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The Long-Term Risk of Metachronous Advanced Adenoma Recurrence After Endoscopic Submucosal Dissection for Colorectal Neoplasia: A Propensity-Score Matched Longitudinal Cohort With 5-Year Follow-Up

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ABSTRACT

Introduction: Long-term data on metachronous advanced adenoma (AA) recurrence after endoscopic submucosal dissection (ESD) remain scarce, leading to a lack of a standardized surveillance strategy. This study aims to evaluate the long-term risk of recurrent AA after ESD.

Materials and Methods: A longitudinal retrospective cohort study with propensity-score matching was conducted in a tertiary hospital in Hong Kong. Subjects who underwent colorectal ESD between 2011 and 2017 were enrolled and defined as the post-ESD group. Selected subjects who underwent polypectomy in their index colonoscopy between 2011 and 2017 were enrolled and stratified into the low- intermediate- and the high-risk groups according to the US Multi-Society Task Force (USMSTF) guideline. The risks of recurrent AA were assessed by Cox proportional hazards regression in the matched cohorts.

Results: A total of 1745 subjects were included, with 203 post-ESD subjects fully matched with 729 high-risk and 813 low-intermediate-risk subjects, respectively. The 5-year cumulative incidence of recurrent AA in the post-ESD group was 7.8%. After 5 years, the post-ESD group was not associated with a higher rate of recurrent AA to the low-intermediate-risk group (7.8% vs. 5.5%; adjusted HR [aHR] 1.64, 95% CI 0.77–3.48, $p = 0.197$) but a lower rate of recurrent AA (7.8% vs. 11.8%; aHR 0.40, 95% CI 0.19–0.85, $p = 0.017$) than the high-risk group.

Conclusion: Subjects who underwent ESD were not associated with an increased 5-year risk of metachronous AA recurrence than low-intermediate or high-risk groups in USMSTF. The findings will inform future guidelines on post-ESD surveillance colonoscopy strategies.

Summary

- Summarise the established knowledge on this subject
  - Long-term data on metachronous recurrence of advanced adenoma (AA) after endoscopic submucosal dissection remain scarce, leading to a lack of standardized surveillance strategies.
- What are the significant and/or new findings of this study?
  - In a longitudinal retrospective cohort study with propensity-score matching, we found that subjects who underwent ESD were not associated with an increased 5-year risk of metachronous AA recurrence than low-intermediate or high-risk groups stratified by the US Multi-Society Task Force guidelines. The per annum risk of AA recurrence was highest in the first year post-ESD and tended to be steady in the following years.
  - The findings will inform future guidelines on post-ESD surveillance strategies. A surveillance colonoscopy in 1 year followed by standard intervals after curative ESD may be considered.

1 | Introduction

Endoscopic submucosal dissection (ESD) is an effective endoscopic treatment for en bloc resection of large colorectal neoplasms [1]. ESD can facilitate precise pathological diagnosis to assess the risk of lymph node metastasis of early colorectal cancer (CRC) to decide the necessity of salvage surgery [2]. A low local recurrence rate (0.5%–1.5%) after ESD for colorectal neoplasia was demonstrated in both short-term (1-year) [3] and long-term (5-year) follow-up [4, 5], while data on the metachronous adenoma recurrence after ESD are limited [6, 7]. Two small retrospective cohort studies reported the metachronous adenoma recurrence rate to be 20.8%–22.9% after ESD with a 30–36 months follow-up [6, 7]. Large-scale, high-quality, long-term data on the metachronous advanced adenoma (AA) recurrence after ESD is still lacking.

Although ESD has been established to be a minimally invasive treatment for colorectal neoplasms, the optimal and cost-effective surveillance strategy remains a research question to be addressed. The recent US Multi-Society Task Force (USMSTF) consensus recommended that patients with polyps should repeat colonoscopy following risk-stratified surveillance intervals based on the histology, number, and size of polyps [8]. However, considering the special patient subgroup undergoing ESD for much larger (≥ 20 mm) or even early malignant polyps, whether this recommendation is adaptable for post-ESD surveillance is unclear. The latest American Gastroenterological Association (AGA) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommended a colonoscopy at 12 months after ESD and further surveillance in accordance with standard intervals for curative ESD, which was only a weak recommendation based on low-quality evidence [9, 10]. Therefore, more longitudinal data are urgently needed to provide robust evidence for an ideal surveillance strategy after colorectal ESD.

Therefore, the current study aims to investigate the incidence of metachronous AA recurrence after colorectal ESD—a presumably "ultra-high-risk" group, compared with those after simple polypectomy with different risk profiles. Our findings will generate important epidemiological data to inform an optimal surveillance strategy after colorectal ESD.

2 | Materials and Methods

2.1 | Study Design and Data Source

This was a retrospective cohort study with propensity score-matching conducted in a tertiary hospital (Prince of Wales Hospital) in Hong Kong from January 2011 to December 2017, with a longitudinal 5-year follow-up until December 2022. Part of the clinical parameters, including demographics, procedure records, diagnoses, and drug prescriptions, were retrieved through the Clinical Data Analysis and Reporting System (CDARS), an electronic healthcare database covering all public hospitals and 90% of the 7.5 million population. Several territory-wide population-based studies were conducted using CDARS with data validity verified [11, 12]. Details in endoscopic procedures and pathological results were manually reviewed and extracted from the Clinical Management System by an independent research member. The study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (CREC reference no. 2022. 474).

2.2 | Patients

A list of patients who underwent colorectal ESD during the study period was retrieved from CDARS. Patients who met the following criteria were enrolled and defined as the post-ESD group. Inclusion criteria were (1) aged 45–80 years during the index ESD; (2) had lesion size ≥ 20 mm amendable by ESD; (3) received high-quality colonoscopy (i.e., successful cecal incubation and Boston Bowel Preparation Score [BBPS] ≥ 2 in each colonic segment) before or during the ESD procedure; (4) had no residual colorectal lesion (except diminutive hyperplastic polyps); and (5) received at least one complete surveillance colonoscopy within 5 years after ESD. Exclusion criteria were: (1) previous history of CRC/inflammatory bowel diseases (IBD)/polyposis syndrome; (2) non-neoplastic histology (e.g., hyperplastic polyp); (3) piecemeal resection; and (4) with non-curative resection and received salvage colectomy within 6 months after ESD.

Detailed information on the ESD procedure and pathological results, including endoscopist, BBPS, lesion site and size, morphology, resection type (en bloc or piecemeal), histology, degree of dysplasia, invasion depth and resection margins, were manually reviewed and collected. Synchronous adenoma was defined as an adenoma detected before or during the ESD procedure. Data on the number, site, size, histology, and degree of dysplasia of synchronous adenoma were manually reviewed and collected.

As the control group, selected patients aged 45–80 years who underwent simple polypectomy during the study period were included and further stratified into low-intermediate-risk group (with 1–4 NAAs) and high-risk group (with 5–10 adenomas and/or AA) in accordance with the USMSTF guideline. Inclusion criteria were (1) with at least one surveillance colonoscopy within 5 years after index colonoscopy. Exclusion criteria were: (1) previous history of CRC/IBD/polyposis syndrome; (2) previous history of AA; and (3) inadequate quality of the index colonoscopy (poor bowel preparation, failed cecal intubation, etc.). AA was defined as an adenoma with a size ≥ 10 mm, the presence of a villous component, or high-grade dysplasia.

2.3 | Surveillance Colonoscopy

Surveillance colonoscopy records within 5 years after index colonoscopy in the post-ESD, high-risk and low-intermediate-risk groups were reviewed for metachronous recurrent adenomas. In the present study, the definition of metachronous recurrent adenoma was a lesion that was found at least 6 months after the index procedure to avoid synchronous lesions. Data on the polyp site, size, histology, and degree of dysplasia during surveillance colonoscopy were collected.

2.4 | Outcomes

The primary outcome was the cumulative incidence of metachronous recurrent AA after index procedures. The secondary outcome was the cumulative incidence of metachronous recurrent NAA after index procedures.

2.5 | Statistics

Data were analyzed using R software (4.2.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean (standard deviation, SD) and categorical variables were expressed as number (percentage). The R package MachIt was used to perform the matching [13]. The full matching method by propensity score was used in this analysis [14, 15]. The full matching algorithm kept all the patients in the cohort and achieved the baseline balance by further dividing the cohort into matched sets based on the propensity score. Each matched set contained either one subject in the post-ESD group and at least one subject in the low-intermediate-risk group (or high-risk group) or vice versa. Covariables that may affect the adenoma recurrence risk were selected for matching—sex, age, comorbidities, concurrent drugs, number of synchronous adenomas and AA, and histological features at baseline. The standardized mean differences (SMDs) for the covariates < 0.1 indicated adequate balance. Primary and secondary outcomes and risk factors were analyzed using Cox proportional hazards regression. The matching weights of the matched cohorts were included in the regression model for outcome analysis. The per annum risk was calculated by the difference in cumulative incidence per year. Each patient was counted only at their first recurrence if they had multiple recurrences during subsequent surveillance colonoscopies. Statistical significance was defined as $p < 0.05$ on 2-sided.

3 | Results

3.1 | Patient Selection and Characteristics

A total of 448 patients who underwent colorectal ESD between January 2011 and December 2017 were reviewed. After excluding 233 patients (with one or more exclusion criteria) due to lesion size < 20 mm ($n = 51$), colectomy within 6 months ($n = 48$), a history of CRC/IBD/polyposis syndrome ($n = 44$), without full surveillance colonoscopy ($n = 40$), other pathology ($n = 27$), inappropriate age group ($n = 18$) and piecemeal resection ($n = 17$), 203 patients were included into the post-ESD group (Figure 1). A total of 2822 patients aged 45–80 years who underwent polypectomy for colorectal adenomas between January 2011 and December 2017 and had at least one complete surveillance colonoscopy within 5 years were screened. After excluding 1280 patients due to a history of CRC/IBD/polyposis syndrome ($n = 946$), a history of AA ($n = 193$), and other reasons (e.g., poor bowel preparation) ($n = 141$), 1542 patients were enrolled and further stratified into the low-intermediate-risk ($n = 813$) and high-risk groups ($n = 729$) (Figure 1). The baseline characteristics of patients in the three groups are shown in Table 1. The mean age of post-ESD, high-risk and low-intermediate-risk groups was 65.7 ± 7.9, 65.7 ± 7.4, and 64.8 ± 7.4 years, respectively.

3.2 | Clinical and Pathological Features

The clinical and pathological characteristics are shown in Table 1. There were 203, 771, and 906 lesions in the post-ESD, high-risk and low-intermediate-risk groups, respectively. The mean size of lesions in the post-ESD, high-risk and low-intermediate-risk groups were 32 ± 12.1, 11.6 ± 5.1, and 4.5 ± 1.9 mm, respectively. The number of synchronous adenomas was 2.8 ± 2.4, 3.2 ± 2.1, and 1.8 ± 1.0 in the three groups, respectively. The number of synchronous AA was 1.3 ± 0.8 and 1.2 ± 0.8 in the post-ESD and high-risk group, respectively. In the post-ESD group, the R0 resection rate was 84.7% (172/203). Five delayed bleedings occurred as adverse events (AEs), and no perforation occurred.

3.3 | Surveillance Colonoscopy Time Points and Frequency

In the post-ESD group, 190 (93.6%), 10 (4.9%), and 3 (1.5%) patients underwent their first surveillance colonoscopy at 1, 1–3, and 3–5 years after ESD, respectively. In the high-risk group, 190 (26.1%), 384 (52.7%), and 155 (21.3%) patients underwent their first surveillance colonoscopy at 1, 1–3, and 3–5 years after polypectomy, respectively. In the low-intermediate-risk group, 33 (4.1%), 256 (31.5%), and 524 (64.5%) underwent their first surveillance colonoscopy at 1, 1–3, and 3–5 years after polypectomy, respectively. The details of surveillance colonoscopy

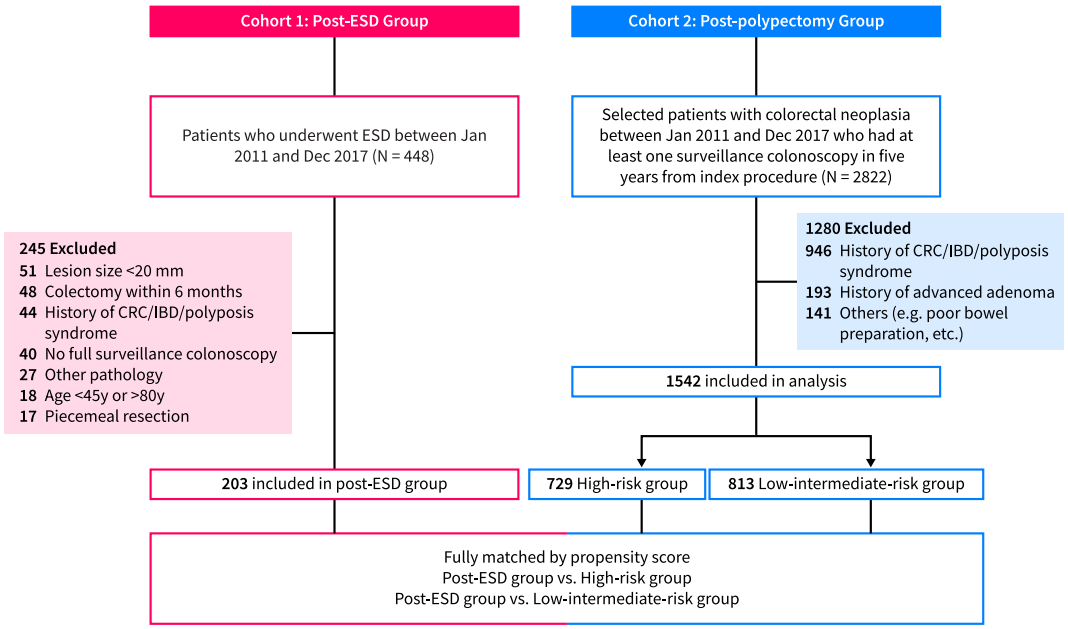

FIGURE 1 | Study flow chart.

time points and frequency of post-ESD, high-risk, and low-intermediate risk groups are shown in Table 2.

3.4 | Short-Term Local and Metachronous Recurrence After ESD

Among the 190 (93.6%) patients who underwent full surveillance colonoscopy 1 year after ESD, the local recurrence rate was 2.1% (4/190). The cumulative incidences of metachronous AA and NAA recurrence at 1 year were 4.7% and 40.0%, respectively (Figure S1).

3.5 | Long-Term Metachronous Recurrence of Advanced and Non-Advanced Adenomas

Covariables including sex, age, comorbidities (diabetes mellitus, hypertension, stroke, and ischemic heart disease), concurrent drugs (aspirin, statins, and metformin), which were reported to be associated with colorectal neoplasia progression [16–19], and number of synchronous adenomas at baseline were included in the propensity-score matching for post-ESD versus low-intermediate-risk and post-ESD versus high-risk groups, respectively. Besides, the number of synchronous AA and histological features (with/without villous component and/or high-grade dysplasia) at baseline were included in the propensity-score matching for post-ESD versus high-risk groups.

In the matching process, 203 patients in the post-ESD group were fully matched with 729 patients in the high-risk group by propensity score (i.e., weights). Similarly, 203 patients in the post-ESD group were fully matched with 813 patients in the low-intermediate risk group by propensity score (i.e., weights). SMDs before and after matching are shown in Table 1. After matching, all the SMDs were < 0.1, indicating adequate balance.

The cumulative incidences of recurrent AA at 5 years in the post-ESD, high-risk and low-intermediate-risk groups were 7.8%, 11.8%, and 5.5%, respectively. The cumulative incidences of recurrent NAA at 5 years in the post-ESD, high-risk, and low-intermediate-risk groups were 58.1%, 63.1%, and 52.4%, respectively. Cox proportional hazards regression analysis was performed in the matched cohorts (post-ESD vs. high-risk and post-ESD vs. low-intermediate-risk). The post-ESD group was associated with a lower rate of recurrent AA than the high-risk group (7.8% vs. 11.8%; adjusted hazard ratio [aHR] 0.40, 95% confidence interval [CI] 0.19–0.85, $p = 0.017$) (Figure 2a), but not associated with a higher rate of recurrent AA than the low-intermediate-risk group (7.8% vs. 5.5%; aHR 1.64, 95% CI 0.77–3.48, $p = 0.197$) (Figure 2b). The post-ESD group showed a similar rate of recurrent NAA (58.1% vs. 63.1%; aHR 1.06, 95% CI 0.80–1.42, $p = 0.680$) to the high-risk group (Figure 2c) but a higher rate of recurrent NAA (58.1% vs. 52.4%, aHR 2.04, 95% CI 1.48–2.81, $p < 0.001$) than the low-intermediate-risk group (Figure 2d). During the 5-year follow-up, no post-colonoscopy CRC (PCCRC) occurred in the post-ESD group, whereas there were three PCCRCs (0.4%) in the high-risk group and one PCCRC (0.1%) in the low-intermediate-risk group, respectively.

To explore the influence of surveillance time points, a subgroup analysis was conducted to compare the cumulative incidences of recurrent AA in patients who had surveillance colonoscopy at year one in the post-ESD group ($n = 190$), and those with ($n = 190$) or without ($n = 539$) year one surveillance colonoscopy in the high-risk group. The subgroup of patients who had surveillance colonoscopy at year one in the post-ESD group was associated with lower rates of recurrent AA than patients with (7.9% vs. 14.2%, aHR 0.40, 95% CI 0.17–0.96, $p = 0.039$) or without (7.9% vs. 10.9%, aHR 0.37, 95% CI 0.16–0.87, $p = 0.022$) surveillance colonoscopy at year one in the high-risk group (Figure S2). Additional analysis inclusive of all lesion sizes ($n = 254$) in the expanded post-ESD cohort is shown in Figure S3. The findings were consistent with the main analysis.

TABLE 1 | Baseline patient characteristics and lesion features.

Variables	Post-ESD group ($N = 203$)	High-risk group ($N = 729$)	Low-intermediate-risk group ($N = 813$)	SMDs of post-ESD versus high-risk group		SMDs of post-ESD versus low-intermediate-risk group	
				Before matching	After matching	Before matching	After matching
Age, mean (SD)	65.7 (7.9)	65.7 (7.4)	64.8 (7.4)	0.006	0.022	0.114	0.005
Sex, male, *n* (%)	116 (57.1)	492 (67.5)	490 (60.3)	0.209	0.061	0.063	0.032
Comorbidities, *n* (%)							
Diabetes mellitus	58 (28.6)	91 (12.5)	98 (12.1)	0.356	0.050	0.366	0.016
Hypertension	101 (49.8)	122 (16.7)	147 (18.1)	0.660	0.006	0.634	0.030
Stroke	11 (5.4)	15 (2.1)	27 (3.3)	0.149	0.099	0.093	0.041
Ischemic heart disease	22 (10.8)	37 (5.1)	44 (5.4)	0.185	0.004	0.175	0.004
Concomitant drugs, *n* (%)							
Statins	89 (43.8)	276 (37.9)	343 (42.2)	0.121	0.030	0.033	0.037
Aspirin	55 (27.1)	131 (18.0)	196 (24.1)	0.205	0.031	0.067	0.013
Metformin	39 (19.2)	150 (20.6)	166 (20.4)	0.035	0.049	0.031	0.037
Index adenoma number, mean (SD)	2.8 (2.4)	3.2 (2.1)	1.8 (1.0)	0.164	0.001	0.230	0.052
Index AA number, mean (SD)	1.3 (0.8)	1.2 (0.8)	N/A	0.213	0.039	N/A	N/A
"High-risk" histology[a], *n* (%)				0.273	0.058	N/A	N/A
Total number of lesions at index	203	771[b]	906[b]	N/A	N/A	N/A	N/A
Lesion size, mean (SD), mm	32.0 (12.1)	11.6 (5.1)	4.5 (1.9)	N/A	N/A	N/A	N/A
Lesion site, *n* (%)							
Right-sided colon	107 (52.7)	258 (33.5)	454 (50.1)	N/A	N/A	N/A	N/A
Left-sided colon	50 (24.6)	369 (47.9)	355 (39.2)	N/A	N/A	N/A	N/A
Rectum	46 (22.7)	144 (18.7)	97 (10.7)	N/A	N/A	N/A	N/A
Histology, *n* (%)							
TA	72 (35.5)	437 (56.7)	895 (98.8)	N/A	N/A	N/A	N/A
TVA/VA	92 (45.3)	332 (43.0)	N/A	N/A	N/A	N/A	N/A
SSA/TSA	29 (14.3)	2 (0.3)	11 (1.2)[c]	N/A	N/A	N/A	N/A
Adenocarcinoma	10 (4.9)	N/A	N/A	N/A	N/A	N/A	N/A
Degree of dysplasia, *n* (%)							
LGD	127 (62.6)	685 (88.8)	895 (98.8)	N/A	N/A	N/A	N/A
HGD	66 (32.5)	84 (10.9)	N/A	N/A	N/A	N/A	N/A
Tis/T1a	4 (2.0)	N/A	N/A	N/A	N/A	N/A	N/A
T1b	6 (3.0)	N/A	N/A	N/A	N/A	N/A	N/A
Morphology type, *n* (%)							
LST-G	94 (46.3)	N/A	N/A	N/A	N/A	N/A	N/A
LST-NG	53 (26.1)	N/A	N/A	N/A	N/A	N/A	N/A
LST (undetermined)	19 (9.4)	N/A	N/A	N/A	N/A	N/A	N/A

(Continues)

TABLE 1 | (Continued)

Variables	Post-ESD group ($N = 203$)	High-risk group ($N = 729$)	Low-intermediate-risk group ($N = 813$)	SMDs of post-ESD versus high-risk group		SMDs of post-ESD versus low-intermediate-risk group	
				Before matching	After matching	Before matching	After matching
Protruded (0-Is, 0-Ip)	26 (12.8)	N/A	N/A	N/A	N/A	N/A	N/A
Flat (0-IIa)	11 (5.4)	N/A	N/A	N/A	N/A	N/A	N/A
Assessment of resection margins, *n* (%)							
Lateral margins							
Clear	172 (84.7)	N/A	N/A	N/A	N/A	N/A	N/A
Involved	31 (15.3)	N/A	N/A	N/A	N/A	N/A	N/A
Vertical margins							
Clear	202 (99.5)	N/A	N/A	N/A	N/A	N/A	N/A
Involved	1 (0.5)	N/A	N/A	N/A	N/A	N/A	N/A
Lymphovascular invasion, *n* (%)	1 (0.5)	N/A	N/A	N/A	N/A	N/A	N/A
R0 resection, *n* (%)	172 (84.7)	N/A	N/A	N/A	N/A	N/A	N/A
Curative resection, *n* (%)	166 (81.8)	N/A	N/A	N/A	N/A	N/A	N/A
Adverse events, *n* (%)	5 (2.5)	N/A	N/A	N/A	N/A	N/A	N/A
Perforation	0 (0.0)	N/A	N/A	N/A	N/A	N/A	N/A
Delayed bleeding	5 (2.5)	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: AA, advanced adenoma; Curative resection, R0 resection with no unfavorable histological features such as a deep submucosal cancer invasion > 1000 μm from the muscularis mucosa, lymphovascular invasion, poor differentiation or tumor budding; HGD, high-grade dysplasia; left-sided colon, descending colon to sigmoid colon; LGD, low-grade dysplasia; LST, lateral spreading tumor, which is classified into granular (LST-G) and non-granular (LST-NG) types; N/A, not applicable; R0 resection, en bloc resection with free lateral and vertical resection margins; right-sided colon, cecum to transverse colon; SD, standard deviation; SMD, standardized mean differences; SSA, sessile serrate adenoma; T1a, submucosal superficial invasive cancer with < 1000 μm of submucosal tumor invasion; T1b, submucosal deep invasive cancer with 1000 μm or deeper; TA, tubular adenoma; Tis, carcinoma in situ, cancer cells are found only in the epithelium or lamina propria; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma; VA, villous adenoma.

[a]"High-risk" histology refers to lesions with villous component and/or high-grade dysplasia.

[b]The most advanced lesions were included.

[c]Only SSA.

3.6 | Per Annum Risk of Metachronous Recurrence in Post-ESD Group

The Kaplan–Meier curves of 5-year cumulative incidences of recurrent AA and NAA after ESD are shown in Figure 3a. The per annum risk of NAA during years 1–5 were 26.8%, 18.7%, 8.1%, 7.6%, and 11.6%, respectively. The per annum risks of AA during years 1–5 were 4.7%, 2.0%, 0%, 0%, and 2.9%, respectively (Figure 3b).

3.7 | Risk Factors of Long-Term Metachronous Adenoma Recurrence After ESD

Univariate and multivariate analyses were conducted to look for risk factors of metachronous adenoma recurrence after ESD (Table 3). In the multivariate analysis, the presence of >2 synchronous adenomas (HR 2.34, 95% CI 1.52–3.58, $p < 0.001$) was an independent risk factor of long-term metachronous adenoma recurrence after ESD.

4 | Discussion

The safety data of low local recurrence risk after colorectal ESD has been well established [3–5], while data on the metachronous adenoma recurrence are limited and only based on short-term follow-up [6, 7]. This leads to a lack of evidence to support the optimal post-ESD surveillance strategy by existing guidelines. Both the USMSTF and Asia-Pacific guidelines did not provide specific recommendations on surveillance colonoscopy after colorectal ESD [8, 20]. The ESGE guideline recommended a surveillance colonoscopy at 1 year after curative ESD based on low-quality evidence [9], while a longer-term plan has not been addressed. Hence, it is important to assess the long-term risk of metachronous recurrence after colorectal ESD to draft future surveillance guidelines.

The current propensity-score matched cohort study compared the risk of metachronous AA recurrence in the post-ESD group versus risk-stratified post-polypectomy groups with 5-year longitudinal follow-up. Our results indicated that the 5-year cumulative incidence of metachronous recurrent AA was 7.8% in

TABLE 2 | Surveillance colonoscopy time points and frequency of post-ESD, high-risk, and low-intermediate-risk groups.

Surveillance time point	Times of surveillance colonoscopy	Post-ESD (*N* = 203)	High-risk group (*N* = 729)	Low-intermediate-risk group (*N* = 813)
1 year	1st	190 (93.6%)	190 (26.1%)	33 (4. 1%)
1–3 years	1st	10 (4.9%)	384 (52.7%)	256 (31.5%)
	2nd	78 (38.4%)	45 (6.2%)	7 (0.9%)
3–5 years	1st	3 (1.5%)	155 (21.3%)	524 (64.5%)
	2nd	52 (25.6%)	78 (10.7%)	9 (1.1%)
	3rd	25 (12.3%)	8 (1.1%)	4 (0.5%)

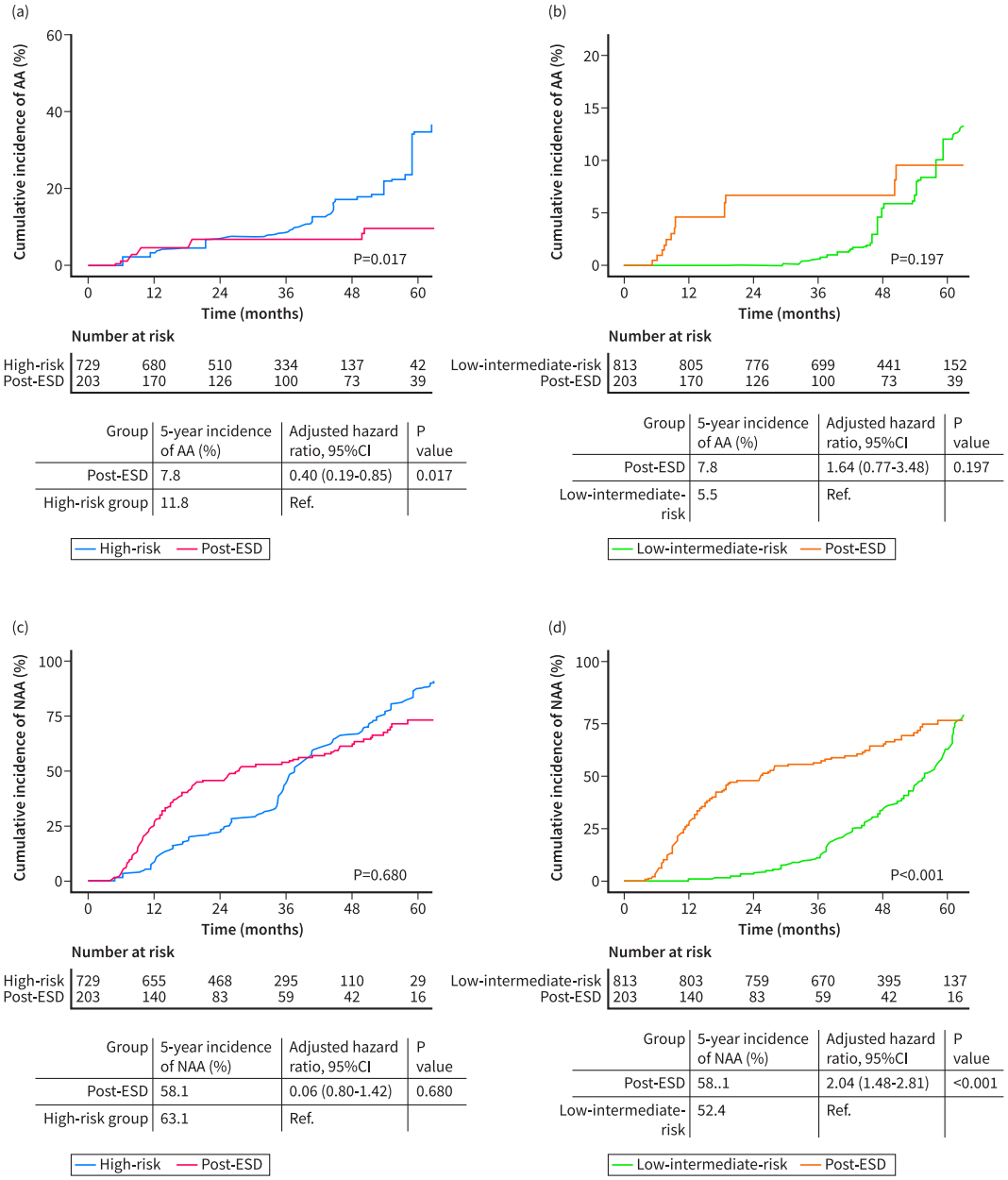

FIGURE 2 | Cumulative incidences of metachronous recurrent advanced adenoma (AA) during 5-year follow-up among post-ESD versus high-risk group (a) and post-ESD versus low-intermediate-risk group (b) matched cohorts; cumulative incidences of metachronous recurrent non-advanced adenoma (NAA) during 5-year follow-up among post-ESD versus high-risk group (c) and post-ESD versus low-intermediate-risk group (d) matched cohorts.

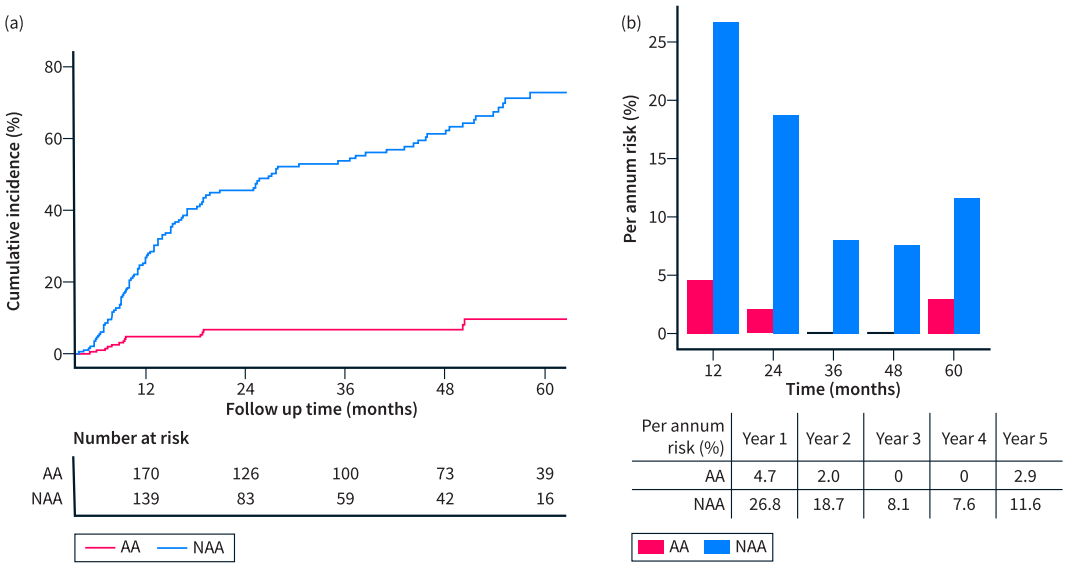

FIGURE 3 | Cumulative incidences of metachronous recurrent advanced adenoma (AA) and non-advanced adenoma (NAA) during 5 years after ESD (a), per annum risk plot for recurrent AA and NAA during 5 years after ESD (b).

TABLE 3 | Risk factors of long-term metachronous adenoma recurrence after ESD for colorectal neoplasia.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age > 65 years	1.51 (1.04–2.17)	0.029	1.36 (0.94–1.99)	0.106
Sex, male	1.27 (0.88–1.85)	0.204	—	—
Lesion size > 30 mm	0.92 (0.63–1.34)	0.648	—	—
Histology				
TA	Reference	—	—	—
TVA/VA	0.91 (0.61–1.35)	0.635	—	—
SSA/TSA	0.63 (0.34–1.15)	0.132	—	—
Adenocarcinoma	0.47 (0.19–1.2)	0.114	—	—
Degree of dysplasia				
LGD	Reference	—	—	—
HGD	1.25 (0.85–1.83)	0.255	—	—
Tis/T1a/T1b	0.57 (0.23–1.43)	0.234	—	—
Synchronous adenoma number > 2	2.34 (1.61–3.4)	< 0.001	2.34 (1.52–3.58)	< 0.001
Synchronous advanced adenoma number > 1	1.54 (1.02–2.32)	0.042	0.90 (0.55–1.45)	0.653

Abbreviations: HGD, high-grade dysplasia; HR, hazard ratio; LGD, low-grade dysplasia; SSA, sessile serrated adenoma; T1a, submucosal superficial invasive cancer with < 1000 μm of submucosal tumor invasion; T1b, submucosal deep invasive cancer with 1000 μm or deeper; TA, tubular adenoma; Tis, carcinoma in situ, cancer cells are found only in the epithelium or lamina propria; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma; VA, villous adenoma.

the post-ESD group, with no occurrence of PCCRC. The recurrence rate in our cohort was lower than that in a previous study conducted by Yoshida et al. (7.8% vs. 22.9%), which could be attributed to the difference in patient characteristics of the two cohorts (e.g., cancer rates, 4.9% vs. 52.7%) [7] and the discrepancy in the pathological diagnosis of CRC between Japan and Western countries [21]. Our cohort adopted the WHO classification and consisted of more benign lesions, which may better reflect the real-world scenario. We demonstrated that patients who underwent colorectal ESD had a lower recurrence rate of advanced neoplasia than the high-risk group and a comparable recurrence rate to the low-intermediate-risk group. To the best of our knowledge, our study was the first one to investigate the long-term outcomes of patients receiving ESD and directly compare them with different risk-stratified groups to provide valuable longitudinal data on post-ESD follow-up. In general, patients with "significant" colorectal lesions requiring ESD were thought to be "ultra-high-risk" with the necessity of extra close surveillance. Our results were reassuring and offered a guide to clinicians and patients for better resource allocation to avoid unnecessary colonoscopies.

Moreover, our study found that the cumulative incidences of metachronous adenoma recurrence at 1-year after ESD were particularly high (4.7% for AA and 40.0% for NAA). In addition, the per annum risks of recurrent AA and NAA peaked in the

first year (4.7% and 26.8%) and tended to be steady in the following years, with another increment in the fifth year. These findings might provide the much-needed evidence to support the current ESGE guideline, which recommends a surveillance colonoscopy at 1 year after curative ESD [9]. Our results also supported that the second surveillance colonoscopy can be arranged in the fifth year after ESD without additional risk factors. More well-designed, prospective studies are warranted to validate this recommendation.

This study also attempted to determine the risk factors of metachronous adenoma recurrence after ESD. Multivariate analysis showed that the presence of > 2 synchronous adenoma was an independent risk factor for long-term adenoma recurrence. Accumulating evidence has demonstrated that the gut microbiome plays an important role in the development and progression of colorectal adenoma to CRC [22, 23]. Presence of multiple adenomas at baseline might be associated with an underlying altered gut microbiota, which may, in return, lead to a persistently elevated risk of adenoma recurrence.

The current study provided supplementary evidence on the long-term outcomes of colorectal ESD to existing literature and essential pilot data for the future development of post-ESD surveillance strategies. The strengths of this study included the use of two well-defined risk-stratified post-polypectomy groups (USMSTF high-risk and low-intermediate-risk groups) as the control, which were fully matched with the post-ESD group by propensity score to assess the adenoma recurrence risk thoroughly, and the complete longitudinal data from a 5-year follow-up period with manually verified endoscopic and pathological records. Most importantly, our novel results will inform clinical decisions and potentially change practices. However, there are several limitations to the current study. First, this is a retrospective cohort study conducted at a single center. Limited by the study design, some patients had no surveillance data after index colonoscopy and were excluded from the analysis. This might cause some inaccuracy in estimating the risk of metachronous recurrence (e.g., a selection bias of higher risk control compared to the general population). A more well-designed, prospective, population-based study will be ideal to provide more robust evidence. Second, due to the limited healthcare resources and long colonoscopy waiting time, some patients who underwent colonoscopy deviated from the recommended surveillance schedule. We adopted a 6-month window period at each time point to allow complete data capture. Third, the study period was relatively long with some variations in the indications of ESD with time, which might cause heterogeneity in the whole cohort. Fourth, despite our extensive propensity-score matching to minimize the potential bias between groups, some unidentified or unknown factors for adenoma recurrence may remain in the cohorts.

5 | Conclusion

Patients who underwent ESD for colorectal neoplasia demonstrated a lower 5-year rate of AA recurrence than the high-risk group and a similar 5-year rate of AA recurrence to the low-intermediate-risk group following USMSTF risk stratification. Moreover, the per annum risk of recurrence peaked in the first year after ESD and became steady in the following years. The findings will inform future guidelines on post-ESD surveillance strategies. A 1-year surveillance colonoscopy followed by standard intervals after curative ESD may be considered.

Conflicts of Interest

Rashid N. Lui has served as an advisory board member for Gilead Sciences and as a speaker for GenieBiome, Gilead Sciences, and Pierre Fabre, and owns equity in Pfizer. Philip W. Y. Chiu has served in a research collaboration with Boston Scientific; and as an advisor for EndoVision and EndoMaster; and as a lecture speaker for Olympus. Siew C. Ng has served as an advisory board member for Pfizer, Ferring, Janssen, and Abbvie and received honoraria as a speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie, and Takeda. Siew C. Ng has received research grants through her affiliated institutions from Olympus, Ferring, and Abbvie. Siew C. Ng is a scientific co-founder and shareholder of GenieBiome Ltd. Siew C. Ng receives patent royalties through her affiliated institutions. Francis K. L. Chan is a Board Member of CUHK Medical Centre. He is a co-founder, non-executive Board Chairman, and shareholder of GenieBiome Ltd. He receives patent royalties through his affiliated institutions. He has received fees as an advisor and honoraria as a speaker for Eisai Co. Ltd., AstraZeneca, Pfizer Inc., Takeda Pharmaceutical Co., and Takeda (China) Holdings Co. Ltd. Louis H. S. Lau has received research grant from GenieBiome Ltd. and served as an advisory board member for GenieBiome Ltd. and AstraZeneca. He has served as lecture speaker for Olympus Co. Ltd., Boston Scientific Co. Ltd. and GenieBiome Ltd. The remaining authors disclose no conflicts.

Data Availability Statement

De-identified individual data from this article will be made available to the corresponding author on reasonable request with an approved study protocol and valid methodology.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.