Rate and Risk Factors of the Advanced Adenomas Among Diminutive Colorectal Polyps

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Abstract Only 49 % of diminutive colorectal polyps are neoplastic, but a tiny percentage contains advanced histology. We aimed to determine the rate of advanced diminutive polyps and to evaluate the influence of age, gender, number, and localization. Patients undergoing a videocolonoscopy in October 2010 and April 2012 were collected prospectively. Subjects with polyps ≤ 5 mm in diameter were recruited into the study. The presence of a villous component of >25 % and a high degree of dysplasia were categorized as polyps with advanced histology. Two hundred eight diminutive polyps were identified in 102 patients. Twenty (9.6 %) diminutive polyps in 13 (12.74 %) patients showed advanced histology. The probability of having an advanced diminutive polyp was higher in patients who have more than one polyp or have polyps localized all along the colon or only to the distal part ($p < 0.001$ and $p = 0.002$). Having more than one polyp increases the likelihood of having advanced diminutive polyp according to a multivariate analysis ($p = 0.003$). Polyps accompanying any dysplastic diminutive polyp, being one of multiple polyps, and distributed all along the colon or localized to only the distal part have an increased probability of being an advanced diminutive polyp ($p < 0.001$, $p = 0.047$, $p < 0.001$, and $p = 0.008$). Multivariate logistic regression demonstrated that only any accompanying dysplastic diminutive polyp increases the probability of a polyp being advanced diminutive ($p = 0.034$).

Diminutive polyps could have advanced histology. Multiple polyps located in the whole colorectum or to the distal part or accompanying any advanced polyps may harbor an advanced histology and should be removed.

Keywords Colonoscopy · Colorectal polyps · Diminutive · Advanced histology

Abbreviations

CRC Colorectal cancer
DP Diminutive polyp
ADP Advanced diminutive polyp

Introduction

Colorectal cancer (CRC) is one of the most prevalent types of cancer, and a frequent cause of mortality. Virtual colonoscopy is commonly used to screen for CRC. CRC develops with an adenoma–carcinoma sequence, allowing prevention by removal of colorectal polyps [1–4]. Colon polyps are classified into two histological categories: epithelial and nonepithelial. Epithelial polyps can either be hyperplastic/serrated, conventional adenomas, or malignant carcinomas.

The majority of polyps removed during colonoscopy are diminutive (≤ 5 mm), and 49 % of diminutive polyps (DP) are neoplastic [5–12]. An advanced polyp is an adenoma that meets one or more of the following criteria: size of ≥ 10 mm, presence of a substantial villous component, and high-grade dysplasia [1, 3]. A small percentage of DPs contain advanced histological evidence of neoplastic transformation (villous element or high-grade dysplasia) [5–12]. The main goal of screening programs is to identify polyps with advanced pathological features and patients at risk of developing advanced diminutive polyps (ADP).

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This study determined the rate of ADP among diminutive polyps and evaluated the influence of age, gender, and location within the colon on the development of ADP. We also ascertained whether pathological examination of some diminutive polyps is neglected.

Methods

Patients

Data were collected prospectively from patients who underwent videocolonoscopy between October 2010 and April 2012. Patients in the study were older than 18 years and had undergone a total colonoscopy in which polyps ≤ 5 mm in diameter were detected. Patients eligible for the study were referred for colon cancer screening or diagnostic colonoscopy to evaluate abdominal pain, a change in bowel habits, unexplained weight loss, unexplained iron deficiency anemia, and a positive fecal occult blood test. Exclusion criteria were as follows: presence of a coagulopathy, an incomplete colonoscopy, poor bowel preparation, a polyp with a diameter >6 mm, history or presence of inflammatory bowel disease, polyposis syndrome, Lynch syndrome, CRC, and a previous surgical resection of the colon or rectum. The age and gender of patients were recorded.

Endoscopic Protocol

Bowel preparation was performed in all patients by means of a clear liquid diet for 1 day using 4 l of polyethylene glycol solution. Procedures were performed under conscious sedation (intravenous midazolam and meperidine), and patients were monitored with a pulse oximeter and intermittent automated blood pressure measurements.

Colonoscopy

Colonoscopy was performed using a high-resolution endoscope with white light. The majority of sigmoidoscopy examinations with positive findings were followed up with a total colonoscopy. The endoscopist was permitted to decide the removal technique of either cold snaring or biopsy forceps. Appropriate polyps were completely removed with a snare, and in total polypectomy, multiple piecemeal biopsies were obtained from other polyps. The numbers, sizes, and locations of polyps were recorded. Lesion size was estimated by comparing the span of open (7 mm) biopsy forceps with the polyp. Colorectal polyps were classified according to size: smaller and/or equal to 5 mm or larger than 5 mm. Positions of DPs were defined according to the distance, either proximal or distal, from the splenic flexure of the transverse colon.

Adenomas located in both colon segments were considered to be present along the entire colon.

Histopathology and Classification of Colorectal Polyps

All specimens were fixed in 10 % formalin and stained with hematoxylin and eosin for histological examination. All pathological analyses were performed at our center by a pathologist experienced in evaluation of the gastrointestinal tract. Polyps were classified as epithelial or nonepithelial. Epithelial polyps were categorized as hyperplastic, a conventional adenoma, or a mixed sessile serrated polyp according to World Health Organization classifications [13]. Conventional adenomas were classified as tubular (<25 % villous elements), tubulovillous (25–75 %), or villous (>75 %) according to the proportion of villous elements. Serrated polyps were classified as either hyperplastic or a serrated adenoma (including sessile serrated adenoma, traditional serrated adenoma, and mixed serrated polyp) according to the terminology published by Snover et al. [14]. Dysplasia was described according to the revised Vienna classification of gastrointestinal epithelial neoplasia [15, 16]. Adenoma dysplasia was classified as either low or high grade [13]. Low-grade dysplasia has architecturally noncomplex crypts containing nuclei, which are pseudostratified or partially stratified, to the point where the nuclei reach only the lower half of the cell. Mitotic activity may be present, but atypical mitoses, significant loss of polarity, and pleomorphism are minimal. The crypts are arranged in parallel without significant back-to-back configuration, cribriforming, or complex budding. High-grade dysplasia is characterized by marked pseudostratification or stratification of the neoplastic nuclei that extends to the luminal half of the cell. It usually contains significant pleomorphism, increased mitotic activity, atypical mitoses, and marked loss of polarity. Architectural changes, such as back-to-back gland configuration and cribriforming, may also be noted [17].

The study protocol was approved by the Institutional Review Board. The procedures were performed by three fully trained and experienced gastroenterology surgeons.

Statistical Analyses

We analyzed the variables by patient and individual DPs. For qualitative variables, patient characteristics (gender, age, total polyp number, and location of polyps) and polyp characteristics (gender, age, accompanying dysplastic polyp, accompanying nondysplastic polyp, and location of polyp and accompanying polyps) were compared using a chi-squared test or Fisher's exact test. The Mann–Whitney *U* test was used for quantitative variables. An independent-sample *t* test was used for evaluation of differences in continuous variables between groups. All variables were included, and a *p*-value of <0.05 was taken to indicate statistical significance. A multivariate

logistic regression was performed to assess independent risk factors. A p -value of <0.05 was considered to indicate significance with a 95 % confidence interval. All analyses were performed using the SPSS statistical software, version 13.0.

Results

Of the 386 colonoscopy procedures performed between October 2010 and April 2012, 208 polyps of ≤ 5 mm were identified in 102 patients. Of the 102 patients in the study, 65 were male and 37 were female. Mean age was 55.55 (range 27–86) years. The distributions of patients and polyps are reported in Tables 1 and 2. Nearly half (49 %) of the 208 DP had neoplastic qualities. The distribution of epithelial and nonepithelial neoplastic polyps is shown in Table 3. Twenty (20/208, 9.6 %) DPs in 13 (13/102, 12.74 %) patients showed advanced histologic evidence of neoplastic transformation. In patients with DP, there was no difference in risk for development of malignancy according to gender or age ($p=0.126$ and 0.103 , respectively). The probability of having an ADP was higher in patients with more than one polyp, with polyps distributed throughout the colon, or with polyps localized to the distal part of the colon ($p<0.001$ and $p=0.002$, respectively). Having more than one polyp increased the probability of having an ADP according to a multivariate analysis ($p=0.003$; odds ratio: 19.524; Table 4).

The probability that a polyp is an ADP is increased if it is accompanied by a dysplastic diminutive polyp, the polyp is one of multiple polyps, or the accompanying polyps are located throughout the colon or the distal portion of the colon ($p<0.001$, $p=0.047$, $p<0.001$, and $p=0.008$, respectively).

Age, gender, and location of the polyp do not increase the probability that a polyp is an ADP ($p=0.099$, 0.077 , and 0.845 , respectively). Multivariate logistic regression analysis demonstrated that the presence of an accompanying dysplastic diminutive polyp increased the probability of a polyp being an ADP ($p=0.034$; odds ratio 5.489; Table 5).

Discussion

Early diagnosis of CRC is important. Many reports focus on polyps since they are the preliminary lesions of CRC. Polyps less than 5 mm in diameter are poorly described in the literature, and the optimal approach for DP management remains controversial. There is convincing evidence that advanced histology, defined as the presence of a villous component and/or high-grade dysplasia, increases the risk of CRC [2, 3, 18, 19]. It was previously reported that relatively high numbers of carcinomas originated from diminutive lesions. Some authors believed that benefits of diminutive polypectomy were minimal, and the majority of these polyps never progressed to cancer. This made DP removal of low benefit and exposed patients to increased risk and costs due to the procedure [6, 11, 20]. A multicenter Korean study found that the cancer rate was 0.03 % for DP [21]. Rex et al. reported a similar rate (0.05 %) for such lesions [12]. The rates of DP advanced adenomas were 1.2 and 0.87 % in studies by Lieberman et al. and Rex et al., respectively [5, 12]. Chaput et al. reported advanced histology in 4.7 % of 342 DPs [22]. Butterfly et al. reported advanced histology in 1.7 % of DPs (<4 mm) and carcinoma in 0 % of DPs [6]. In those reports, approximately 0.87–4.7 % of all DPs were advanced adenoma

Table 1 Comparisons of patients having advanced and nonadvanced diminutive polyps

			Advanced diminutive polyps	Nonadvanced diminutive polyps	p
Gender	Male, n (%)	65 (63.64)	11 (10.7)	54 (52.94)	0.126 (Fisher's exact test)
	Female, n (%)	37 (36.21)	2 (1.9)	35 (34.31)	
Age, years (mean $\pm$ SD)	55.55 $\pm$ 13.50		62.00 $\pm$ 11.90	54.61 $\pm$ 13.52	0.065 (Student's t test)
	<40 years		0	15	0.103 (Pearson chi-squared)
	41–60 years		5	43	
	60<years		8	31	
Number of total polyps	Median 2, mod 1			Median 4, mod 4	Median 2, mod 1
	1–3		3	81	<0.001 (Pearson chi-squared)
	4–6		8	8	
	≥ 7		2	0	
Localization of all polyps, n (%)	Proximal	18 (17.4)	0 (0)	18 (17.4)	0.002 (Pearson chi-squared test)
	Distal	55 (53.9)	4 (3.9)	51 (50)	
	Whole colon	29 (28.4)	9 (8.8)	20 (19.6)	
Total patients, n (%)	102 (100)		13 (12.74)	89 (87.25)	

Table 2 Distribution of advanced and nonadvanced diminutive polyps according to patient gender, age, accompanying dysplastic polyp, any other accompanying polyp and localization of all of them together, and polyp localization

			Advanced diminutive polyps	Nonadvanced diminutive polyps	<i>p</i>
Gender	Male, <i>n</i> (%)	143 (68.75)	17 (8.17)	126 (60.57)	0.099 (Pearson chi-squared test)
	Female, <i>n</i> (%)	65 (31.25)	3 (1.44)	62 (29.80)	
Age, years (mean±SD)	57.93±13.37		62.80±12.677	57.41±13.37	0.087 (Student <i>t</i> test)
	≤40 years		0	26	0.077 (Pearson chi-squared test)
	41–60 years		7	82	
	≥60 years		13	80	
Accompanying dysplastic polyp, <i>n</i> (%)	Present	56 (26.92)	15 (7.2)	41 (19.71)	<0.001 (Fisher's exact test)
	Not present	152 (73.07)	5 (2.4)	147 (7.67)	
Number of polyps, <i>n</i> (%)	Being a single polyp	44 (21.15 %)	1 (0.4 %)	43 (20.67 %)	0.047 (Fisher's exact test)
	Being one of multiple polyps	164 (78.84 %)	19 (9.13 %)	145 (69.71 %)	
	Being one of polyps in 1–3	124	4	120	<0.001 (Pearson chi-square test)
	4–6	66	10	56	
	≥7	18	6	12	
Localization of each polyp, <i>n</i> (%)	Proximal	79 (37.98)	8 (38.4)	71 (34.13)	0.845 (Pearson chi-squared test)
	Distal	129 (62.01)	12 (5.76)	117 (56.25)	
Localization of accompanying polyps, <i>n</i> (%)	Proximal	25 (12.01)	0 (0)	25 (12.01)	0.008 (Pearson chi-squared test)
	Distal	93 (44.71)	5 (2.4)	88 (42.30)	
	Whole colon	90 (43.26)	15 (7.21)	75 (36.05)	
Total, <i>n</i> (%)	208		20 (9.61)	188 (90.38)	

and represented benign lesions, but they have potential to transform to carcinoma [5, 12, 23]. In our study, nearly half of DPs (49 %) were neoplastic, and 20 (20/208, 9.6 %) DPs in

13 (13/102, 12.74 %) patients showed advanced histology. This percentage was higher than that of previous reports, making the reevaluation of the current approach to DP

Table 3 Histological features of the polyps (*n* (%))

Epithelial polyps, 166 (79.8)	
Hyperplastic polyp	54 (26.0)
	Microvesicular type 10 (4.8)
	Goblet cell rich 19 (9.1)
	Mucin depleted type 4 (1.9)
	Nonsubclassifying 20 (9.6)
Classical adenoma	102 (49.0)
	Tubular adenoma 96 (46.2)
	Tubulovillous adenoma 7 (3.4)
	Hyperplastic/tubular adenoma mixed 2 (1.0)
Mixed	2 (1.0)
SSP	8 (3.8)
Nonepithelial polyps, 42 (20.2)	
Lipoma	1 (0.5)
Lymphoid polyp	7 (3.4)
Lymphoid follicle	4 (1.9)
Inflammatory myoglandular polyp	1 (0.5)
Inflammatory polyp	4 (1.9)
Pseudoinflammatory polyp	1 (0.5)
Colitis	1 (0.5)

Table 4 Multivariate logistic regression of factors affect the distribution of patients carrying advanced and nonadvanced diminutive polyps

		<i>B</i>	SE	Wald	<i>df</i>	Sig.	Exp(<i>B</i>)
Step 1 ^a	Gender	−0.500	1.030	0.236	1	0.627	0.607
	Age (years)	0.980	0.678	2.090	1	0.148	2.664
	Number of total polyp	2.972	0.859	11.956	1	0.001	19.524
	Localization of all polyps	1.139	0.673	2.859	1	0.091	3.122
	Constant	−10.479	3.061	11.716	1	0.001	0.000

^a Variable(s) entered on step 1: gender, age (years), number of total polyp, and localization of all polyps

management crucial. Such lesions should not be ignored as they may continue to enlarge over time. The polypectomy selection criteria for DPs are critical. The risk factors of developing or having an ADP should be well documented, and these high-risk polyps should be removed.

Although risk factors for adenomatous colonic polyps have been researched, data are lacking among polyps ≤5 mm. Old age was correlated with a higher rate of advanced histology among polyps <10 mm, whereas some studies did not confirm this correlation [5, 23–26]. In our study, no correlation was found between having an ADP and gender or age ($p=0.126$ and 0.103 , respectively). The probability of having an ADP was higher in patients with multiple polyps located throughout or in the distal part of the colon ($p<0.001$ and $p=0.002$, respectively). Having any accompanying dysplastic diminutive polyp, being one of multiple polyps, being located throughout the colon or localized to the distal part of the colon increased the probability of a polyp being an ADP ($p<0.001$, $p=0.047$, and $p<0.001$ or $p=0.008$, respectively). Multivariate logistic regression analysis indicated that the presence of more than one polyp or any additional dysplastic diminutive polyps increased the probability of a polyp being an ADP ($p=0.003$ and 0.034 , respectively).

Removing all DPs may expose healthy individuals to unnecessary risks and create unnecessary costs. In a large cohort study, the rate of serious complications was 0.7 %, and the

perforation rate in individuals undergoing polypectomy was 0.1 % [27]. A computed tomography (CT) colonography-based screening strategy has been shown to be effective in clinical practice and caused a marked decrease in the number of polypectomies and complications. Some DPs may be ignored during screening by CT colonography [28]. Endoscopic diagnosis of polyp histology during colonoscopy and forgoing of a pathologic examination can lower costs of the procedure. Santos et al. reported that magnifying virtual and indigo carmine chromo-endoscopies had high accuracy for the histopathological diagnosis of colorectal lesions less than 5 mm in diameter [29]. We did not observe any complications due to the polypectomy procedure during this study. Procedure-related risks and costs should be considered carefully preoperatively as half of the DPs removed were not neoplastic. According to our study, patients with a single proximal DP were at low risk of having an ADP. We believe that a DP is probably not an ADP if it is a single polyp, is located in the proximal colon, and has accompanying polyps that are not dysplastic DPs. Low-risk patients may be monitored by virtual colonoscopy or CT colonography.

In conclusion, the incidence of ADP was higher than expected. Multiple DPs located along the entire colon or the distal colon with accompanying dysplastic polyps would increase the likelihood of ADP. Polyps fitting these criteria should be removed.

Table 5 Multivariate logistic regression of factors affect the advanced and nonadvanced diminutive polyps

		<i>B</i>	SE	Wald	<i>df</i>	Sig.	Exp(<i>B</i>)
Step 1 ^a	Gender	−0.293	0.743	0.155	1	0.694	0.746
	Age (years)	0.132	0.534	0.061	1	0.804	1.141
	Accompanying dysplastic polyp	1.703	0.803	4.491	1	0.034	5.489
	Being single or one of multiple polyps	0.141	1.182	0.014	1	0.905	1.152
	Being one of 1–3, 4–7, or more than 7 polyps	0.485	0.475	1.043	1	0.307	1.625
	Localization of all polyps	0.664	0.566	1.379	1	0.240	1.943
	Localization of each polyp	0.343	0.681	0.254	1	0.614	1.410
	Constant	−5.928	2.446	5.873	1	0.015	0.003

^a Variable(s) entered on step 1: gender, accompanying advanced polyp, number of total polyp, localization of all polyps, localization of polyp, and age (years)

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