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Colorectal sessile serrated lesion with large size or synchronous neoplasm: a prospective study

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Abstract

Background—Colorectal sessile serrated lesion (SSL) with synchronous neoplasm or large size are linked to higher risk of cancer, but their characteristics are unclear.

Methods—We prospectively included consecutive colorectal hyperplastic polyp and SSL collected at our institution from August 2011 to August 2012. The following data were collected and analyzed: age, gender, polyp site, aggregated polyp size, history of polyp, and synchronous neoplasm.

Results—We collected 437 specimens including 353 (80.8%) hyperplastic polyp and 84 (19.2%) SSL. Compared with hyperplastic polyp, SSL was independently associated with proximal colon [odds ratio (OR) 3.61, $P < 0.001$], larger size (OR 3.98, $P < 0.001$), but not history of polyp, age or gender. Large SSL (≥ 1 vs < 1 cm) was associated with polyp site ($P = 0.035$) and synchronous advanced adenoma and cancer ($P < 0.001$). SSL with synchronous adenoma and cancer were more likely found in males (OR 1.91, $P = 0.001$), elderly (OR 1.02, $P = 0.033$), and patients with the index polyp in proximal colon (OR 1.32, $P = 0.022$), but not related to history of adenoma and cancer. Moreover, synchronous adenoma, SSL and cancer were independently associated with male gender (OR 1.90, $P < 0.001$), but surprisingly not older age, histology of index polyp (SSL vs hyperplastic polyp), index-polyp site or history of adenoma and cancer.

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†Dr. Xiong and Dr. Zhang equally supervised the works.

Conflicts of interest

There are no conflicts of interest.

Conclusions—This prospective study shows male gender is associated with both synchronous adenoma and cancer, and synchronous adenoma, SSL and cancer, while index polyp site is associated with synchronous adenoma and cancer.

Keywords

colorectal cancer; history; sessile serrated adenoma; synchronous neoplasm

Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women in the USA [1]. The serrated neoplastic pathway accounts for up to one-third of all sporadic CRCs [2]. Of particular concern, a disproportional number of interval CRCs (i.e., cancers occurred after a negative screening-colonoscopy) are associated with serrated lesion [3]. In contrast to conventional adenomas, which tend to be slow-growing and polypoid, serrated lesions are flat, predominately right-sided and often missed by endoscopists [4–6], and thought to have the potential for rapid growth [7]. Moreover, colorectal serrated lesions are subject to wide variations in endoscopic detection and pathologic interpretation, which have undermined current screening and surveillance practices. The histological classification of colorectal serrated polyps has evolved over the last two decades. The 2019 WHO classifications of colorectal tumors categorized three major types of colorectal serrated polyp as hyperplastic polyp, sessile serrated lesion (SSL, formerly known as sessile serrated adenoma/polyp) and traditional serrated adenoma (TSA) [8]. Studies show that SSL links to synchronous and future CRC, but hyperplastic polyp does not [9–11]. Therefore, it is important to distinguish these two entities.

The USA, British, European and Korean guidelines on postpolypectomy surveillance all recommended shorter intervals (3–5 years, depending on polyp histology) for the patients who had 1 adenoma detected during colonoscopy, primarily based on a higher risk of future CRC and colorectal neoplasm [12–16]. Recent works show that synchronous SSL and larger polyp sizes (endoscopic or microscopic measures) link to the presence of advanced neoplasms [10,17,18]. Another two studies also find that family history of CRC is associated with a higher rate of detectable SSL [19,20]. However, it is not clear whether the synchronous SSL and (personal) history of CRC, adenoma or SSL are associated with an increased risk of SSL. Indeed, some scholars recently called for more studies on the subject, and tentatively recommend close follow-ups on the patients with a history of large and proximal serrated polyps or SSL [21]. In addition, other clinicopatho-logical features associated with SSL, such as the polyp location and herniation of crypts [22,23], could help to identify high-risk population and detect these deviants before they progress to advanced neoplasms. To address these knowledge gaps, we analyzed the factors associated with presence, synchronous neoplasm and large-size (>1 cm) of SSL.

Synchronous adenoma was found in 45–50% of the patients with SSL, and synchronous cancer in 4–5% of them [24,25], while the detection rate of synchronous adenoma might be slightly higher (55%) in the patients with sessile serrated polyposis syndrome [23]. Pai *et al.* [26] reported a link between SSL and synchronous SSL without reporting odds ratios.

Moreover, SSL was also found linked to synchronous advanced neoplasm [9,11,27]. Recently, SSL and TSA together were associated with metachronous (detected within 12 months of the index case' diagnosis) high-risk adenoma and serrated polyp >1 cm [18]. However, the prior works are mostly descriptive studies, with few multivariate analyses. More importantly, the most common diagnostic mimicker of SSL, namely hyperplastic polyp, has rarely been compared with. Therefore, we also aimed to conduct multivariate analyses on the synchronous neoplasm of SSL and hyperplastic polyp, adjusted for the confounders such as age, gender, polyp size and polyp location.

Methods

Study population

The study population comprised all patients who underwent screening colonoscopy and their respective specimens were collected in the University Medical Center of Princeton from August 2011 to August 2012. An Institutional Review Board (IRB) approval has been obtained at the University Medical Center of Princeton at Plainsboro, New Jersey, USA.

All colonoscopy procedures were performed by one of the four staff gastroenterologists, who were all board certified in gastroenterology and had more than 5 years of experience as of 2012. The bowel preparation was deemed acceptable or excellent by the caring gastroenterologist. The following data were collected and analyzed: patient's age, gender, polyp site, aggregated polyp size (APS) on hematoxylin and eosin slides, personal history of colorectal polyp, and synchronous neoplasm including adenoma, SSL and carcinoma detected during the same colonoscopy procedure. The polyp site was categorized into right, transverse and left colons according to the clinician's designation. The APS was measured under a microscopy which was calibrated with a micrometer. The personal history of colorectal polyp was obtained by searching our pathology database and using clinical information provided by the caring gastroenterologists. The synchronous neoplasm was defined as a neoplasm identified during the same endoscopic procedure as an index polyp, and submitted for pathologic examination. Synchronous adenoma included synchronous tubular adenoma, tubulovillous adenoma and TSA with or without high-grade dysplasia, while synchronous adenoma and cancer also included cancers. We did not include any polyp that was identified during the endoscopic procedure, but not submitted for pathologic examination due to the lack of pathologic evidence.

Histopathology

The histopathological diagnosis was based on the morphological features according to the established diagnostic criteria, namely the WHO classifications of tumors on digestive system and the USA consensus on serrated polyps [28,29]. Specifically, SSL was defined based on predominantly architectural distortion with irregular dilated crypts, including dilation of the base of the crypts that often have an 'L' or inverted 'T' shape. Hyperplastic polyps are similar to SSL except their glands with serrations limited mostly to the upper one half of the crypts, and no evidence of dilated crypt at the base. We have carefully rereviewed the slides to ensure the diagnostic accuracy without knowledge of prior diagnosis (i.e., being blinded). Advanced adenoma was defined as an adenoma ≥ 10 mm, having >30% of villous

component (also known as villous or tubulovillous adenoma), or with high-grade dysplasia [15,30,31]. Advanced neoplasia comprised advanced adenoma and CRC together.

Statistical analyses

Statistical analyses were conducted using Stata (version 15, Stata Corp, College Station, Texas, USA). Continuous variables are expressed as mean $\pm$ SD, while categorical variables are expressed as counts and percentages. Differences between variables were assessed by the χ^2 , Fisher exact or ANOVA test. The factors associated with SSL were identified using logistic regression analysis. We included the variables in multivariable regression if they had borderline statistical significance ($P < 0.20$) in the univariable analyses. All P values were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Table 1 presents the characteristics of 437 serrated polyps from 270 subjects, including the consecutive hyperplastic polyp ($n = 353$, 80.8%) and SSL ($n = 84$, 19.2%). Among the SSL, 66 (78.57%) were less than 1 cm in size, and 18 (21.43%) $\geq$ 1 cm (Table 1). Approximately, 54% of the subjects were women and the mean age was 59 years (SD = 10.1). The distribution of the subjects among each age category was as follows: the cases of hyperplastic polyp included mean age of 59.4 years (SD = 10.4), mean APS 0.47 cm (SD = 0.39), females with 5% and higher proportion located in left of colon ($n = 276$, 78.41%). The cases of SSL were with a mean age 57.7 years (SD = 9.12), larger size APS 0.80 cm (SD = 0.56) than with hyperplastic polyp, females ($n = 162$, 51.81%) and greater proportion located in right side of colon ($n = 41$, 48.81%).

Patients with hyperplastic polyp and SSL significantly differed by APS, location, synchronous SSL and personal history of previous hyperplastic polyp /SSL/adenoma/ carcinoma (Table 1). A higher proportion of cases with previous adenoma history were seen among patients having hyperplastic polyp 90/353 (25.50%) compared with SSL 13/84 (15.48%). Patients with SSL more likely had a history of SSL than those with hyperplastic polyp (6/353, 1.13% in hyperplastic polyp vs 4/84, 4.76% in SSL, Table 1). Because SSL larger than 1 cm had much higher risk of metachronous SSL or high-risk adenoma [18], we characterized the factors associated with large SSL ($\geq$ 1 cm). Large SSLs were linked to polyp site and synchronous advanced adenoma or cancer, but not other included factors (Table 1). Additional analysis also showed no association between the number of synchronous adenoma and polyp histology (Fisher exact test, $P = 0.61$).

In the univariate analysis for identifying factors associated with a diagnosis of SSL (Table 2), compared to hyperplastic polyp, SSL was associated with increasing APS and proximal colon. The best-fit multivariate regression analysis showed that SSL was more likely diagnosed with index polyp in the proximal colon, and larger APS (Table 2).

The multivariate regression analysis also showed that synchronous adenoma and cancer were more likely found in the patients of male gender, of older age, and with the index polyp in the proximal colon, but not related to history of adenoma and cancer (Table 3). We also

found that synchronous adenoma, SSL and cancer were only associated with male gender, and surprisingly not with SSL diagnosis (Table 4).

Discussion

This to our knowledge is the first prospective study on the factors linked to synchronous neoplasm and large-size SSL. Among the 437 serrated polyps, large SSL (≥ 1 cm) was associated with polyp site (more common in right or transverse colon) and synchronous advanced adenoma or cancer. The multivariable regression analyses also show that only size and site were associated with diagnosis of SSL (vs hyperplastic polyp). Furthermore, male gender, advanced age and index-polyp site were interdependently associated with synchronous adenoma and cancer, while only male gender, not even SSL diagnosis, was linked to synchronous adenoma, SSL and cancer.

Patients with SSL are more likely to have a greater polyp burden, and may have synchronous CRC, advanced adenomas and metachronous neoplasms [6,10,32,33], while our recent small-scale study on crypt-herniation in SSL identified no association of synchronous SSL with presence of SSL [22]. Consistent with prior studies, we here provide early evidence that SSL patients more likely have synchronous SSL than hyperplastic polyp (Table 1), which can be explained by their unique molecular alterations and excessive cancer risks [28,34–39]. This is in line with the reported association of SSL with synchronous neoplasm and synchronous advanced neoplasms [9,11,18,23–26]. Indeed, both large and proximal serrated lesions have been found associated with an increased risk of synchronous advanced conventional neoplasms [40], and advanced neoplasia has been associated with the presence of large serrated lesions [41,42]. The findings appear to support more careful, thorough endoscopic examinations in the patients with (index) SSL to identify synchronous SSL.

Two noteworthy strengths of this study are the use of multivariate models and the prospective study design, which would significantly reduce the biases and confounding. Most of the prior works were retrospective studies, except a handful of prospective studies [9,17,22,32,43]. Moreover, several related studies were descriptive or without reporting an OR [23–26]. Several related studies on the synchronous advanced adenoma of serrated polyp conducted only univariate or bivariate association (regression) analyses [9,27,40]. Furthermore, one recent study on the metachronous advanced adenomas of serrated polyp was adjusted for age, sex, BMI, but not histology, history of adenoma or synchronous SSL [18]. In addition, one of our studies on Chinese patients with serrated polyp included gender, age, polyp size and location, but not history of polyp or synchronous SSL [10]. Finally, another study of ours, despite of using similar multivariate models, was mainly focused on synchronous advanced adenoma and cancer, and synchronous adenoma and cancer and mostly agreed with our findings on the subjects [22]. It, however, did not include synchronous SSL in the model outcome (dependent variable) which was assessed in this study.

The recent guidelines on postpolypectomy surveillance recommended shorter intervals for the patients who had one or more adenomas detected during colonoscopy [12–16]. However, to our best knowledge, the association between history of polyp and SSL is not clear. This

prospective study found that, despite of the potential positive link, there was not statistically significant association of history of cancer, history of adenoma or history of SSL with the presence of SSL. This finding is consistent with our recent work [22]. It is noteworthy that our studies' sample sizes might not be large enough to detect the potential link. Moreover, SSLs are more likely missed in the patients with history of polyps [4]. SSL thus might too be underdetected or missed, which then introduced a missing-data bias. Therefore, large prospective studies are needed to validate these findings.

Among the different subtypes of serrated polyps, SSL and TSA have been recently recognized as the precursors of up to 20% of sporadic CRC through the serrated-carcinoma pathway [43]. SSL and TSA are premalignant lesions, but SSL is the principle serrated precursor of colorectal cancers [28]. Despite of the increasing knowledge in the categorization of serrated polyps and the progress in defining the molecular pathogenesis, most works were retrospective studies. This study to our knowledge is the first prospective analysis of consecutively collected SSL and hyperplastic polyp in average-risk asymptomatic subjects, and would have significantly reduced recall biases than retrospective studies. We found that SSL account for 19.2% of all serrated polyps and 80.8% of hyperplastic polyp, and no difference in age and gender between SSL and hyperplastic polyp. However, SSLs are reportedly associated with male gender [44], while the other studies showed relatively more among females [24,45,46]. The different findings regarding gender may be attributable to different patient populations and criteria, because most of these works were published before publication of the diagnostic criteria or guidelines [28,29,47]. Besides gender and age, there are other risk factors such as alcohol or tobacco use, BMI, a history of inflammatory bowel disease and a personal or family history of colonic neoplasia, etc., are contributing to the pathogenesis of serrated polyps and CRC [44,48], but were not available for examination in this study.

Anatomic locations and sizes of serrated polyps were analyzed in our study. Our data confirm the previous finding that SSLs were concentrated in the cecum and ascending colon and transverse colon, and less frequently present in the distal colon [46,49]. We also found that larger APS linked to the presence of SSL, compared with hyperplastic polyp, which is consistent with prior studies and diagnostic criteria [28,29,47]. Li *et al.* [41] first observed an association between the presence of large serrated CRC polyps and synchronous advanced colorectal neoplasia, but did not examine whether the association with advanced neoplasia differs among subsets of serrated polyps, particularly SSLs and hyperplastic polyps. Subsequently, Hazewinkel *et al.* [27] in their study on the individuals undergoing primary screening colonoscopy showed that proximal and large hyperplastic polyp and SSL were associated with synchronous advanced neoplasia. Finally, Burgess *et al.* [32] also demonstrate that larger sizes SSL and age are associated with SSL with dysplasia.

This study has several limitations. First, although the established guideline on managing serrated polyp was published in 2010 [29,47] and 2012 [28], the learning process for endoscopists and pathologists and implementation of diagnostic criteria may vary from center to center. Our patients' prior history of SSL before 2012 therefore may not exactly align with the updated diagnostic criteria [28]. Second, the detection of serrated polyps was not a primary objective of screening endoscopy. Although all endoscopists were instructed to

detect and remove all colonic polyps irrespective of their endoscopic appearance or size, some serrated polyps may still have been missed or misdiagnosed as reported before [4–6]. Third, this is a single-center-based study with a medium number of cases. A larger and long-term study is therefore needed to validate our finding and to examine the clinic-pathological progress of SSL and its association to advanced carcinoma. We will keep following up this population of patients for additional 5–10 years to better understand the progression of serrated lesions.

In conclusion, we show that the polyp size and location are linked to the diagnosis of SSL, but not history of CRC or history of adenoma. Large SSL in this study is linked to polyp size and synchronous advanced adenoma and cancer. Thus, its presence should prompt more thorough examination of the rest of the colon as shown before [18]. Our data highlight the unique clinical characteristics of SSL, and suggest that despite of its link to CRC, history of CRC or history of adenoma is not associated with presence of SSL. Our findings also show that serrated polyp patients of older age, proximal polyp and male gender are associated synchronous adenoma and cancer, and perhaps warrant closer follow-up.

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Table 1.

Characteristics of the included hyperplastic polyp and sessile serrated lesion

	Hyperplastic polyp (n = 353)	SSL (n = 84)	Total (n = 437)	P value ^a	SSL < 1 cm (n = 66) ^b	SSL 1 cm (n = 18) ^b	P value ^a
Aggregated polyp size (cm, mean ± SD)	0.47 ± 0.39	0.80 ± 0.56	0.53 ± 0.45	<0.001	0.6 ± 0.2	1.6 ± 0.7	<0.001
Age (year, mean ± SD)	59.4 ± 10.4	57.7 ± 9.12	59.0 ± 10.1	0.175	58.0 ± 9.3	56.3 ± 8.7	0.486
Gender, n (%)				0.715			>0.99
Female	191 (54.11)	162 (51.81)	234 (53.64)		34 (52.31)	9 (50.00)	
Male	162 (45.89)	40 (48.19)	202 (46.33)		31 (47.69)	9 (50.00)	
Site in colon, n (%)				<0.001			0.035
Right	46 (13.07)	41 (48.81)	87 (19.95)		35 (53.03)	6 (33.33)	
Transverse	30 (8.52)	29 (34.52)	59 (13.53)		18 (27.27)	11 (61.11)	
Left	276 (78.41)	14 (16.67)	290 (66.51)		13 (19.7)	1 (5.56)	
Case with synchronous hyperplastic polyp, n (%)				0.113			>0.99
None	285 (80.74)	61 (72.62)	345 (78.95)		48 (72.73)	13 (72.22)	
Yes	68 (19.26)	23 (27.38)	92 (21.05)		18 (27.27)	5 (27.78)	
Case with synchronous SSL, n (%)				0.003			>0.99
None	337 (95.47)	73 (86.90)	410 (93.82)		57 (86.36)	16 (88.89)	
Yes	16 (4.53)	11 (13.1)	27 (6.18)		9 (13.64)	2 (11.11)	
Case with synchronous adenoma and cancer, n (%)				0.240			0.566
None	222 (62.89)	47 (55.95)	269 (61.56)		38 (57.58)	9 (50.00)	
Yes	131 (37.11)	37 (44.05)	168 (38.44)		28 (42.42)	9 (50.00)	
Case with synchronous lesion, n (%)				0.039			<0.001
Hyperplastic polyp or none	221 (62.61)	47 (55.95)	268 (61.33)		38 (57.58)	9 (50.00)	
Nonadvanced adenoma	110 (31.16)	25 (29.76)	135 (30.89)		25 (37.88)	0 (0.00)	
Advanced adenoma	22 (6.23)	11 (13.1)	33 (7.55)		2 (3.03)	9 (50.00)	
Carcinoma	0 (0)	1 (1.19)	1 (0.23)		1 (1.52)	0 (0.00)	
Case with past history, n (%)				0.044			0.328
None	215 (60.91)	59 (70.24)	274 (62.70)		48 (72.73)	11 (61.11)	
Hyperplastic polyp	37 (10.48)	5 (5.95)	42 (9.61)		3 (4.55)	2 (11.11)	
SSL	6 (1.70)	4 (4.76)	10 (2.29)		2 (3.03)	2 (11.11)	
Adenoma	90 (25.50)	13 (15.48)	103 (23.57)		10 (15.15)	3 (16.67)	

	Hyperplastic polyp (<i>n</i> = 353)	SSL (<i>n</i> = 84)	Total (<i>n</i> = 437)	<i>P</i> value ^a	SSL < 1 cm (<i>n</i> = 66) ^b	SSL 1 cm (<i>n</i> = 18) ^b	<i>P</i> value ^a
Carcinoma	5 (1.42)	3 (3.57)	8 (1.83)		3 (4.55)	0 (0.00)	
Case with size 1 cm, <i>n</i> (%)				0.009			
No	315 (89.24)	66 (78.57)	381 (87.19)		NA		
Yes	38 (10.76)	18 (21.43)	56 (12.81)				

The counts (n) refer to the number of patients with certain diagnosis.

NA, not applicable; SSL, sessile serrated lesion.

^aChi-square test or Fisher exact test as appropriate.

^bAggregated polyp size.

Table 2.

Univariate and multivariate logistic regression analyses on the factors associated with diagnosis of sessile serrated lesion

	Univariate analysis			Multivariate analysis		
	OR	OR 95% CI	P value	OR	OR 95% CI	P value
Gender (male vs female)	1.10	0.68 1.77	0.705			
APS	4.49	2.54 7.91	<0.001	3.98	2.06 7.68	<0.001
Age	0.98	0.96 1.01	0.176	0.99	0.96 1.01	0.476
Polyp site	3.82	2.82 5.16	<0.001	3.61	2.64 4.94	<0.001
Personal history						
Hx of polyp vs none	0.89	0.73 1.07	0.218			
Hx of colorectal cancer vs none	2.58	0.60 11.01	0.201			
Hx of adenoma and cancer vs none	0.64	0.35 1.16	0.139	0.86	0.44 1.66	0.643
Hx of SSL, adenoma and cancer	0.78	0.45 1.35	0.377			
Hx of hyperplastic polyp vs none	0.71	0.39 1.29	0.257			
Hx of SSL vs none ^a	2.08	0.87 5.00	0.101			

Polyp site ranking: Right > Transverse > Left colons.

APS, aggregated polyp size; CI, confidence interval; Hx, history; OR, odds ratio; SSL, sessile serrated lesion.

^aHistory of SSL was also used to replace history of adenoma and cancer in multivariate analysis, which led to similar odds ratios of APS, age and polyp site and no statistical significance for history of SSL (95% CI of OR, 0.48–4.43, $P = 0.508$).

Univariate and multivariate logistic regression analyses on the factors associated with synchronous adenoma and cancer

Table 3.

	Univariate analysis			Multivariate analysis		
	OR	OR 95% CI	P value	OR	OR 95% CI	P value
Gender (Male vs female)	1.88	(1.27–2.78)	0.001	1.91	(1.28–2.86)	0.002
Age (continuous variable, by year)	1.02	(1.00 ^a –1.04)	0.027	1.02	(1.00 ^a –1.04)	0.033
History of adenoma and cancer	1.76	(1.14–2.73)	0.011	1.51	(0.95–2.40)	0.084
Polyp site (left vs transverse vs right)	1.28	(1.01–1.62)	0.037	1.33	(1.04–1.69)	0.022
Size (1 cm vs <1 cm)	1.46	(0.83–2.57)	0.190	1.40	(0.78–2.50)	0.261
Histology of index polyp (SSL vs hyperplastic polyp)	1.33	(0.82–2.16)	0.241			

CI, confidence intervals; OR, odds ratio; SSL, sessile serrated lesion.

^a 1.002, but shown as 1.00 due to rounding.

Univariate and multivariate logistic regression analyses on the factors associated with synchronous sessile serrated lesion, adenoma and cancer

Table 4.

	Univariate analysis			Multivariate analysis		
	OR	OR 95% CI	P value	OR	OR 95% CI	P value
Gender (male vs female)	1.86	(1.26–2.73)	0.002	1.90	(1.28–2.81)	0.001
Age (continuous variable, by year)	1.02	(1.00–1.04)	0.102	1.02	(1.00–1.04)	0.078
History of adenoma and cancer	1.48	(0.96–2.28)	0.076	1.30	(0.82–2.05)	0.271
Polyp site (left vs transverse vs right)	1.24	(0.98–1.56)	0.073	1.18	(0.90–1.54)	0.239
Histology of index polyp (SSL vs hyperplastic polyp)	1.56	(0.97–2.51)	0.069	1.44	(0.83–2.51)	0.194
Size (1 cm vs <1 cm)	1.31	(0.75–2.31)	0.341			

Synchronous neoplasm included synchronous SSL, adenoma and cancer.

CI, confidence intervals; OR, odds ratio; SSL, sessile serrated lesion.