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Total Number of Polyps are Associated with an Increased Risk of Recurrent Adenomatous Polyps

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1. Abstract

1.1. Background

Current guidelines on interval between surveillance colonoscopy is limited by insufficient understanding about the rate of polyp re-growth.

1.2. Aim

To determine the prevalence and predictors of recurrent adenomas and advanced adenomas (AAs) in individuals with high-risk adenomas (defined as having one polyp>10 mm in size, >3 polyps or one AA).

1.3. Method

One-hundred-and-sixty-eight patients with high-risk adenomas at index colonoscopy were recruited into this study. All patients underwent a second colonoscopy 3 months later to ensure clearance of all polyps. Further colonoscopies were performed at 12, 24 and 36 months after index colonoscopy.

1.4. Results

At 36 months, 91 of the 168 patients (54.2%) had recurrent adenomas. The cumulative probability of recurrent adenomas at 12, 24 and 36 months were 19.0%, 47.0% and 54.2%. On multivariate analysis, total number of adenomas and sessile serrated lesions at index colonoscopy was the only independent factor associated with recurrent adenomas [RR 1.066, 95% CI 1.004-1.095; p= 0.034]. Twelve of the 168 patients (7.1%) had recurrent AAs at 36 months. The cumulative probability of recurrent AAs at 12, 24 and 36 months were 1.2%, 4.8% and 7.1%. Total number of adenomas and sessile serrated lesions at index colonoscopy was the only independent factor associated recurrent AAs [RR 1.145, 95% CI 1.043-1.257; p= 0.004].

1.5. Conclusion

The total number of adenomas and sessile serrated lesions at index colonoscopy was associated with recurrent adenomas and recurrent AAs. Those with high-risk adenomas at index colonoscopy had a high prevalence of recurrent adenomas and recurrent AAs.

2. Introduction

Colorectal cancer (CRC) is the third most common malignancy in the world today [1,2]. Adenomas and serrated lesions, especially sessile serrated adenomas, are precursor lesions in CRC development [3,4,5]. The malignant transformation of serrated adenomas and traditional adenomas are usually via the serrated neoplastic pathway and the traditional adenoma-carcinoma pathway, respectively [6,7].It has been shown that those with high-risk adenomas have a 15.5% risk of developing AAs five years after the index colonoscopy versus 6.9% risk for those with low-risk adenomas [8,9]. High-risk adenomas were defined as advanced adenomas (AAs), at least one polyp ≥ 10 mm in size and/or more than 3 synchronous adenomas and low-risk adenoma were defined as less than 3 adenomas with low grade dysplasia where all adenomas were less than 10 mm in size. A similar outcome was found in those with large serrated polyp of more than 10 mm in size at index colonoscopy [10]. Based on these characteristics, screening and surveillance of CRC with colonoscopy remains the main strategy to reduce mortality through the detection and excision of these premalignant lesions. The recommended intervals between surveillance colonoscopies are based on the size, number and histology of the resected polyps at index colonoscopy. Individuals with high-risk adenomas are recommended to have a follow-up surveillance colonoscopy 3 years after the index colonoscopy. However, these guidelines are based on indirect evidence while recent observational studies have found that colonoscopy in the last 10 years was able to reduce CRC incidence and mortality by 60% only [11,12,13]. CRC or post-colonoscopy CRC can occur in those undergoing

colonoscopy surveillance. This could be due to incomplete resection or missed polyp during index colonoscopy. For example, studies have shown that 8% of polyps ≥ 10 mm in size and 15% of polyps ≤ 10 mm in size may be missed on colonoscopy [14,15]. This bought into question the reliability of surveillance procedures and the ramification delayed detection of these missed lesions. Another concern about the adequacy of surveillance colonoscopy is the possible non-linear nature of polyp growth or re-growth, like liver fibrosis progression [16,17]. A rapidly progressive lesion may develop in between regular surveillance colonoscopy. Current guidelines on the optimal interval between surveillance colonoscopies based on the size, number and histopathology of the resected polyps, may be limited by our lack of understanding on the rate of polyp growth or re-growth, especially in those with high-risk adenomas at index colonoscopy. This may be the reason why one study showed that 34% of patients with high-risk adenomas underwent surveillance colonoscopy earlier than recommended. Furthermore, only 29% of patients were found to have undergone surveillance colonoscopy according to the guideline recommended by the American Gastroenterological Association [18].Therefore, we have undertaken a study to determine the prevalence of recurrent adenomas and recurrent AAs in those with high-risk adenomas on index colonoscopy.

3. Patients and Methods

3.1. Patients

Consecutive asymptomatic faecal occult blood positive Asian patients referred for an index colonoscopy at the Centre for Digestive Diseases from 20th January 2017 to 10th December 2018 with high-risk adenomas; defined as either at least one polyp more than 10 mm in size, more than 3 polyps or at least one AA detected on index colonoscopy were recruited into this study. All patients recruited into this study were colonoscopy-naïve.Patients with history of inflammatory bowel disease, serrated polyposis syndrome, familial adenomatous polyposis or Lynch syndrome, personal history of CRC and more than 75 years of age were excluded from the study. Serrated polyposis syndrome was defined according to World Health Organisation (WHO) criteria as at least five serrated polyps proximal to the sigmoid colon, of which two or more were more than 10 mm in sizes, and/or more than 20 serrated polyps of any size throughout the colon [4].

4. Colonoscopy

Colonoscopy was performed with a high-definition variable stiffness colonoscope (Olympus, Tokyo, Japan) under Midazolam and Pethidine as previously described.19 A second colonoscopy was performed three months after the index colonoscopy to ensure the colon has been cleared of all polyps. All patients had colonoscopy repeated at 12, 24 and 36 months after the index colonoscopy. All colonoscopies were performed by one endoscopist with more than 10 years' experience in therapeutic colonoscopy.A complete examination was defined as the colonoscope cannulating the caecum as evidenced by the ileo-caecal valve or appendiceal orifice. A standardised withdrawal time of at least 8 minutes was practiced. The whole procedure was timed and recorded on video. The withdrawal time was measured as the time when the colonoscope was withdrawn from the caecum to the time the anal verge was reached. Data on the quality of the bowel preparation, caecal or terminal ileum intubation time, withdrawal time and immediate or delayed complications were recorded. The quality of the bowel preparation was graded according to the Boston Bowel Preparation Scale by the endoscopist. An adequate bowel preparation was defined as a total score ≥6 while a segment score ≥2 was defined as adequate for that segment as previously described [19].The size, location and morphology of all colonic lesions were documented. The size of lesions was measured using an open cold snare and the location of the polyp was determined upon withdrawal of colonoscope.

5. Histology

All polyps removed endoscopically were assessed according to the World Health Organisation Classification [20].

High-risk adenomas were defined as presence of AAs, at least one polyp > 10 mm in size and/or more than 3 synchronous adenomas as previously described [8,9]. AAs was defined as either an adenoma measuring > 10 mm in diameter, villous or tubulovillous architecture (i.e. more than 25% villous), high-grade dysplasia or intramucosal carcinoma or any combinations thereof. Pathology proximal to the splenic flexure on withdrawal of the colonoscope was classified as a right sided lesion.The primary aim of this study was to determine recurrent adenomas on surveillance colonoscopy. The secondary aims of the study were to determine the recurrent AAs; and; to determine the variables associated with recurrent adenomas and recurrent AAs.

4.Statistical Analysis

All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, New York, USA). Mann–Whitney U-test was used for continuous variables with skewed distribution and Chi-square with Yates' correction factor or Fisher's exact test for categorical variables. Continuous variables were expressed as mean (standard deviation) (SD). The Kaplan-Meier method was used for calculation of the cumulative probability of recurrent adenomas and recurrent AAs, and, where appropriate, the Mantel-Haenszel log-rank test was applied for comparisons. Variables with a p value ≤ 0.10 were included in the Cox proportional analysis model with a forward stepwise procedure to determine the most significant factors associated with recurrent adenomas and recurrent AAs. The relative risk (RR) of recurrent adenomas and recurrent AAs were also estimated using the Cox proportional hazards model. The validity of each Cox proportional hazards model was checked by examining the corresponding Martingale and standardized score residuals. The 95% confidence interval (95%CI) for all estimates was provided where appropriate. All statistics were performed on the intention to treat population which included all patients recruited into the study initially. Statistical significance was defined as $p < 0.05$ (two-tailed).

5. Result

5.1. Study Population

During this period, 433 asymptomatic Asian patients with positive faecal occult blood were referred to our Centre for an index colonoscopy (Figure 1). One hundred and ninety-one of these 433 (44.1%) consecutive patients had high-risk adenomas detected at index colonoscopy. Twenty-three of

the 191 (12.0%) patients were excluded from the study; 11 patients as they were on combination Aspirin and Clopidogrel or oral anticoagulants, 10 patients declined to participate and 2 patients for colorectal cancer at index colonoscopy (Figure 1). The characteristics of these 168 patients are shown in Table 1.A total of 750 polyps were detected at index colonoscopy in these 168 patients. Out of these 750 polyps, 620 (82.7%) were adenomatous polyp, 95 (12.7%) were serrated lesions and 35 (4.7%) were hyperplastic polyps [Table 1].

5.2. Polyps found on Colonoscopy 6 Months after Index Colonoscopy

Twenty-nine of these 168 patients (17.3%) had polyps found on colonoscopy three months after the index colonoscopy. A total of 35 polyps, all measuring 2-4 mm in size respectively, were found on colonoscopy 3 month after the index colonoscopy. Thirty-two of these 35 polyps (91.4%) were adenomas while three of these 35 polyps (8.6%) were sessile serrated adenomas. This meant that 35 out a combined total 785 polyps (4.5%) were missed at index colonoscopy.

5.3. Recurrent Adenomas on Follow-up Colonoscopy

At the end of 36 months, 91 of the 168 patients (54.2%) had recurrent adenomas. The cumulative probability of recurrent adenomas at 12, 24 and 36 months were 19.0%, 47.0% and 54.2%, respectively (Figure 1 and Figure 2A). Baseline characteristics of patients with and without recurrent adenomas are shown in Table 2.Factors predictive of recurrent adenomas were right sided adenomas at index colonoscopy [78/91 (85.7%) patients vs. 53/77 (68.8%) patients, respectively; p=0.011 (by log-rank)] (Figure 2B), a higher total number of adenomas and sessile serrated lesions at index colonoscopy [mean (SD) 5.38 (4.70) vs. 3.38 (3.25), respectively; p=0.005], 5-10 adenomas at index colonoscopy [39/91 (42.9%) vs. 20/77 (26.0%), respectively; p= 0.009 (by log-rank)] (Figure 2C), >10 adenomas at index colonoscopy [11/91 (12.1%) vs. 3/77 (3.9%), respectively; p= 0.019 (by log-rank)] (Figure 2D), history of hypertension [43/91 (47.3%) vs. 23/77 (29.9%), respectively; p= 0.007 (by log-rank), history of ischemic heart disease [13/91 (14.3%) vs. 3/77 (3.9%), respectively; p= 0.049 (by log-rank)], history of smoking [45/91 (49.5%) vs. 19/77 (24.7%), respectively; p< 0.001] and a higher body mass index [84.06 (22.75) vs. 77.34 (14.46) kg/m2, respectively; p=0.008] [Table 2].

When multivariate Cox regression analysis was used to assess recurrent adenomas, total number of adenomas and sessile serrated lesions at index colonoscopy was the only independent factor associated with recurrent adenomas [RR 1.066, 95% CI 1.004-1.095; p= 0.034].

5.4. Recurrent AAs on Follow-up Colonoscopy

At the end of 36 months, 12 of the 168 patients (7.1%) had recurrent AAs. The cumulative probability of recurrent AAs at 12, 24 and 36 months were 1,.2%, 4.8% and 7.1%, respectively (Figure 3A). Baseline characteristics of patients with and without recurrent AAs are shown in Table 3.Those with a higher total number of adenomas and sessile serrated lesions at index colonoscopy were significantly more likely to have recurrent AAs [mean (SD) 7.58 (8.10) vs. 4.22 (3.69); p< 0.001] (Table 3). The presence of >10 adenomas at index colonoscopy was also associated with a higher chance of recurrent AAs [3/12 (25.0%) vs. 11/156 (7.1%), respectively; p= 0.021 (by log-rank)] (Figure 3B) [Table 3]. There was a trend that those with right sided adenomas at index colonoscopy [12/12 (100%)] when compared with those without right sided adenomas at index colonoscopy [119/156 (76.3%); p= 0.059 (by log-rank)] (Figure 3C) [Table 3] was associated with recurrent AAs.Those with a history of hypertension were also more likely to recurrent AAs [9/12 (75.0%) vs. 57/156 (36.5%), respectively; p= 0.009 (by log-rank) [Table 3].When multivariate Cox regression analysis was used to assess recurrent AAs, total number of adenomas and sessile serrated lesions at index colonoscopy was again the only independent factor associated with recurrent AAs [RR 1.145, 95% CI 1.043-1.257; p= 0.004].

6. Discussion

Classically, there are two main types of polyps with malignant potential. These are adenomatous polyps which can be classified according to size, degree of dysplasia and proportion of villous component and serrated polyps which are hyperplastic polyps, sessile serrated lesions and traditional serrated polyps [20,21]. Current guidelines on the follow-up interval for surveillance colonoscopy after polypectomy based their recommendations on these classifications and components along with the number of polyps resected [22].In reality, determining the appropriate interval between surveillance colonoscopy is more difficult. Studies have found that many patients can have both adenomatous and serrated polyps [23,24].Making it difficult to determine which polyp type posed a higher risk for recurrent adenomas and recurrent AAs, and thus should have more frequent surveillance colonoscopies. It is also uncertain if the site/location of the polyp, number of polyps without any histologic evidence of AA or AA that poses a greater risk for recurrent adenomas or recurrent AAs.Our study found that in those with high-risk adenomas, 19.0% had

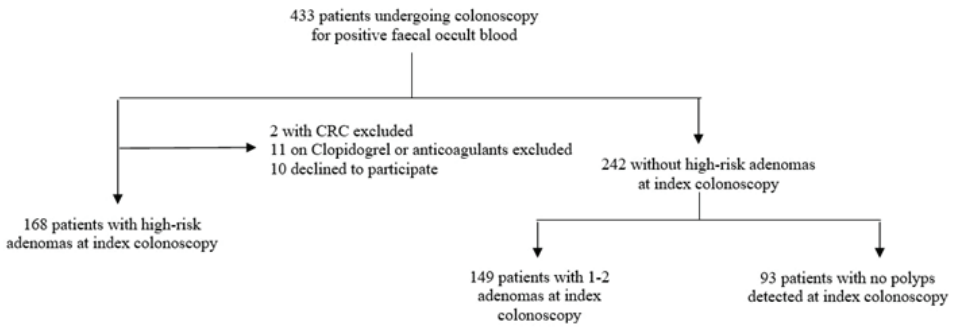

Figure 1: Graph showing patient population.

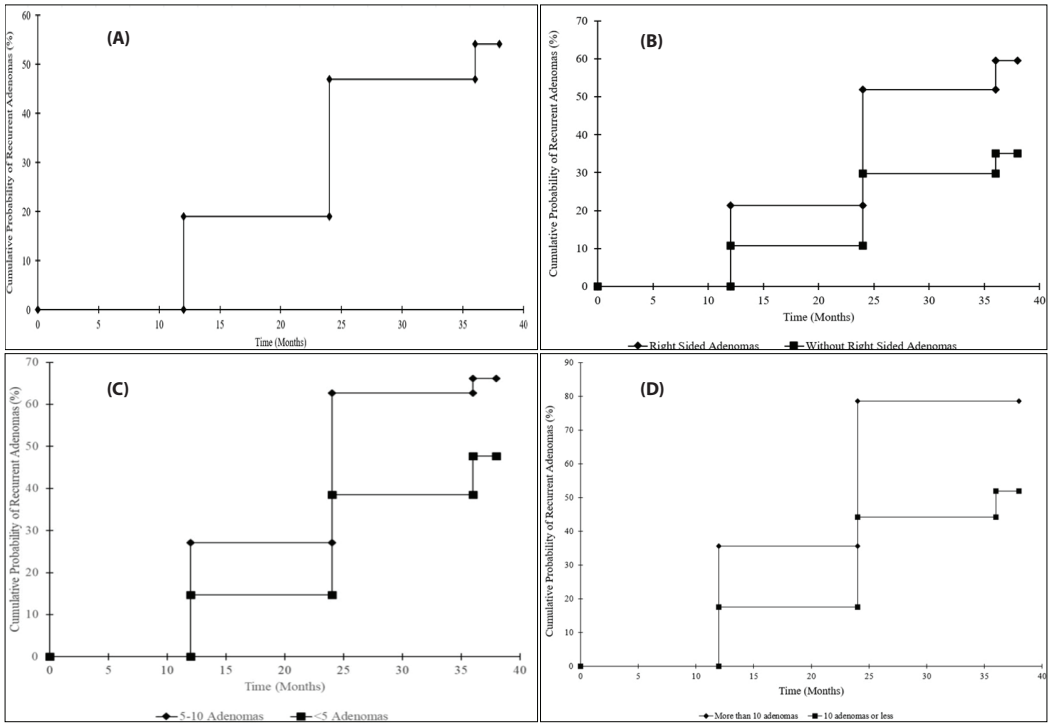

Figure 2: (A) Cumulative probability of recurrent adenomas on surveillance colonoscopy, **(B)** Cumulative probability of recurrent adenomas on surveillance colonoscopy according to presence of right sided adenomas at index colonoscopy, **(C)** Cumulative probability of recurrent adenomas on surveillance colonoscopy according to the presence of 5-10 adenomas at index colonoscopy and **(D)** Cumulative probability of recurrent adenomas on surveillance colonoscopy according to >10 adenomas at index colonoscopy.

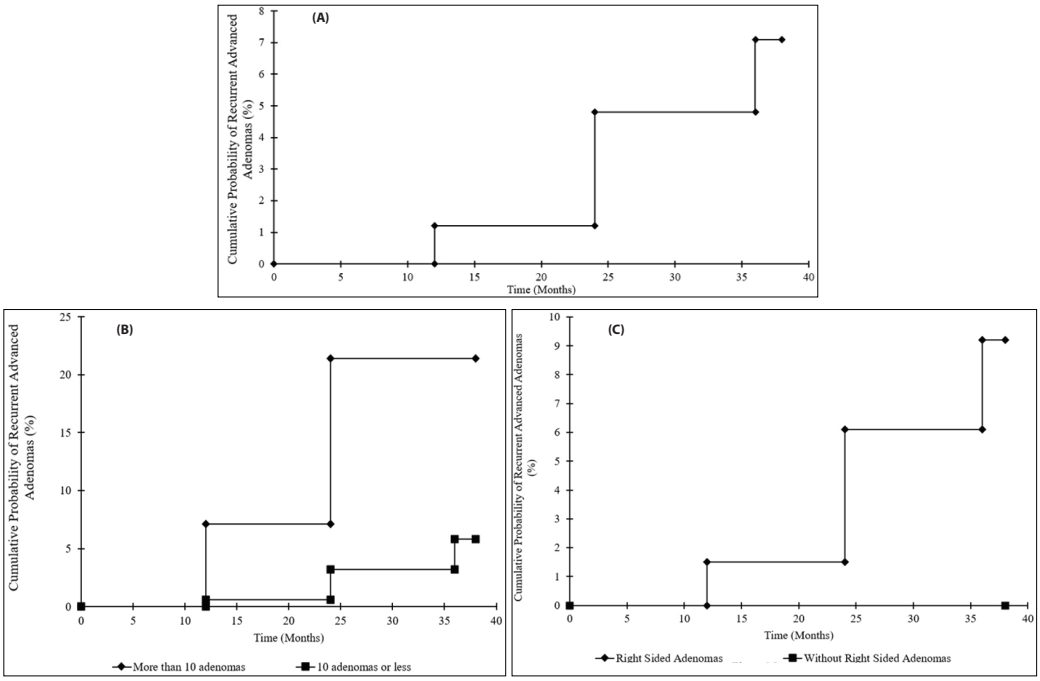

Figure 3: (A) Cumulative probability of recurrent advanced adenomas (AAs) on surveillance colonoscopy, **(B)** Cumulative probability of recurrent advanced adenomas on surveillance colonoscopy according to >10 adenomas at index colonoscopy and **(C)** Cumulative probability of recurrent advanced adenomas on surveillance colonoscopy according to presence of right sided adenomas at index colonoscopy.

recurrent adenomas at 12 months and this increased to 54.2% in 36 months. Importantly, a higher total number of adenomas and sessile serrated lesions on index colonoscopy was the only independent risk factor for recurrent adenomas. Furthermore, 1.2% of patients had recurrent AAs at 12 months and this increased to 7.1% in 36 months. As with recurrent adenomas, a higher total number of adenomas and sessile serrated lesions at index colonoscopy was the single most independent factor associated with recurrent AAs.These findings correspond to previous two studies which also showed that the total number of polyps at index colonoscopy were associated with a higher risk of metachronous polyps after index polypectomy

[24,26].In those with > 10 adenomas at index colonoscopy, the recommendation to repeat a surveillance colonoscopy at 12 months was based on a Korean study [27]. Although those with > 10 adenomas at index colonoscopy had a higher chance of recurrent adenomas and recurrent AAs, it was not an independent factor associated with either recurrent adenomas or recurrent AAs in this study.However, as the cumulative probability of recurrent AAs in those with > 10 adenomas at index colonoscopy was 7.1% at 12 months (Figure 3B) and the cumulative probability of recurrent adenomas was 35.7% at 12 months (Figure 2D), the findings from this study suggested that those with > 10 adenomas at index colonoscopy may require a shorter surveillance colonoscopy interval, preferably starting at six months rather than 12 months [22,27]. Moreover, those with 5-10 adenomas at index colonoscopy also had a higher risk of recurrent adenomas. The cumulative probability of recurrent adenomas in those with 5-10 adenomas at index colonoscopy was 27.1% in 12 months (Figure 2C). Although the presence of 5-10 adenomas at index colonoscopy was not associated with a higher chance of recurrent AAs, the findings suggested that this group should be considered for a repeat surveillance colonoscopy at 12 months rather than the current recommended three years [22].Similar to the study this study found that those with right sided adenomas and pre-existing co-morbidities such a hypertension, ischemic heart disease and smokers were more likely to have recurrent adenomas [24]. However, the presence of right sided sessile serrated lesions was not associated with recurrent adenomas. This implies that proximal adenomas may be considered as a marker for a higher probability of recurrent adenomas. Those with pre-existing co-morbidities such as hypertension, ischemic heart disease and active smoking can also be used as to stratify the risk of developing recurrent adenomas, thereby requiring closer surveillance colonoscopy. This is similar to the findings

Table 1: Data at Index Colonoscopy.

	Subjects
Caecal intubation rate, n (%)	168 (100%)
Terminal ileum intubation rate, n (%)	168 (100%)
Sex; M: F	95: 73
Mean age (SD), years	64 (10)
Number of sessile serrated lesions	95 (12.7%)
Sessile serrated lesions with low grade dysplasia	16 (2.1%)
Sessile serrated lesions with no dysplasia	79 (10.5%)
Number of adenomas	620 (82.7%)
Number of Advanced Adenomas	236 (31.5%)
Hyperplastic polyps	35 (4.7%)
Right sided adenomas	131 (17.5%)
Right sided sessile serrated lesions	44 (5.9%)
Polyp ≥ 20 mm in size	142 (18.9%)

Table 2: Factors associated with recurrent adenomas on surveillance colonoscopy.

	Recurrent Advanced Adenomas. (n=12)	No Recurrent Advanced adenomas. (n=156)	p-value.
Mean age (SD); years	66 (7)	63 (11)	0.139#
Sex; M:F	6:6	89:67	0.610
Total number of adenomas and sessile serrated lesions on index colonoscopy; mean (SD)	7.58 (8.10)	4.22 (3.69)	<0.001#
5-10 adenomas at index colonoscopy	5 (41.7%)	54 (34.6%)	0.612
>10 adenomas at index colonoscopy	3 (25.0%)	11 (7.1%)	0.021
Right sided adenomas at index colonoscopy; n	12 (100%)	119 (76.3%)	0.059
Advanced adenomas at index colonoscopy; n	10 (83.3%)	135 (86.5%)	0.770
Sessile serrated lesions at index colonoscopy; n	3 (25.0%)	48 (30.8%)	0.669
Sessile serrated lesions with dysplasia at index colonoscopy; n	3 (25.0%)	38 (24.4%)	0.970
Right sided sessile serrated lesions at index colonoscopy; n	4 (33.3%)	40 (25.6%)	0.580
Right sided sessile serrated lesions with dysplasia at index colonoscopy; n	4 (33.3%)	29 (18.6%)	0.229
Polyp≥ 20 mm in size at index colonoscopy; n	10 (83.3%)	132 (84.6%)	0.903
Co-existing Medical Illness:			
Hypertension	9 (75.0%)	57 (36.5%)	0.009
Ischemic heart disease	1 (8.3%)	15 (9.6%)	0.886
Diabetes Mellitus	4 (33.3%)	30 (19.2%)	0.224
Cerebrovascular accident	1 (8.3%)	3 (1.9%)	0.17
Active smoking	7 (58.3%)	57 (36.5%)	0.138
Mean body mass index SD); kg/m^2	74.67 (16.71)	81.65 (19.96)	0.592

P-value by log-rank for all except #

Table 3: Factors associated with recurrent advanced adenomas on surveillance colonoscopy.

	Recurrent Advanced Adenomas. (n=12)	No Recurrent Advanced adenomas. (n=156)	p-value.
Mean age (SD); years	66 (7)	63 (11)	0.139#
Sex; M:F	6:6	89:67	0.610
Total number of adenomas and sessile serrated lesions on index colonoscopy; mean (SD)	7.58 (8.10)	4.22 (3.69)	<0.001#
5-10 adenomas at index colonoscopy	5 (41.7%)	54 (34.6%)	0.612
>10 adenomas at index colonoscopy	3 (25.0%)	11 (7.1%)	0.021
Right sided adenomas at index colonoscopy; n	12 (100%)	119 (76.3%)	0.059
Advanced adenomas at index colonoscopy; n	10 (83.3%)	135 (86.5%)	0.770
Sessile serrated lesions at index colonoscopy; n	3 (25.0%)	48 (30.8%)	0.669
Sessile serrated lesions with dysplasia at index colonoscopy; n	3 (25.0%)	38 (24.4%)	0.970
Right sided sessile serrated lesions at index colonoscopy; n	4 (33.3%)	40 (25.6%)	0.580
Right sided sessile serrated lesions with dysplasia at index colonoscopy; n	4 (33.3%)	29 (18.6%)	0.229
Polyp≥ 20 mm in size at index colonoscopy; n	10 (83.3%)	132 (84.6%)	0.903
Co-existing Medical Illness:			
Hypertension	9 (75.0%)	57 (36.5%)	0.009
Ischemic heart disease	1 (8.3%)	15 (9.6%)	0.886
Diabetes Mellitus	4 (33.3%)	30 (19.2%)	0.224
Cerebrovascular accident	1 (8.3%)	3 (1.9%)	0.17
Active smoking	7 (58.3%)	57 (36.5%)	0.138
Mean body mass index SD); kg/m^2	74.67 (16.71)	81.65 (19.96)	0.592

P-value by log-rank for all except #

by Chan etal. [28]. On the other hand, hypertension was the only pre-existing co-morbidity associated with recurrent AAs. There was a trend that those with right sided adenomas at index colonoscopy may have a higher recurrent AA. There were several strengths to this study. A colonoscopy was performed three months after index colonoscopy to ensure that all synchronous polyps were resected. Therefore, the polyps detected at 12, 24 and 36 months after the index colonoscopy were likely to be newly developed polyps, rather than missed or incompletely removed polyps. All patients had a colonoscopy annually for the three consecutive years which facilitated better understanding of the natural history of recurrent adenomas and recurrent AAs, and, to analyse the risk of recurrent adenomas and recurrent AAs accurately. As all specimens were interpreted by one pathologist, this study minimised the risk of inter-observer variation. There were limitations to this study. Repeat colonoscopy at three months after the index colonoscopy does not eliminate the possibility of missed polyps being picked up on later interval colonoscopy. However, we think this possibility is low. Also, genetic information on CRC such as BRAF mutations, K-ras mutations and microsatellite instability were not available or included into the analysis. In conclusion, the total number of adenomas and sessile serrated lesions at index colonoscopy was an independent risk factor for both recurrent adenoma and recurrent AAs. Those with high-risk adenomas at index colonoscopy had a high prevalence of recurrent adenomas and recurrent AAs. Those with > 10 adenomas at index colonoscopy should be considered for a repeat surveillance colonoscopy at 6 months.

7. Ethical Approval

This study was approved by the Institutional Review Board of the Centre for Digestive Diseases (CDDIRB-2017-0001). Written informed consents were obtained from all patients.

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