. The median age of patients with SSL was 54 years (interquartile range, 39–66), and 43.3% were male. After pathologist review, 24 SSLds were confirmed in 20 patients. The median size of SSLd was 8 mm (interquartile range, 5.75–15.25), and 13 of 24 SSLds were <10 mm in size. After multivariate analysis, older age (odds ratio = 1.07, 95% confidence interval = 1.03–1.1) and higher number of synchronous SSLs (odds ratio = 1.12, 95% confidence interval = 1.02–1.23) were associated with the presence of dysplasia. Patient sex and number and size of synchronous adenomas were not associated with the presence of SSLd. Seven of 20 patients with SSLd had synchronous or metachronous SSLd. Six of 20 patients with SSLd met the diagnostic criteria for serrated polyposis syndrome. **CONCLUSION:** The overall SSL detection rate was 15.9%, and 0.9% of SSLs were dysplastic. Older age and higher number of synchronous SSL were risk factors for the presence of dysplasia in SSLs. Thirty percent of patients with SSLd had serrated polyposis syndrome, and 35% had multiple SSLd.

Keywords: Cancer Prevention; Colorectal Carcinoma; Sessile Serrated Syndrome; Polypectomy; Polyp Detection Rate

Introduction

Sessile serrated lesions (SSLs) are the most common polyps giving rise to carcinomas developing via the serrated neoplasia pathway and are responsible for 25%–30% of all colorectal cancers (CRCs).[1–6] These lesions progress to cancer, through a key intermediary step of SSLs with cytological dysplasia (SSLd).[7] Moreover, SSLs are thought to be responsible for a significant proportion of interval CRCs owing to variety of factors including under-detection, incomplete resection, and rapid progression of dysplasia to cancer.[1,8–10] Given their malignant potential, detection and removal of SSLs are important to reduce the risk of CRC.

Significant heterogeneity has been reported in the SSL detection rate (SSLDR), likely due to operator-dependent factors as well as interobserver variability at pathology evaluation. For example, the overall SSLDR has been reported to vary from 0.6% to 11% in various screening populations.[11–15] In a recent Dutch study, a simple educational intervention led to a significant increase in the proximal serrated lesion detection rate from 9.3% to 15.6%.[16] Consequently, colonoscopy series with a low SSLDR are at risk of bias as many SSLs may not have been identified or described. We have previously reported a high SSLDR up to 20% in our population with an expert proceduralist and a specialist gastrointestinal (GI) pathologist.[17]

Furthermore, studies describing characteristics of SSLd are limited. SSLds are rarely encountered at colonoscopy because of short dwell time and rapid progression of cytological dysplasia to overt malignancy.[7] In retrospective pathology series, only 2%–5% of SSLs were found to have cytological dysplasia.[7,18,19] Data generated from pathology

Abbreviations used in this paper: **AA, advanced adenoma; CA, conventional adenoma; CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; HGD, high-grade dysplasia; IQR, interquartile range; OR, odds ratio; SPS, serrated polyposis syndrome; SSL, sessile serrated lesions; SSLd, sessile serrated lesions with dysplasia; SSLDR, SSL detection rate; TSA, traditional serrated adenoma.**

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archives have shown a mean SSLd size between 8.5 mm and 12 mm; however, the size estimate may not be as accurate as that obtained at colonoscopy.[7,18,20–22] In 2014, in a prospective case series, the endoscopic appearance of SSLd was described showing a median size of 15 mm.[23] In a retrospective series of lesions confined only to SSLs >20 mm, 32.4% of SSLs were found to harbor cytological dysplasia.[24] Another colonoscopy series found 58% of SSLs were <6 mm in size; however, the overall SSLDR was only 1.9%.[25] In a colonoscopy cohort study by Sano et al,[26] 8% of SSLs were found to be SSLd, and the risk of dysplasia correlated with SSL size; however, the baseline SSLDR was only 1.7%. Because interobserver variability at histological diagnosis of SSLs is well recognized, lack of a second pathologist review in abovementioned studies can further introduce bias and needs to be considered.[27–29]

Overall, data on clinicopathological characteristics of SSLd are sparse and heterogenous owing to several limitations as discussed previously. Recognition of risk factors associated with SSLd may help in identification of at-risk patient groups who require careful colonoscopy surveillance so as to minimize the risk of missing these lesions. The present study aims to determine the clinicopathological characteristics and prevalence of SSLd in a recent, large prospective colonoscopy cohort in the setting of a high SSLDR and expert pathology review.

Methods

Consecutive patients undergoing colonoscopy from January 2018 until December 2019 at a large tertiary care hospital were prospectively enrolled in the database. All colonoscopies were performed either by senior endoscopists (gastroenterologists or surgeons) or trainees under direct supervision.

The diagnosis of SSL was based on fulfilling the histological criteria as per the updated World Health Organization classification of tumors of the digestive system.[30] No lesions classified as hyperplastic polyps, regardless of their location in the colorectum, were included in the SSL cohort.

Patients diagnosed with one or more SSLs (with or without dysplasia) were identified from the database. Demographic, clinical, endoscopic, and pathology data were collected. Polyp size was determined based on endoscopic description in the procedure report. In addition, for patients diagnosed with SSLd, detailed case-note analyses were undertaken, and all colonoscopies performed until February 2021 were reviewed. Diagnosis of serrated polyposis syndrome (SPS) was based on the revised World Health Organization (2019) classification of tumors.[31]

Pathological Analysis

As a standard practice, all colonoscopy polypectomy specimens at our institution are reported by general pathologists and second opinion sought from specialist GI pathologists on case by case basis. SSLds share histological features with traditional serrated adenoma (TSA) as well as conventional tubular or tubulo-villous adenoma (CA); therefore, careful histological assessment is required for accurate diagnosis. In the present study, histological specimens for patients originally diagnosed as SSLd were retrieved. These specimens were independently reassessed by 2 specialist GI pathologists (IB and MB) in a blinded manner, and lesions were only considered to be SSLd if the diagnosis was confirmed by consensus by these 2 pathologists.

Statistical Analysis

SPSS statistical software (IBM SPSS Statistics, New York), version 27, was used for analysis. Differences in categorical variables were examined using the chi-squared test or Fisher's exact test, whereas continuous variables were assessed using the Student t-test. Multiple logistic regression analysis was performed on per-patient basis to examine for predictors associated with development of SSLd. Two-sided P values of <.05 were considered significant, and odds ratios (ORs) are presented with 95% confidence interval (95% CI).

Ethical approval was granted by the RBWH Human Research Ethics Committee.

Results

A total of 6425 patients underwent 7423 colonoscopies during the 2-year study period. A total of 2671 SSLs were resected in 1041 patients during 1180 colonoscopies. The overall SSLDR per colonoscopy was 15.9%. SSL prevalence was observed to be higher in women (OR = 1.2, 95% CI = 1.05–1.37, P = .0069); however, it did not vary based on patient age (P = .92) (Figure). The mean number of SSLs per patient with any SSL was 2.5 (range = 1–32). A total of 23.4% of all SSLs were ≥10 mm in size.

Thirty-six SSLs were originally reported to have cytological dysplasia. However, after re-evaluation by specialist GI pathologists, the diagnosis was confirmed in 24 SSLds in 20 patients. Of the 12 lesions originally diagnosed as SSLd but not confirmed, re-evaluation showed 4 lesions to be collision lesions of tubular adenoma with SSL and 8 lesions to be TSA. Only the 24 confirmed SSLds were further analyzed.

The prevalence of SSLd among all patients undergoing colonoscopy was 0.31% (95% CI = 0.2–0.48). On per-polyp analysis, 0.9% of all SSLs were found to have cytological dysplasia. Baseline demographic characteristics of patients with SSL and SSLd are shown in Table 1. Patients with SSLd were significantly older than patients with nondysplastic SSL (median age [interquartile range {IQR}]: 68.5 years (57–78.3) and 54 years (39–66) respectively, P < .01). There was, however, no significant difference in sex distribution between SSLd and nondysplastic SSL (P = .95).

Many SSLds were relatively small polyps, and the median size of SSLd was 8 mm (IQR = 5.75–15.25). Of all nondysplastic SSLs, 23.3% were ≥10 mm in size, compared with 11 of 24 (45.8%) SSLds (Table 2). SSLds were predominantly located in the proximal colon with 19 of 24 SSLds proximal to the splenic flexure.

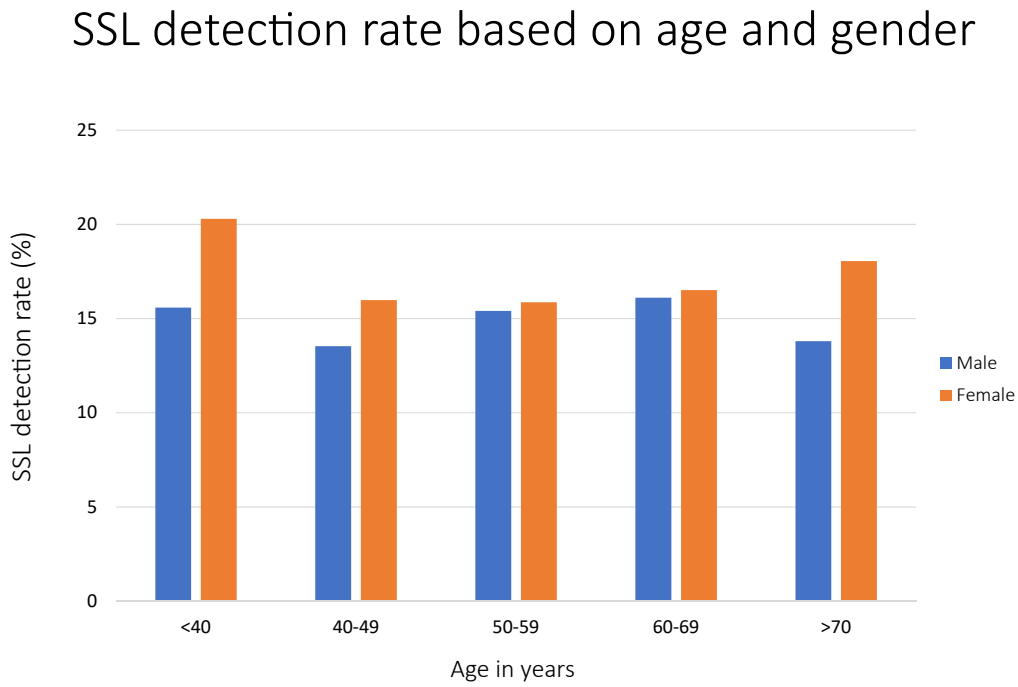

Figure. SSL prevalence per colonoscopy in accordance with age and sex.

Synchronous Lesions in Patients With SSLd

Patients with SSLd were overall found to have a higher number of synchronous nondysplastic SSLs at colonoscopy (median [IQR] = 3 [1–6.5]) than patients without SSLd (median [IQR] = 1 [1–3]), ($P < .01$) (Table 2). There was no significant difference in prevalence of synchronous TSA. One of 20 patients with SSLd had synchronous TSA, compared with 16 of 1027 patients without SSLd ($P = .23$). A total of 48.52% (508) of patients with SSLs were found to have CAs, and 13.37% (140) of patients had advanced adenomas (AA) defined as 10 mm or greater, villous or with severe dysplasia. There was no significant difference in the prevalence of CA or AA in patients with SSLd, when compared with patients with nondysplastic SSLs (Tables 2 and 3).

Predictors of SSLd

After multivariable adjustment, older age (OR [95% CI] = 1.07 [1.03–1.10], for each year) and higher number of SSLs per patient (OR [95% CI] = 1.12 [1.02–1.23]) were found to be associated with the presence of cytological dysplasia in SSLs (Table 3).

Characteristics of Patients With SSLd

We further performed detailed case-note analyses of patients with SSLd (Table 4). Four of 20 patients were found to have synchronous SSLd at the time of diagnosis. An additional 3 of 20 patients were found to have had SSLd resected at previous colonoscopy, at a median interval of 3.1 years. Two of 20 patients had history of previous colorectal cancer (rectal cancer in both patients). Based on their cumulative colonoscopy findings to date, 6 of 20 patients fulfilled the diagnostic criteria for SPS.

Adenoma Detection Rate

The adenoma detection rate during the study period (January 2018 to December 2019) at our institution was

Table 1. Baseline Demographic Characteristics of Patients Diagnosed With Sessile Serrated Lesions

Characteristics	Overall	Patients with SSLd (n = 20)	Patients with SSLs without dysplasia (n = 1027)
Age, Median (IQR)	54 y (39–66)	68.5 y (57–78.3)	54 y (39–66)
20–29 y, n	66	1	65
30–39 y, n	199	1	198
40–49 y, n	157	1	156
50–59 y, n	212	3	209
60–69 y, n	229	4	225
70–79 y, n	161	6	155
> 80 y, n	43	4	39
Sex, male (%)	464 (44.3%)	9 (45%)	455 (44.3%)

Table 2. Characteristics of Polyps Resected at Colonoscopy in Patients With At Least One Sessile Serrated Lesion

Characteristics of polyps resected	Patients with SSLd (n = 20)	Patients with SSLs without dysplasia (n = 1027)
Sessile serrated lesion (SSL)		
Total no. of SSLs	100	2571
Median no. of SSLs per patient, (IQR)	3 (1–6.5)	1 (1–3)
Number of SSLs ≥10 mm	26 (26%)	598 (23.3%)
Number of patients with at least 1 SSL ≥10 mm	13 (65%)	381 (37.1%)
Conventional adenoma (CA)		
Total number of CAs	64	1561
Median number of CAs per patient, (IQR)	1 (0–4)	0 (0–2)
Number of patients with ≥1 CAs	12 (60%)	496 (42.4%)
Number of patients with ≥1 CAs with HGD	1 (5%)	22 (2.1%)
Number of patients with ≥1 AAs	4 (20%)	136 (13.2%)
Traditional serrated adenoma (TSA)		
Total number of TSAs	1	17
Median number of TSAs per patient, IQR	0 (0)	0 (0)
Number of patients with ≥1 TSAs	1 (5%)	16 (1.6%)

HGD, high-grade dysplasia.

52.9%. The adenoma detection rate assessment was based on patients 50 years or older undergoing colonoscopy for screening or surveillance of CRC (excluding patients with a known history of inflammatory bowel disease or polyposis syndrome).

Discussion

SSLs are responsible for most of the CRCs developing via the serrated neoplasia pathway, and SSLd is a critical intermediary step. Because SSLds have a short dwell time before rapidly progressing to carcinoma, these are rarely encountered at colonoscopy, and consequently, their clinicopathological characteristics are not well defined. In the present study, using a prospectively collated colonoscopy series from a large tertiary center with a high SSLDR and strict histological criteria after expert pathologist review, we aimed to describe characteristics of patients with SSLd.

The overall SSLDR at our center was 15.9%. Overall, 0.9% of all SSLs were found to harbor cytological dysplasia. The prevalence of cytological dysplasia in SSLs in our cohort is lower than that in large pathology series from Australia[18] and the United States,[19] where 2%–5% of SSLs were observed to be dysplastic. Two retrospective colonoscopy series from the United States found 14%–37% of SSLs to have dysplasia.[25,32] However, the latter results are likely biased and may not represent true prevalence of dysplasia among SSL polyps because the baseline SSLDR in these series was very low at <2% and the likelihood of polyp detection may have been influenced by the presence of dysplasia.

The risk of harboring high-grade dysplasia in conventional adenomatous polyps correlates with size and is generally seen in polyps >1 cm in size.[33,34] However, this is not true for SSLd. We observed that the median size of SSLd was 8 mm (IQR = 5.75–15.25) and over half of SSLds were <10 mm in size. Our findings are in line with previous reports, where the reported median SSLd size was 9–12 mm and approximately 40% of all SSLds were found to be subcentimeter polyps.[7,18,35]

Table 3. Univariable and Multivariable Analyses of Predictors Associated With the Presence of SSLd in Per-patient Analysis

	Univariable analysis		Multivariable analysis	
Predictors	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Older age[a]	1.05 (1.02–1.09)	.001	1.07 (1.03–1.10)	<.001
Male sex	0.97 (0.4–2.37)	.95		
CA	0.62 (0.25–1.54)	.30		
CA with HGD	0.42 (0.05–3.24)	.40		
AA	0.61 (0.20–1.85)	.38		
Total number of SSLs	1.1 (1.04–1.18)	.003	1.12 (1.02–1.23)	.015
Number of SSLs >10 mm	1.34 (1.09–1.66)	.007	1.21 (0.91–1.61)	.184
TSA	0.28 (0.03–2.24)	.23		

HGD, high-grade dysplasia.
[a]The odds ratio for every 1-y increase in age.

Table 4. Description of Patients With SSLd

Patient	Sex	Age at the current procedure in years	Location of SSLd	Estimated size in mm	Metachronous SSLd	SPS
Patient 1	Female	63	Transverse colon	8		
Patient 2	Male	82	Ascending colon	5	Yes	
			Recto-sigmoid	6		
Patient 3	Female	82	Caecum	30	Yes	Yes
			Transverse colon	6		
Patient 4	Female	68	Ascending colon	20		
			Ascending colon	2		
Patient 5	Female	74	Hepatic flexure	40		
Patient 6	Female	74	Hepatic flexure	40		
Patient 7	Female	80	Ascending colon	6		
Patient 8	Male	77	Transverse colon	5	Yes	Yes
			Descending colon	10		
Patient 9	Female	67	Ascending colon	13		
Patient 10	Female	74	Hepatic flexure	5	Yes	
Patient 11	Male	41	Recto-sigmoid	10		
Patient 12	Female	61	Ascending colon	8		
Patient 13	Male	29	Ascending colon	18		Yes
Patient 14	Female	89	Transverse colon	15		
Patient 15	Female	59	Caecum	16		Yes
Patient 16	Male	80	Ascending colon	4	Yes	Yes
Patient 17	Male	55	Recto-sigmoid	11		
Patient 18	Male	71	Transverse colon	6	Yes	Yes
Patient 19	Female	35	Sigmoid colon	6		
Patient 20	Female	78	Caecum	3	Yes	

Patients 2, 3, and 8 had 2 synchronous SSLd each.

In multivariable analysis, older age and number of SSLs resected were found to be associated with the presence of cytological dysplasia in SSLs. Our findings are concordant with previous studies. For example, Lash et al[19] reported the mean age of patients with SSLd was 66–72 years, compared with 61 years in patients with nondysplastic SSLs. In a Japanese cohort study, Murukami et al[35] made similar observation, where the mean age of patients with SSLd was 64.9 years, compared with 62 years in nondysplastic SSLs. Similarly, Bettington et al,[7] while comparing 2 separate cohorts of patients from pathology databases, concluded that patients with SSLd were 17 years older than patients with nondysplastic SSLs. It is postulated that oncogenic *BRAF* mutation in the SSL-carcinoma pathway drives the development of the *CpG* island methylator phenotype, and accumulation of methylation over time leads to progression of SSLs, with eventual development of overt dysplasia.[7,36,37]

The association between sex and SSLs with or without dysplasia is, however, less clear. In the present study, the overall SSLDR was observed to be higher in women (OR = 1.2, 95% CI = 1.05–1.37, P = .0069). Our findings are in contrast to the recent systematic review and meta-analysis by Meester et al,[38] comprising studies published till 2018, where pooled SSL prevalence rates in North-American and European studies were higher in men (4.9%, 95% CI = 2.8%–7.2%) than those in women (4.1%, 95% CI 2.7%–5.5%). The reason for observed difference in findings is uncertain; however, a low baseline polyp detection rate in previous studies and possibly genetic or environmental factors may be responsible. In concordance with findings from a pathology series by Bettington et al[7] and colonoscopy series from Sano et al,[26] we did not find association between sex and risk of cytological dysplasia in SSLs.

In the present study, 7 of 20 patients with SSLd were found to have 2 or more dysplastic SSLs (synchronous or metachronous). It is known that the presence of SSLd is associated with significantly increased risk of developing metachronous CRC at follow-up.[39] It is therefore likely that individuals with SSLd may have an inherent predisposition (genetic or environmental) to accumulate molecular changes required for development of dysplasia. In addition, we found that 6 of 20 patients with SSLd had underlying SPS. Association between SPS and SSLd was also demonstrated in a multicenter study by Dekker et al, where 26.3% patients with SPS were found to have had at least 1 SSLd during surveillance.[40] Because patients with SSLd are at increased risk of developing high-risk lesions, our findings support more frequent colonoscopy surveillance in this group as per the current guidelines.[41–43]

Our study also underscores the importance of an expert GI pathologist review for diagnosis of SSLd. The dysplastic foci in SSLs often share some architectural resemblance to TSA, as described by Bettington et al.[44] As demonstrated in our series, 36 polyps were initially reported as SSLd.

However, on expert pathologist review, only 24 polyps (66.6%) were confirmed to be SSLd. The most common alternative diagnoses were TSA (8) and a collision-type polyp (4). Given that clinical relevance and risk of cancer progression are significantly higher in SSLd, when compared with TSA or collision-type polyps, it is pertinent that a second expert pathologist review is sought to risk-stratify and consider an appropriate colonoscopy follow-up interval.

There are several limitations to our study which ought to be acknowledged. On a per-patient basis, we were unable to classify if whether colonoscopies were index or follow-up procedures. Consequently, our SSL prevalence rate is not true population prevalence, but rather reflects a prevalence rate encountered in a general gastroenterology practice in a tertiary care hospital. Environmental factors such as smoking,[45] alcohol consumption,[45,46] and obesity[47] have been linked to development of SSLs and consequently may influence the risk of developing cytological dysplasia. However, data on these variables were not available for analyses. Detailed data on size and location of all nondysplastic SSLs were not available, precluding assessment of these predictors. The main strengths of our study, however, include prospective case ascertainment in a large series, expert GI pathologist review to confirm diagnosis of SSLd, and proceduralists with a high SSLDR. Thus, we are able to present contemporary epidemiology and clinicopathological correlates associated with the presence of SSLd.

Conclusion

In a prospective colonoscopy series with a high SSLDR, 0.9% of SSLs were found to have cytological dysplasia. The predictors associated with development of SSLd include increasing age and higher number of synchronous SSL. In our study, 30% of patients with SSLd were diagnosed with SPS, and 35% were found to have 2 or more SSLds during follow-up.

References

1. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology 2010; 138:2088–2100.
2. Bettington M, Walker N, Clouston A, et al. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology 2013;62:367–386.
3. Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol 2011;42:1–10.
4. O'Brien MJ, Zhao Q, Yang S. Colorectal serrated pathway cancers and precursors. Histopathology 2015; 66:49–65.
5. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 2007;50:113–130.
6. Crockett SD, Nagtegaal ID. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. Gastroenterology 2019;157:949–966.e4.
7. Bettington M, Walker N, Rosty C, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut 2017; 66:97–106.
8. East JE, Atkin WS, Bateman AC, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017;66:1181–1196.
9. Arain MA, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol 2010;105:1189–1195.
10. Sawhney MS, Farrar WD, Gudiseva S, et al. Microsatellite instability in interval colon cancers. Gastroenterology 2006;131:1700–1705.
11. Hetzel JT, Huang CS, Coukos JA, et al. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. Am J Gastroenterol 2010; 105:2656–2664.
12. Hazewinkel Y, de Wijkerslooth TR, Stoop EM, et al. Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy. Endoscopy 2014;46:219–224.
13. Freedman JS, Harari DY, Bamji ND, et al. The detection of premalignant colon polyps during colonoscopy is stable throughout the workday. Gastrointest Endosc 2011;73:1197–1206.
14. Buda A, De Bona M, Dotti I, et al. Prevalence of different subtypes of serrated polyps and risk of synchronous advanced colorectal neoplasia in average-risk population undergoing first-time colonoscopy. Clin Transl Gastroenterol 2012;3:e6.
15. Gurudu SR, Heigh RI, De Petris G, et al. Sessile serrated adenomas: demographic, endoscopic and pathological characteristics. World J Gastroenterol 2010;16:3402–3405.
16. Bleijenberg AGC, van Leerdam ME, Bargeman M, et al. Substantial and sustained improvement of serrated polyp detection after a simple educational intervention: results from a prospective controlled trial. Gut 2020; 69:2150–2158.
17. Bettington M, Walker N, Rahman T, et al. High prevalence of sessile serrated adenomas in contemporary outpatient colonoscopy practice. Intern Med J 2017; 47:318–323.
18. Liu C, Walker NI, Leggett BA, et al. Sessile serrated adenomas with dysplasia: morphological patterns and correlations with MLH1 immunohistochemistry. Mod Pathol 2017;30:1728–1738.
19. Yang JF, Tang SJ, Lash RH, et al. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. Arch Pathol Lab Med 2015; 139:388–393.
20. Sheridan TB, Fenton H, Lewin MR, et al. Sessile serrated adenomas with low- and high-grade dysplasia and early carcinomas: an immunohistochemical study of serrated lesions "caught in the act". Am J Clin Pathol 2006; 126:564–571.
21. Goldstein NS. Small colonic microsatellite unstable adenocarcinomas and high-grade epithelial dysplasias in sessile serrated adenoma polypectomy specimens: a

study of eight cases. Am J Clin Pathol 2006; 125:132–145.
22. Fujita K, Yamamoto H, Matsumoto T, et al. Sessile serrated adenoma with early neoplastic progression: a clinicopathologic and molecular study. Am J Surg Pathol 2011;35:295–304.
23. Nanda KS, Tutticci N, Burgess N, et al. Caught in the act: endoscopic characterization of sessile serrated adenomas with dysplasia. Gastrointest Endosc 2014; 79:864–870.
24. Burgess NG, Pellise M, Nanda KS, et al. Clinical and endoscopic predictors of cytological dysplasia or cancer in a prospective multicentre study of large sessile serrated adenomas/polyps. Gut 2016;65:437–446.
25. Bouwens MW, van Herwaarden YJ, Winkens B, et al. Endoscopic characterization of sessile serrated adenomas/polyps with and without dysplasia. Endoscopy 2014;46:225–235.
26. Sano W, Fujimori T, Ichikawa K, et al. Clinical and endoscopic evaluations of sessile serrated adenoma/polyps with cytological dysplasia. J Gastroenterol Hepatol 2018;33:1454–1460.
27. Wong NA, Hunt LP, Novelli MR, et al. Observer agreement in the diagnosis of serrated polyps of the large bowel. Histopathology 2009;55:63–66.
28. Ensari A, Bilezikci B, Carneiro F, et al. Serrated polyps of the colon: how reproducible is their classification? Virchows Arch 2012;461:495–504.
29. Payne SR, Church TR, Wandell M, et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol 2014; 12:1119–1126.
30. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182–188.
31. Rosty CBL, Dekker E, Nagtegaal ID. Serrated polyposis. In: WHO classification of tumours of the digestive system. 5th ed. Lyon: International Agency for Research on Cancer, 2019:532–534.
32. Lash RH, Genta RM, Schuler CM. Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. J Clin Pathol 2010;63:681–686.
33. Gibson JA, Odze RD. Pathology of premalignant colorectal neoplasia. Dig Endosc 2016;28:312–323.
34. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. Gastrointest Endosc Clin N Am 2002;12:1–9, v.
35. Murakami T, Sakamoto N, Ritsuno H, et al. Distinct endoscopic characteristics of sessile serrated adenoma/polyp with and without dysplasia/carcinoma. Gastrointest Endosc 2017;85:590–600.
36. Bettington M, Brown I, Rosty C, et al. Sessile serrated adenomas in young patients may have limited risk of malignant progression. J Clin Gastroenterol 2019; 53:e113–e116.
37. Satorres C, Garcia-Campos M, Bustamante-Balen M. Molecular features of the serrated pathway to colorectal cancer: current knowledge and future directions. Gut Liver 2021;15:31–43.
38. Meester RGS, van Herk M, Lansdorp-Vogelaar I, et al. Prevalence and clinical features of sessile serrated polyps: a systematic review. Gastroenterology 2020; 159:105–118.e25.
39. Erichsen R, Baron JA, Hamilton-Dutoit SJ, et al. Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology 2016; 150:895–902.e5.
40. IJspeert JE, Rana SA, Atkinson NS, et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. Gut 2017;66:278–284.
41. Rutter MD, East J, Rees CJ, et al. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. Gut 2020;69:201–223.
42. Hassan C, Antonelli G, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) guideline - update 2020. Endoscopy 2020;52:687–700.
43. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-Society task force on colorectal cancer. Gastrointest Endosc 2020;91:463–485.e5.
44. Bettington M, Rosty C, Whitehall V, et al. A morphological and molecular study of proposed early forms of traditional serrated adenoma. Histopathology 2018;73:1023–1029.
45. Bailie L, Loughrey MB, Coleman HG. Lifestyle risk factors for serrated colorectal polyps: a systematic review and meta-analysis. Gastroenterology 2017;152:92–104.
46. Burnett-Hartman AN, Passarelli MN, Adams SV, et al. Differences in epidemiologic risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. Am J Epidemiol 2013; 177:625–637.
47. He X, Wu K, Ogino S, et al. Association between risk factors for colorectal cancer and risk of serrated polyps and conventional adenomas. Gastroenterology 2018; 155:355–373.e18.

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Correspondence:
Address correspondence to: Mehul Lamba, MD, FRACP, Department of Gastroenterology and Hepatology, Royal Brisbane and Women's Hospital, Butterfield St, Herston, Queensland 4029, Australia. e-mail: mehul.lamba@health.qld.gov.au.

Authors' Contributions:
Mehul Lamba contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Ian Brown contributed to review of histology slides and critical revision of the manuscript for important intellectual content. Mark Bettington contributed to review of histology slides. Kimberley Ryan contributed to administrative support and critical revision of the manuscript for important intellectual content. Katherine Hanigan contributed to acquisition of data, administrative support, and critical revision of the manuscript for important intellectual content. Kay Lasenby and

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