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Large serrated polyps indicate a greater risk of advanced metachronous colorectal neoplasia than high-grade adenomas

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ABSTRACT

Background and study aims The risk of developing total metachronous advanced neoplasia (TMAN) in patients with index serrated lesions (SL) or adenoma with high-grade dysplasia (HGD) is unknown. We evaluated this risk in patients with either HGD, SL < 10 mm or SL ≥ 10 mm at index colonoscopy, who underwent surveillance colonoscopies.

Patients and methods This retrospective cohort study evaluated all consecutive patients (n = 2477) diagnosed between 2010 and 2019 with colorectal HGD, SLs < 10 mm or SLs ≥ 10 mm. We excluded patients aged < 45 or > 75 years or those who had inflammatory bowel disease, hereditary colorectal cancer (CRC) syndromes, previous or synchronous CRC, or no follow-up colonoscopy. Descriptive variables were compared using analysis of variance or Pearson chi-squared tests. Multivariate Cox regressions were used to compare the risk of TMAN between the HGD, SL < 10 mm and SL ≥ 10 mm groups.

Results Overall, 585 patients (mean age 63 years; 55% male; mean follow-up 3.67 years) were included (226 with SLs < 10 mm, 204 with SLs ≥ 10 mm, 155 with HGD). Compared with SLs < 10 mm, patients with HGD did not have a significantly different rate of TMAN (HR = 0.75 [0.39–1.44]) and patients with SLs ≥ 10 mm had a higher rate of TMAN (HR = 2.08 [1.38–3.15]). Compared with HGD, patients with SLs ≥ 10 mm had a higher rate of TMAN (HR = 1.87 [1.04–3.36]).

Conclusions The risk for TMAN was higher for patients with SLs ≥ 10 mm than with HGD or SLs < 10 mm. This risk should be considered when planning surveillance intervals for patients diagnosed with large SLs.

Introduction

Colorectal cancer (CRC) is the second cause of cancer mortality worldwide and has the third highest cancer incidence [1]. CRC screening programs reduce morbidity and mortality associated with this cancer [2, 3]. After detection of neoplastic polyps, guideline-recommended intervals have been proposed to establish adequate and safe follow-up timing for patients [4, 5].

The 2020 United States Multi-Society Task Force (USMSTF) guidelines and the 2020 European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend that adenomas with high-grade dysplasia (HGD) are followed at 3 years [4, 5]. However, given that HGD is relatively rare and, therefore, a difficult lesion to study, and given that results on risk after detection of HGD have been conflicting, the supporting evidence for this recommendation is of moderate quality [4, 5]. Research on HGD has suffered from lack of analysis adjusting for synchronous adenomas, inclusion of HGD within a group of advanced adenomas (AA) without separate evaluation, comparisons to groups with different follow-up periods, and lack of time-based analysis incorporating each patient's follow-up [6, 7, 8, 9].

For serrated lesions (SLs), which include sessile serrated lesions (SSLs) and traditional serrated adenomas (TSAs), the 2020 USMSTF guidelines recommend a 5- to 10-year surveillance interval for one to two SSLs, a 3- to 5-year interval for three to four SSLs, a 3-year interval for five or more SSLs, and a 3-year interval is recommended for SL ≥ 10 mm and SL with dysplasia [4]. In contrast, the 2020 ESGE guidelines recommend stopping endoscopic follow-up for patients with any SSL < 10 mm without dysplasia, and group SL ≥10 mm and SL with dysplasia under the recommendation of 3 years for AAs [5]. Overall, these discrepancies reflect the multiple limitations in the studies on SLs [10, 11, 12, 13].

No study has directly compared SLs with HGD. We were interested in studying the risk of total metachronous advanced neoplasia (TMAN) (metachronous advanced neoplasia [AN] or metachronous advanced serrated lesions [ASL]) in patients diagnosed with HGD, SL ≥ 10 mm or SL < 10 mm at index colonoscopy.

Patients and methods

This study was reported according to the STROBE checklist for cohort studies [14].

Study design and patient selection

A retrospective cohort study was conducted. The Montreal University Hospital Center (CHUM) pathological database allows identification of all patients with any pathology diagnosis for any organ system of interest for any given year using natural language search. Using the search terms "high-grade dysplasia" and "serrated", we were able to identify all consecutive patients diagnosed with colorectal HGD or SL from 2010 to 2019. Electronic medical records were then accessed to determine exclusions and inclusions for a cohort study of consecutive screening-aged patients (45–74 years) who underwent screening, surveillance, or diagnostic colonoscopy from 2010 to 2019 at CHUM. A sample size calculation was not conducted given the retrospective nature of this study and given the patient selection method, which allowed to identify all consecutive patients diagnosed with HGD or SL during the study period and to include the largest number of eligible patients. This study is part of a larger project comparing outcomes for colonoscopy findings. Part of the study cohort has been previously reported, however, there are no data overlap in reported outcomes [15].

Inclusion criteria were that the patients were diagnosed with at least one HGD (conventional adenoma with HGD) or SL (SSL or TSA) at index colonoscopy and that endoscopic follow-up data within 10 years from index colonoscopy were available. Patients aged ≥ 75 at index were not included in any group, to apply same age range inclusion criteria to all groups, and to evaluate results for a routine screening population without including higher risk patients. For SLs, the study was limited to patients with SSL or TSA, as identifying hyperplastic polyps (HPs) through the pathology department database would have yielded a very high number of patients as to render data collection unfeasible. Endoscopic polyp size was not available through the pathology database and needs to be accessed through patient endoscopy reports which prohibits specifically targeting HPs ≥ 10 mm. Exclusion criteria were: (1) inflammatory bowel disease; (2) hereditary CRC syndromes; (3) personal history of CRC; (4) synchronous CRC at index; (5) no follow-up after index; (6) first follow-up colonoscopy less than 12 months after a complete index colonoscopy; and (7) concomitant HGD or SL. All reasons for exclusion were counted in the hierarchical fashion shown in ▶ **Fig. 1**. The study protocol was approved by the Montreal University Hospital Research Center (CRCHUM) Institutional Review Board (CER #21.170).

Data collection and outcomes

Individual patient data were collected from electronic medical records at CHUM. Data collected included: age; sex; past medical history; family history of CRC; number, pathology and size of polyps at index and follow-up colonoscopies; quality of index and follow-up colonoscopies; time between index colonoscopy and each event of interest or time to the last colonoscopy within 10 years. The lesion size was determined by the measurement from the colonoscopy report, and, if unavailable, from the pathology report.

Three groups were compared: HGD, SL < 10 mm (small SL), and SL ≥ 10 mm (large SL). Small lesions were defined as < 10 mm in size, and large lesions as ≥ 10 mm in size. If a patient had both a small and large SL, they were included in the large SL group. Data were entered into a database by six researchers (EM, RD, TK, AZ, MZN, WS), and a quality review of the entered data (by blinded replication of data collection by EM and RD) was performed every month for all data collected to that point during the study to ensure consistency and reduce bias between researchers in data entry. Disagreement over data collection was then resolved by a seventh researcher (DvR). There were no differences in data collection or assessment methods between the SL < 10 mm, SL ≥ 10 mm, and HGD groups.

The definitions of the primary and secondary metachronous outcomes and of other terms used are detailed in **Supplemen-**

tary Table 1. Advanced neoplasia (AN) was defined as either colorectal cancer, adenoma ≥ 10 mm, tubulovillous or villous adenoma, or adenoma with HGD. High-risk adenoma (HRA) was defined as the presence of either AN or three or more adenomas < 10 mm. AA was defined as either adenoma ≥ 10 mm, tubulovillous or villous adenoma, or adenoma with HGD. ASL was defined as hyperplastic polyp ≥ 10 mm, sessile SLs ≥ 10 mm, sessile SLs with dysplasia, or traditional serrated adenoma. TMAN was specifically defined as the presence of any AN or ASL. HPs ≥ 10 mm were included in the definition of metachronous ASL and TMAN, as was done in studies that have evaluated the risk after index adenomatous and serrated polyps [10, 16]. Death was not counted as an event in the definitions of TMAN, AN and ASL.

The primary outcome was the rate of TMAN (AN or ASL) detection on a per-patient basis for the SL < 10 mm, SL ≥ 10 mm, and HGD groups.

Secondary outcomes are listed in detail in **Supplementary Table 1**, and also included: (1) adherence to the 2012 USMSTF guidelines and 2013 Canadian Association of Gastroenterology guidelines [17, 18]; (2) proportion of HGD requiring multiple procedures or advanced endoscopic methods for resection; and (3) adjusted survival rates in the three groups, with associated cumulative risk of TMAN at 2, 3, 4, and 5 years.

If a patient had multiple colonoscopies within 10 years from index, follow-up was continued beyond the first surveillance colonoscopy until the outcome was observed or until the last colonoscopy within 10 years. Proximal HGD or SL was defined as proximal to the sigmoid. Follow-up colonoscopy was defined as any colonoscopy that occurred 12 months or more after the index colonoscopy. Findings for colonoscopies performed within 12 months of each other were combined if the initial examination was incomplete, had poor bowel preparation, or if the second colonoscopy was performed to remove an unresected polyp from the initial examination. Poor bowel preparation was defined as a Boston Bowel Preparation Scale score < 6 or a score < 2 in any bowel segment, or mention of inadequate bowel preparation in the colonoscopy report with recommendations for earlier surveillance due to the poor bowel preparation. In the minority of patients with incomplete index colonoscopy (due to lack of cecal intubation or inadequate preparation), lesions at subsequent colonoscopies that were found in segments that were previously unexplored or poorly prepped at index were not counted as metachronous outcomes, but were counted as index lesions given the usually close follow-up after incomplete index.

Statistical analysis

Descriptive statistics are presented in the form of crude numbers, proportions (or percentages) and means, for patient, procedure, and index and outcome polyp characteristics. Descriptive statistics are compared between the three groups using one-way analysis of variance with post hoc tests (Bonferroni, or Games-Howell when unequal variances) for continuous variables, Pearson's chi-squared test with post hoc chi-squared tests (or post hoc Fisher's exact test when required) for nominal categorical variables (including colonoscopy indication, HGD resection method, adherence to recommended follow-up), and Kruskal-Wallis tests with post hoc Mann-Whitney tests for ordinal categorical variables (including American Society of Anesthesiologists [ASA] physical status class and Paris classification).

The rate of the primary outcome (TMAN) and the secondary outcomes were obtained for each group using Cox proportional hazards regression, with hazard rate ratios (HRs) and their 95% confidence intervals (CIs). We performed univariate as well as multivariate Cox regression analysis to adjust for index and follow-up confounders that differed between groups. Variables in the multivariate analysis were selected in a direct fashion.

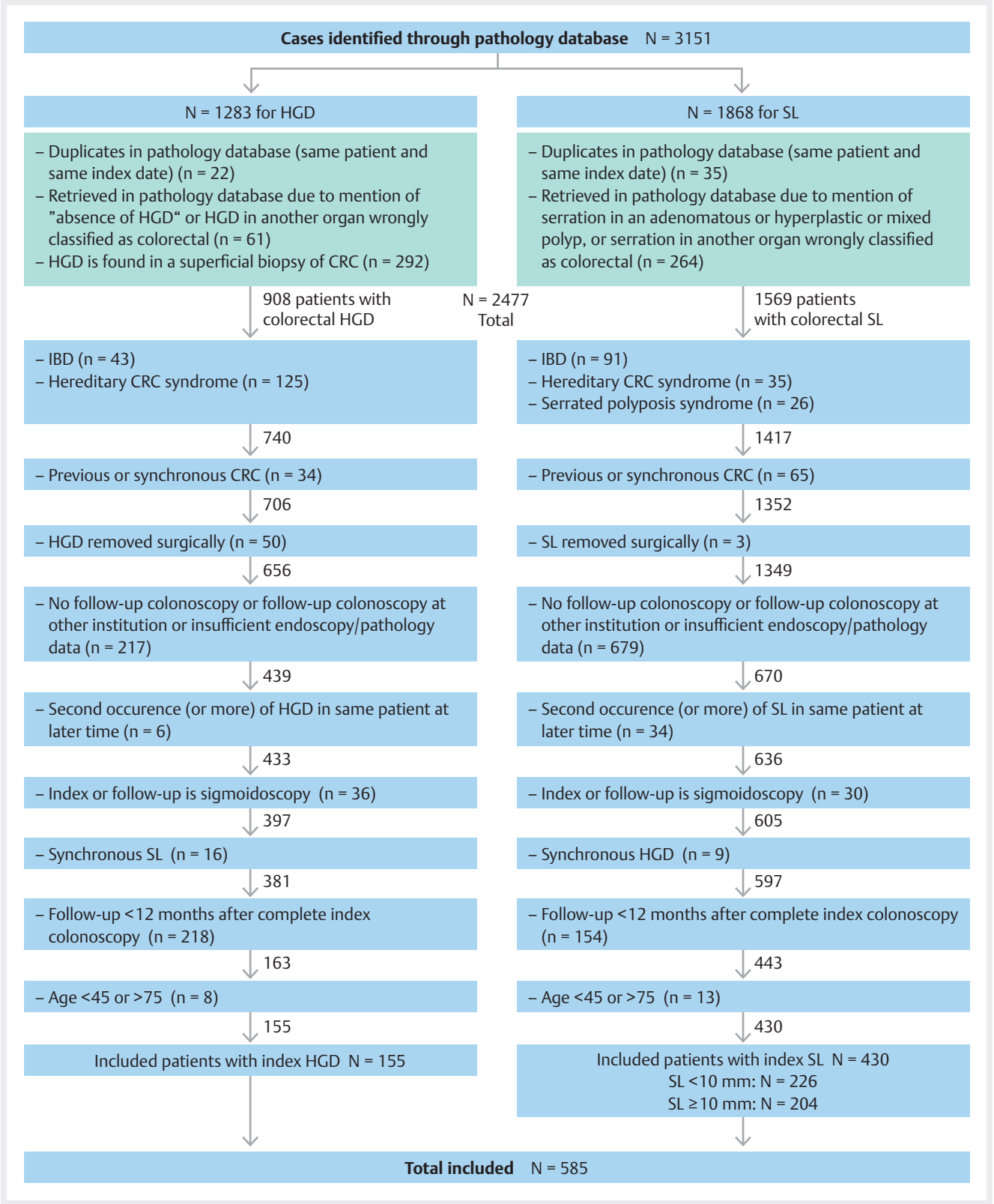
The same covariates were used for all adjusted analyses to allow valid comparisons. Our adjusted model included age, sex, family history of CRC, adenoma ≥ 10 mm, tubulovillous adenoma (TVA) or villous adenoma (VA), proximal location of HGD or SL, and three or more adenomas. Other variables that significantly differed between groups were not adjusted for, to avoid overfitting and obtaining biased HRs, because they had less theoretical impact (ASA class, colonoscopy indication, small HPs, incompletely resected polyps because they were not counted as metachronous findings if seen again at follow-up) or because they had largely similar proportions despite statistical differences (bowel preparation, cecal intubation, large HPs). The number of serrated polyps at index was not adjusted for since the HGD group already had no SSLs or TSAs by definition, and the number of serrated polyps at index was similar between the SL < 10 mm and SL ≥ 10 mm groups.

We performed all analyses using Statistical Package for the Social Sciences version 26 (IBM Corp., Armonk, New York, United States). A two-tailed $P < 0.05$ was considered statistically significant for all analyses.

Results

Patient and polyp characteristics

A total of 2477 patients with colorectal HGD or SL diagnosed at CHUM between 2010 and 2019 were identified. After applying the exclusion criteria, we included a total of 585 patients in the study (mean age 63 years; 55% male): 155 patients with HGD (mean age 65.7 years; 62.6% male; mean follow-up 3.6 years, median follow-up 3.3 years), 226 patients with SL < 10 mm (SSL n = 216; TSA n = 10; mean age 61.2 years; 54.4% male; mean follow-up 4.1 years, median follow-up 3.7 years), and 204 patients with SL ≥ 10 mm (SSL n = 198; TSA n = 6; mean age 62.1 years; 49.0% male; mean follow-up 3.2 years, median follow-up 3.0 years) (▶ **Fig. 1**, ▶ **Table 1**). The mean size of the lesion of interest was 5.3 mm in the SL < 10 mm group, 12.8 mm in the SL ≥ 10 mm group, and 19.0 mm in the HGD group. No patients with TSA had synchronous SSL. The SL < 10 mm and SL ≥ 10 mm groups had almost exclusively one to two SLs at index, with only 8.0% and 6.4% of patients with SL having three or more SLs at index, respectively. The SL < 10 mm and SL ≥ 10 mm groups were not significantly different with regards to most variables, but the HGD group was significantly older, had more male patients, and had less family history of CRC ($P < 0.05$) (▶ **Table 1**). Compared with included SL patients, SL patients



▶ **Fig. 1** Study inclusion flowchart. CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; SL, serrated lesion.

who had no follow-up colonoscopy were not older, had a lower ASA class, and had fewer SLs ≥ 10 mm, fewer SLs with dysplasia, fewer adenomas ≥10 mm, and lower occurrence of three or more adenomas (**Supplementary Table 2**). Patients with HGD who had no follow-up colonoscopy were not significantly different from the included HGD patients (**Supplementary Table 3**).

▶ **Table 1** Patient and polyp characteristics at index colonoscopy.

	SL < 10 mm (n = 226) SSL: n = 216 TSA: n = 10 SSL + TSA: n = 0	SL ≥ 10 mm (n = 204) SSL: n = 198 TSA: n = 6 SSL + TSA: n = 0	HGD (n = 155)	P value
Age, *y*, mean	61.2	62.1	65.7	*P* = 0.0004*
Sex, male, % (n)	54.4 (123)	49.0 (100)	62.6 (97)	*P* = 0.0379*
ASA class				
1	50.4 (114)	55.9 (114)	34.8 (54)	*P* = 0.0005*
2	39.8 (90)	38.2 (78)	55.5 (86)	
3	9.3 (21)	5.9 (12)	9.7 (15)	
4	0.4 (1)	0 (0)	0 (0)	
Family history of CRC, % (n)	24.8 (56)	24.0 (49)	11.0 (17)	*P* = 0.0019*
Index colonoscopy indication, % (n)				
Screening	38.9 (88)	36.3 (74)	16.1 (25)	*P* = 0.0002*
Surveillance	38.1 (86)	45.1 (92)	43.2 (67)	
Diagnostic†	23.0 (52)	18.6 (38)	40.6 (63)	
Cecal intubation, % (n)	99.6 (225)	99.0 (202)	92.3 (143)	*P* < 0.0001*
Adequate preparation, % (n)	93.4 (211)	98.0 (200)	99.4 (154)	*P* = 0.0025
Follow-up time, *y*, mean	4.1	3.2	3.6	*P* < 0.0001
Follow-up time, *y*, median	3.7	3.0	3.3	*P* < 0.0001
Proximal (nonrectosigmoid) HGD or SL, % (n)	65.5 (148)	83.3 (170)	38.7 (60)	*P* < 0.0001
≥ 3 adenomas, % (n)	11.9 (27)	9.8 (20)	32.3 (50)	*P* < 0.0001*
Any adenoma ≥ 10 mm, % (n)	11.5 (26)	12.8 (26)	79.4 (123)	*P* < 0.0001*
Any TVA or VA, % (n)	4.0 (9)	4.4 (9)	63.9 (99)	*P* < 0.0001*
Synchronous HP ≥ 10 mm, % (n)	0.9 (2)	5.9 (12)	1.3 (2)	*P* = 0.0029
Synchronous HP, % (n)	31.0 (70)	27.9 (57)	11.0 (17)	*P* < 0.0001*
Synchronous ≥ 3 SSL, % (n)	8.0 (18)	6.4 (13)	–	*P* = 0.5222*
Any SSL with LGD, % (n)	3.1 (7)	3.9 (8)	–	*P* = 0.6384*
Incomplete resection of any polyp, % (n)‡	2.7 (6)	1.5 (3)	18.7 (29)	*P* < 0.0001*
Incomplete resection of HGD or SL, % (n)	1.8 (4)	1.0 (2)	10.3 (16)	*P* < 0.0001*
Incomplete resection of non-HGD, non-SL polyp, % (n)	0.9 (2)	0.5 (1)	9.0 (14)	*P* < 0.0001*

ASA, American Society of Anesthesiologists; CRC, colorectal cancer; HGD, high-grade dysplasia; HP, hyperplastic polyp; LGD, low-grade dysplasia; SL, serrated lesion; SSL, sessile serrated lesion; TMAN, total metachronous advanced neoplasia; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma; VA, villous adenoma.
*$P > 0.05$ between the SL < 10 mm and the SL ≥ 10 mm group.
†Diagnostic colonoscopy indications were mainly anemia, bleeding, abdominal pain, diarrhea, change in bowel habits, bloating, constipation, and previous imaging showing a colorectal lesion (barium enema, computed tomography of the abdomen and pelvis, virtual colonoscopy or positron emission tomography), but also included fecal urgency, elevated carcinoembryonic antigen, colonoscopy post-diverticulitis, weight loss, suspected ischemic colitis, pre-transplant evaluation, and evaluation for inflammatory bowel disease in the context of rheumatologic disease.
‡Synchronous incompletely resected polyps at index were not considered metachronous and were not counted in the outcomes.

▶ **Table 2** Polyp characteristics at follow-up until total metachronous advanced neoplasia or last colonoscopy within 10 years.

	SL < 10 mm (n = 226)	SL ≥ 10 mm (n = 204)	HGD (n = 155)
Cecal intubation, % (n)	96.9 (219)	98.0 (200)	89.7 (139)
Adequate bowel preparation, % (n)	94.7 (214)	96.6 (197)	98.7 (153)
ADR, % (n)	35.0 (79)	33.8 (69)	47.7 (74)
TMAN, % (n)	18.6 (42)	28.9 (59)	29.0 (45)
Time to TMAN, *y*, mean	3.6	2.8	3.2
Subtype of TMAN*, % (n)			
Advanced neoplasia	9.7 (22)	10.8 (22)	27.7 (43)
Adenoma ≥ 10 mm	8.4 (19)	10.8 (22)	23.9 (37)
TVA	4.0 (9)	1.0 (2)	9.7 (15)
VA	0 (0)	0.5 (1)	3.2 (5)
HGD	0.9 (2)	1.5 (3)	7.1 (11)
CRC	0 (0)	0.5 (1)	1.3 (2)†
Advanced serrated lesion	10.2 (23)	19.6 (40)	3.9 (6)
SSL ≥ 10 mm	4.4 (10)	9.3 (19)	0.6 (1)
SSL with dysplasia	0 (0)	0.5 (1)	0 (0)
HP ≥ 10 mm	6.2 (14)	10.3 (21)	2.6 (4)
TSA	0.4 (1)	0 (0)	0.6 (1)

ADR, adenoma detection rate; CRC, colorectal cancer; HGD, high-grade dysplasia; HP, hyperplastic polyp; SL, serrated lesion; SSL, sessile serrated lesion; TMAN, total metachronous advanced neoplasia; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma; VA, villous adenoma.
*Multiple findings can coexist in the same patient.
†A third CRC also developed in a patient with HGD after more than 12 months, and originated from an initially benign adenoma with HGD that was incompletely resected. Incompletely resected adenomas at index would not be addressed otherwise, and were not considered metachronous lesions.

Risk of total metachronous advanced neoplasia for each group

In the SL < 10 mm group, SL ≥ 10 mm group, and HGD group, 18.6%, 28.9% and 29.0% of patients, respectively, developed TMAN with mean time to TMAN of 3.6 years, 2.8 years, and 3.2 years, respectively (P > 0.05 for time to TMAN) (▶ **Table 2**). Compared with SL < 10 mm, detection of SL ≥ 10 mm resulted in a higher rate of TMAN (HR = 2.08 [95% CI 1.38–3.15]), a non-significantly different rate of AN (HR = 1.50 [95% CI 0.81–2.77]), and a higher rate of ASL (HR = 2.53 [95% CI 1.50–4.25]) (▶ **Table 3**). Compared with SL < 10 mm, detection of HGD did not result in a significantly different rate of TMAN (HR = 0.75 [95% CI 0.39–1.44]) and AN (HR = 1.16 [95% CI 0.55–2.45]), but did result in a lower rate of ASL (HR = 0.16 [95% CI 0.04–0.72]). Compared with HGD, detection of SL ≥10 mm resulted in a higher rate of TMAN (HR = 1.87 [95% CI 1.04–3.36]), a non-significantly different rate of AN (HR = 0.84 [95% CI 0.41–1.73]), and a higher rate of ASL (HR = 8.75 [95% CI 2.83–27.05]) (▶ **Table 3**, ▶ **Fig. 2**). Based on adjusted TMAN-free survival, the cumulative risk of TMAN at 2, 3, 4, and 5 years was 7%, 11%, 17%, and 24%, respectively, in the HGD group and 14%, 21%, 36%, and 46%, respectively, in the SL ≥ 10 mm group (**Supplementary Tables** 6 and **7**).

Stratification of HGD in small adenomas versus large adenomas

HGD with small adenomas (HGD < 10 mm) was present in 32 of 155 patients with HGD (20.6%). HGD ≥ 10 mm (found in a large adenoma or in a small adenoma but with a synchronous large adenoma) was present in 123 of 155 patients with HGD (79.4%). The risk of developing TMAN for patients with SL ≥ 10 mm was higher compared with patients with HGD ≥ 10 mm (▶ **Fig. 3**).

Discussion

In this retrospective cohort study, patients with SL ≥ 10 mm had approximately twice the adjusted HR of TMAN compared with patients with SL < 10 mm and patients with HGD. These findings are important in the context of current CRC screening programs.

Recommendations in previous and current American and European guidelines have been to follow SL ≥ 10 mm and HGD at the same interval of 3 years [4, 5, 17, 18]. For SL ≥ 10 mm, this is based on studies showing that SL ≥ 10 mm poses a similar risk than that for AAs [10, 16, 19, 20]. Two of these studies had > 50 patients with SL ≥ 10 mm and form the main evidence for this

▶ **Table 3** Unadjusted and adjusted hazard ratios and number of events for the primary outcome of total metachronous advanced neoplasia and for the secondary outcomes of advanced neoplasia and advanced serrated lesion, between serrated lesion (SL) < 10 mm, SL ≥ 10 mm, and high-grade dysplasia groups.

				SL ≥10 mm vs SL <10 mm		HGD vs SL <10 mm		SL ≥10 mm vs HGD	
Outcome*	SL < 10 mm group %, n	SL ≥ 10 mm group %, n	HGD group %, n	U	A†	U	A†	U	A†
TMAN	18.6 (42)	28.9 (59)	29.0 (45)	2.16 (1.45–3.21)‡	2.08 (1.38–3.15)‡	1.74 (1.14–2.65)‡	0.75 (0.39–1.44)	1.20 (0.81–1.78)	1.87 (1.04–3.36)‡
AN	9.7 (22)	11.3 (23)	27.7 (43)	1.45 (0.81–2.61)	1.50 (0.81–2.77)	3.22 (1.93–5.40)‡	1.16 (0.55–2.45)	0.44 (0.27–0.73)‡	0.84 (0.41–1.73)
ASL	10.2 (23)	21.1 (43)	3.9 (6)	2.71 (1.63–4.51)‡	2.53 (1.50–4.25)‡	0.35 (0.14–0.86)‡	0.16 (0.04–0.72)‡	7.37 (3.12–17.39)‡	8.75 (2.83–27.05)‡

A, adjusted; AN, advanced neoplasia; ASL, advanced serrated lesion; CI, confidence interval; HGD, high-grade dysplasia; HR, hazard ratio; SL, serrated lesion; TMAN, total metachronous advanced neoplasia; U, unadjusted.
*$P < 0.05$.
†Incompletely removed polyps at index were not considered metachronous.
‡Adjusted for age, sex, family history of CRC, proximal (non-rectosigmoid) location of HGD or SL, presence of three or more synchronous adenomas (including adenoma of HGD), presence of ≥ 10 mm adenoma (including adenoma of HGD), and presence of adenoma with ≥25% villous histology (including adenoma of HGD).

▶ **Fig. 2** *Adjusted total metachronous advanced neoplasia-free survival obtained from multivariate Cox regression modelized graphically to the mean of the covariates to represent a typical patient in each group. TMAN, total metachronous advanced neoplasia. *TMAN was defined as the occurrence of an advanced adenoma, advanced serrated lesion or colorectal cancer. Death was not counted in the definition of TMAN. TMAN-free survival is adjusted for age, sex, family history of colorectal cancer, synchronous adenoma ≥ 10 mm, synchronous tubulovillous adenoma or villous adenoma, proximal location of high-grade dysplasia or serrated lesion, and three or more synchronous adenomas.

▶ **Fig. 3** *Adjusted total metachronous advanced neoplasia-free survival obtained from multivariate Cox regression modelized graphically to the mean of the covariates to represent a typical patient in each group, with additional stratification by size of high-grade dysplasia. TMAN, total metachronous advanced neoplasia. *TMAN was defined as the occurrence of an advanced adenoma, advanced serrated lesion or colorectal cancer. Death was not counted in the definition of TMAN. TMAN-free survival is adjusted for age, sex, family history of colorectal cancer, synchronous tubulovillous adenoma or villous adenoma, proximal location of high-grade dysplasia or serrated lesion, and three or more synchronous adenomas.

comparison with AAs and the 3-year recommendation for SL ≥ 10 mm [10, 16]. One study compared HRA as a group with SLs, and found an HR for metachronous ASL of 14.3 (95% CI 5.0–40.9) in the SL ≥ 10 mm group (65 patients), compared to a group without adenomas and serrated polyps, and of 0.9

(95% CI 0.3–3.1) in the HRA group compared to the same reference group; however, results showed an HR for metachronous HRA of 0.9 (95% CI 0.2–3.6) in the SL ≥ 10 mm group and 3.9 (95% CI 2.8–5.4) in the HRA group [10]. Similarly, our findings revealed AN contributed more toward TMAN after index HGD detection, whereas ASL contributed more toward TMAN after index SL ≥ 10 mm detection. This underscores the importance of using TMAN as a proxy for CRC risk when studying adenomas and SLs. No previous studies on HGD had used a surrogate outcome for CRC that includes ASLs, and the outcome of TMAN in our study fulfilled this purpose. Another study found an HR for metachronous CRC of 5.9 (95% CI 1.9–18.8) for HGD (166 patients), 3.3 (95% CI 1.4–8.1) for SL ≥ 10 mm (566 patients), and 1.2 (95% CI 0.7–2.1) for SL < 10 mm, compared to a group without polyps, but did not adjust for index synchronous adenoma types [16].

Our study is the first to compare HGD with SLs while adjusting for synchronous adenomas. Our findings reveal that HGD alone, when considering synchronous findings, has a lower risk than SL ≥ 10 mm. Adjusting for synchronous adenoma types revealed that the risk of developing early TMAN for patients diagnosed with SL ≥ 10 mm is likely higher compared to patients with HGD. Indeed, of the four largest studies on HGD, the two that found an increased risk from HGD did not adjust for synchronous adenoma types [8] or only adjusted for some adenoma characteristics at index [6]. Studies that adjusted for all synchronous index adenoma types did not find a significantly increased risk from HGD [7, 21]. Our study adds to these findings and further supports the concept that the risk from SL ≥ 10 mm can be underestimated if there is no adjusting for confounding synchronous HRAs (adenomas ≥ 10 mm, TVA, VA, ≥ 3 adenomas) when comparing SL ≥ 10 mm to other lesions. SL ≥ 10 mm, therefore, has an inherent risk that is greater than the risk from HGD taken alone. Although a similar percentage of patients with HGD and with SL ≥ 10 mm developed TMAN, evaluating the time to TMAN in each group and controlling for concomitant AAs resulted in SL ≥ 10 mm having a much higher risk of TMAN than the inherent risk of HGD specifically. The adjusted risk of TMAN at 2, 3, 4, and 5 years was approximately twice as high after detection of SL ≥ 10 mm than after detection of HGD. SL ≥ 10 mm was the group with the highest risk of TMAN even when compared with HGD ≥ 10 mm, potentially due to the described higher risk from SL and HRA combinations compared with HRA alone [22] or other factors. Together, these findings support the high risk associated with SL ≥ 10 mm and the importance of short surveillance intervals for SL ≥ 10 mm.

The idea that HGD is a finding associated with other HRAs that must be adjusted for is also supported by studies showing that the frequency of HGD is mainly driven by adenoma size and number [23, 24], that adenoma size remains the principal indicator of CRC risk [7, 9, 25], and that *KRAS* mutations, an important step toward AN, are more frequent in polyps with HGD if the polyp is large or villous [26, 27].

The scenario of HGD within only one to two small traditional adenomas has been reported in only 3% of patients with HGD in studies [7, 21]. A recent study compared 61 patients with diminutive HGD (≤ 5 mm) with patients with one to two low-grade dysplastic adenomas. It found the diminutive HGD group to have a similar risk of future AA as the one to two low-grade dysplastic adenoma group [28]. In our study, we found HGD in the context of one to two small TAs at index for 14 of 155 patients (9.0%). Four of the 14 patients developed TMAN during follow-up (3 AN and 1 ASL), all at later than 5 years of follow-up. Five of 155 patients (3.2%) had HGD in the context of three or more small TAs and only one of them developed TMAN during follow-up (1 AN), at 3.3 years. Further studies are needed to conclude on the risk of patients with HGD found in small TAs.

The strength of our study lies in its sample size from a very large tertiary center with a high colonoscopy volume (> 10,000 per year). Another strength is the ability to capture, through our pathology database, all consecutive patients diagnosed with HGD or SL during the 10-year study period. Patients in Quebec are usually followed longitudinally at the initial center where they presented. Therefore, exclusion for insufficient or missing data affected a small number of patients, which resulted in a good proportion of available follow-up colonoscopy data, improving the internal validity of our study. In our study, we were able to capture specific pathology and endoscopy data, allowing us to provide a detailed description of the context in which HGD is diagnosed. The use of a time-based analysis avoided issues from different follow-up intervals between patients.

This was, however, a retrospective study, and a minority of patient and polyp data were inevitably missing. Some patients had to be excluded for having no follow-up colonoscopy. A minority of these patients could have received follow-up at a different institution, without it being available, but this was likely uncommon given the previously explained same-center referral system in Quebec. Although all available follow-up data was evaluated for up to 10 years after index for each patient, mean and median follow-up times are under 5 years, and this was expected. Indeed, patients with index colonoscopy after 2012 would automatically have under 10 years of available follow-up. As well, follow-up was stopped at the last colonoscopy occurring earlier than 10 years. With regard to exclusions for first follow-up occurring before 12 months after a complete index colonoscopy, this could favor the exclusion of patients who underwent piecemeal resection of large non-pedunculated colorectal polyps. However, such patients would fall under different surveillance guidelines as opposed to the screening and surveillance cohort studied here. In our study, the adherence to society guidelines was slightly poorer than the mean reported worldwide rate [29], mainly from follow-ups occurring too early. Despite the cited limitations, the data presented here are directly applicable to clinical practice, as they highlight the respective risk of advanced polyps commonly encountered and that mandate appropriate surveillance.

Conclusions

In conclusion, SLs ≥ 10 mm confer a risk of TMAN greater than that of HGD and SLs < 10 mm. This should be reflected in recommended surveillance intervals for these lesions.

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Conflict of Interest

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