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ORIGINAL ARTICLE

불완전하게 절제된 진행성 대장 선종의 국소 재발과 위험 인자: 단일기관 후향 연구

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Local Recurrence and Its Risk Factor after Incomplete Resection of Colorectal Advanced Adenomas: A Single Center, Retrospective Study

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Background/Aims: Colonoscopy can detect precancerous lesions, which can subsequently be removed and reduce incidences of and mortality from colorectal cancer (CRC). However, recently published data have highlighted a significant rate of CRC in patients who previously underwent colonoscopy. Among many reasons, incomplete resection has been considered as a significant contributor. However, to date, there have only been a few studies regarding incompletely resected polyps, especially advanced colorectal adenoma (ACA). Hence, we aimed to evaluate the prognosis of incompletely resected ACA.
Methods: We retrospectively reviewed the medical records of patients with ACA who had underwent endoscopic treatment with incomplete resection. The primary outcomes were (1) the incomplete resection rate of ACA, as determined by a histopathologic examination and (2) the recurrence rate of incompletely resected ACA. We also investigated the probable contributing factors that may have led to a relapse of incompletely resected ACA.
Results: A total of 7,105 patients had their colorectal polyps resected by endoscopic treatment, and 2,233 of these were considered as ACA. Of these, 354 polyps (15.8%) were resected incompletely, and only 163 patients were followed-up. Of those followed-up, 31 patients (19.0%) experienced local recurrence. The risk factors for recurrence after incomplete resection were evaluated; age, morphology of adenoma, and use of rescue therapy, such as argon plasma coagulation, were found to be associated with adenoma recurrence.
Conclusions: Incompletely resected ACA in older patients or in patients with sessile-type adenomas should be monitored strictly, and if incomplete resection is suspected, rescue therapy must be considered. **(Korean J Gastroenterol 2017;70:33-38)**

Key Words: Colonoscopy; Adenoma; Colorectal neoplasms; Colonic polyps; Local neoplasm recurrence

INTRODUCTION

Colorectal cancer (CRC) is an important health issue worldwide, due to its high incidence and mortality rate.[1,2] Adenomatous polyps are generally accepted to be the precursors of most CRC cases. Progression from adenoma to CRC is a multistep process, accompanied by alterations in the expression of several suppressor genes that result in abnormalities in cell

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regulation. Progression takes place over a period of 10 to 15 years.[3] Colonoscopy is a useful tool for the detection and removal of precancerous lesions (adenomatous polyps), and its use can reduce CRC incidence and mortality. However, recent data have highlighted a significant rate of CRC despite previous colonoscopy. The so-called interval cancer, defined as a cancer diagnosed between screening examination and post-screening surveillance,[4,5] has raised concerns regarding the effectiveness of colonoscopy and colonoscopic polypectomy.

There are three plausible reasons for interval CRCs. First, interval cancers may arise from lesions that went unnoticed during a colonoscopy. About 70-80% of interval cancers likely result from lesions that went unnoticed.[6] Second, interval cancers can result from rapidly progressing polyps that were not present at the time of colonoscopy. This is based on the observation that some cancers have genetic features associated with extremely rapid progression.[7] Third, interval cancers can result from incompletely resected lesions. Incomplete resection of lesions may account for 10-27% of interval cancers.[4,8,9] Although incomplete resection has been known as a significant contributor to interval cancer, there has only been a few studies evaluating incomplete resection of polyps, especially regarding advanced colorectal adenoma (e.g. >1 cm in size or containing high-grade dysplasia or a villous component). Hence, we retrospectively studied the recurrence rate of advanced colorectal adenoma that was incompletely resected and investigated the possible contributing factors that may lead to relapse.

SUBJECTS AND METHODS

1. Patients

We retrospectively surveyed patients who had advanced colorectal adenoma and resulted in incomplete resection by either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), between August 2003 and March 2015. Patients who were not followed-up after endoscopic treatment for advanced colorectal adenoma were excluded.

2. Methods

We reviewed patient records by using EMR and a digitalized picture archiving communication system. The institutional review board at our institution approved this study, complying with the Helsinki declaration.

The primary outcomes were (1) the incomplete resection rate of advanced colorectal adenoma, as determined by histopathologic examination, and (2) the recurrence rate of incompletely resected advanced colorectal adenoma. We considered incomplete resection of advanced colorectal adenoma (ACA) if resection margins of obtained specimen by EMR or ESD were involved by adenoma on histopathologic examination. Local recurrence was defined using the criteria of Higaki et al.[10] In brief, local recurrence was defined as new adenomatous lesions reappearing at the site previously treated endoscopically, or lesions with convergent folds or those with nonconvergent folds, but with a clearly identifiable resection site nearby. Additionally, in our study, if a previous resection ulcer scar could not be found on a follow-up colonoscopy, adenomatous lesions in the same colonic segment found 5 cm away from the previous endoscopic treatment site were regarded as local recurrence. The location of lesions was measured by the distance from the anal verge. Furthermore, we surveyed all probable factors that could contribute to a relapse of incompletely resected advanced colorectal adenoma. These included patient's age, sex, size, morphology, histology, anatomic location of polyp, resection performed en bloc vs. piecemeal, resection method (EMR or ESD), performed with or without rescue therapy, such as argon plasma coagulation (APC) and quality of bowel preparation. The quality of bowel preparation was classified as either adequate (good or fair) or inadequate (poor), based on the endoscopist's estimation.[5]

3. Statistical analysis

Data are expressed as the mean±standard deviation. Variables were analyzed using the independent t-test or chi-square test. Analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). p-values of ≤ 0.05 were considered statistically significant.

RESULTS

1. Baseline characteristics

A total of 7,105 patient with colorectal polyps were resected by EMR or ESD between August 2003 and March 2015, and 2,233 patients (31.4%) of these were considered advanced colorectal adenoma. Of these, 354 polyps (15.8%)

were resected incompletely, and only 163 patients were followed-up (Fig. 1).

We finally analyzed these 163 patients (mean age, 66.5±10 years; 65.0% male), who with incompletely resected advanced colorectal adenoma and received at least one colonoscopy after endoscopic treatment. Most colonoscopies were performed for screening purposes (63.1%). Table 1 shows the baseline characteristics of patients with incompletely resected advanced colorectal adenoma.

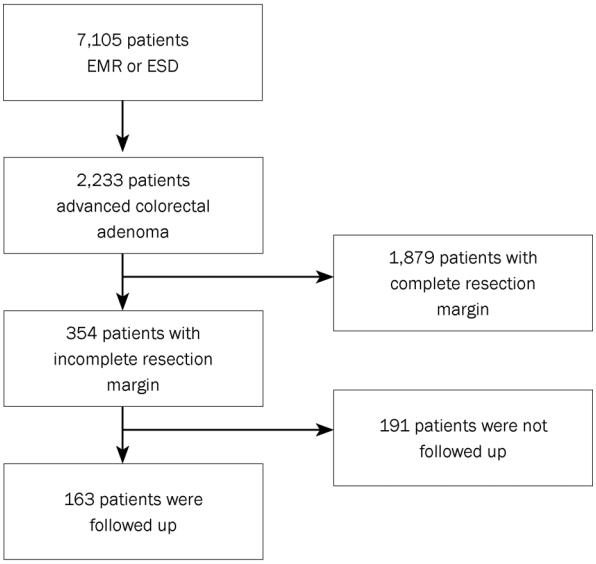

Fig. 1. Flow diagram for the study. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Table 1. Characteristics of Patients with Incompletely Resected Advanced Colorectal Adenoma

Parameters	Patients (n=163)
Age[a]	66.5±10.0
Sex (Male : Female)	106 : 57
Current or ex-smoker, n (%)	43 (26.3)
Alcohol, n (%)	44 (26.9)
Indication, n (%)	
Screening	103 (63.1)
Polyp or cancer surveillance	13 (7.9)
Bleeding/Anemia	13 (7.9)
Others	34 (20.8)
Underlying disease, n (%)	
Hypertension	56 (34.3)
Type 2 DM	22 (13.4)
Vascular disease	14 (8.5)
History of malignancy	11 (6.7)
Others	27 (16.5)

DM, diabetes mellitus.
[a]Data are expressed as mean±standard deviation.

2. Characteristics of incompletely resected advanced colorectal adenoma

A total of 163 cases of incompletely resected advanced colorectal adenoma were followed-up. The time between endoscopic resection and first colonoscopic follow-up in this study was ranged from 3 to 72 months, which was highly variable. The mean polyp size was 12.3 mm (±6.7 mm standard deviation); in 12 cases (7.3%), the polyp was more than 20 mm in size. Most polyps (112, 68.7%) were between 10 mm and 20 mm in size. Ninety polyps (55.2%) were located in the right colon, and 114 cases (69.9%) were morphologically considered the sessile type.

Of the total number of advanced colorectal adenomas, 90 cases (55.2%) were classified as tubulovillous or villous adenomas. High-grade dysplasia was found in 13 cases (7.9%). Thirty- one patients (19.0%), experienced recurrence after incomplete resection of advanced colorectal adenoma. The period from endoscopic treatment of advanced colorectal adenoma to recurrence was 3-36 months. Table 2 shows the characteristics of incompletely resected advanced colorectal adenomas.

3. Risk factors for recurrence after incomplete resection of advanced colorectal adenoma

Risk factors for recurrence after incomplete resection were investigated using univariate analysis with the chi-square test and Fisher's exact test. The age, morphology of adenoma, and use of rescue therapy, such as APC, were

Table 2. Characteristics of Incompletely Resected Advanced Colorectal Adenoma

Parameters	Patients (n=163)
Advanced colorectal adenoma type, n (%)	
Villous component	90 (55.2)
Severe dysplasia (HGD)	12 (7.3)
Greater than 10 mm in diameter	61 (37.4)
Morphology, sessile polyps, n (%)	114 (69.9)
Size, mm, n (%)	
5-9 mm	39 (23.9)
10-20 mm	112 (68.7)
>20 mm	12 (7.3)
Mean size[a]	12.3±6.7
Location, n (%)	
Right colon	90 (55.2)
Left colon[b]	73 (44.7)
Recurrence, n (%)	31 (19.0)

HGD, high-grade dysplasia.
[a]Data are expressed as mean±standard deviation; [b]Left colon: distal to splenic flexure.

considered to be associated with recurrence of adenoma. The sex of patients, type of advanced colorectal adenoma (pathology or size criteria), location, size of polyp, en bloc vs. piecemeal resection, resection method (EMR or ESD), and quality of bowel preparation were not significantly associated with recurrence (Table 3). Moreover, logistic multivariate regression analysis showed that age, morphology of adenoma, and rescue therapy were significant predictors of recurrence after incomplete resection of advanced colorectal adenoma (Table 4).

Table 3. Univariate Analysis for the Risk Factors of Recurrence after Incomplete Resection

Variables	Recurrence rate of incompletely resected ACA[a]	p-value
Sex		0.441
Male (n=106)	20.8 (22/106)	
Female (n=57)	15.8 (9/57)	
Age		0.022
<70 years (n=98)	13.3 (13/98)	
≥70 years (n=65)	27.7 (18/65)	
ACA type		0.137
Pathologic criteria (n=102)	22.5 (23/102)	
Size criteria (n=61)	13.1 (8/61)	
Adenoma morphology		0.021
Sessile (n=114)	23.7 (27/114)	
Others (n=49)	8.2 (4/49)	
Adenoma size		0.572
<20 mm (n=140)	20.0 (28/140)	
≥20 mm (n=23)	13.0 (3/23)	
Location of adenoma		0.450
Right side colon (n=90)	21.1 (19/90)	
Left side colon (n=73)	16.4 (12/73)	
Enbloc vs. Piecemeal		0.966
Enbloc (n=131)	19.1 (25/131)	
Piecemeal (n=32)	18.8 (6/32)	
Resection method		0.584
EMR (n=158)	19.6 (31/158)	
ESD (n=5)	0 (0/5)	
Rescue therapy		0.049
Yes (n=24)	4.2 (1/24)	
No (n=139)	21.6 (30/139)	
Bowel preperation		0.345
Good or Fair (n=161)	18.6 (30/161)	
Poor (n=2)	50 (1/2)	

ACA, advanced colorectal adenoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.
[a]Data are expressed as percentiles (numbers).

DISCUSSION

Generally, advanced colorectal adenoma is present in 9.6% of all asymptomatic patients.[11] However, in our study, the incidence of advanced colorectal adenoma was 31.4%, which is very high compared with previous reports. This difference may be attributable to the differences in the study population; our population consisted of patients who had undergone EMR or ESD, and some patients were referred from the primary health care system for endoscopic treatment due to unusually large colonic polyps. We evaluated patients treated with EMR or ESD, and, generally, large polyps are treated using these methods; therefore, patients with larger polyps were more likely to be included in our study.

Our study shows that recurrence after endoscopic treatment for advanced colorectal adenoma occurs in approximately 19% of cases. It has previously been reported that that the recurrence rate of ACA after endoscopic resection is estimated to be 17.4-19.8%.[12-14] However, these studies only included cases of completely resected ACA[12,13] or ACA regardless of complete resection.[14] Besides, these studies were different from ours in that they included both local recurrence and metachronus recurrence of ACA when evaluating the recurrence of ACA after endoscopic resection. There may be two reasons that we did not include metachronus recurrence in our study. First, we investigated only the incompletely resected ACA; second, the definition of local recurrence has been broader than that used in other studies. In our study, local recurrence included not only the Higaki criteria, but also adenomatous lesions in the same colonic segment found 5 cm away from the previous endoscopic treatment site, if a previous resection site could not be found at the time of follow-up colonoscopy. Therefore, our definition may include lesions that had previously gone unnoticed in the same segment as the

Table 4. Multivariate Analysis for the Risk Factors of Incompletely Resected Advanced Colorectal Adenoma

Variables	β	SE	p-value	OR	95% CI
Age	0.936	0.424	0.027	2.551	1.112-5.851
Morphology of adenoma	1.366	0.577	0.018	3.918	1.264-12.146
Rescue therapy	-2.190	1.055	0.038	0.112	0.014-0.885

β, coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

original incompletely resected polyp, as well as de novo adenomas. Nonetheless, because polyps with a size of less than 10 mm is not easy to find after endoscopic treatment, we had to depend on the distance of the lesion from the anal verge to determine whether or not there was polyp recurrence.

One report found that cancer occurred in 5% of patients with residual lesions after primary endoscopic treatment of an adenoma.[15] The subjects in our study were patients with advanced colorectal adenomas; hence, the incidence of invasive cancer in this population is expected to be higher than in populations with other types of polyps.[16-18] Nonetheless, no patient in our study developed invasive cancer following incomplete resection of advanced colorectal adenoma.

Our study showed that adjunctive ablation of resection sites of advanced colorectal adenomas may be useful in reducing local recurrence. In patients of advanced age or with sessile polyps, the local recurrence rate was higher than in other patients. This result suggests that incompletely resected advanced colorectal adenomas in older patients or in patients with sessile-type adenomas have to be strictly monitored. However, it is worth noting that whether strict monitoring for patients over the age of 70 is valuable or impactful, given that their life expectancies are relatively short.

This study has several limitations to consider. First, the number of patients was small, which introduces the possibility of a type II statistical error. Second, the retrospective nature of the study may have caused selection bias. Accordingly, further large-scale prospective studies are required to confirm our findings.

There have been a few previous studies investigating the recurrence and its risk factors after endoscopic resection of ACA.[12-14] However, our study offers a unique point: We analyzed incompletely resected ACA, unlike the previous studies. Moreover, in our study, local recurrence included not only the Higaki criteria but also adenomatous lesions in the same colonic segment found within 5 cm away from the previous endoscopic treatment site, if the previous resection site could not be found at the time of follow-up colonoscopy. We suggested this criteria because polyps with a size of less than 10 mm are not easily detected after endoscopic treatment and a loop formed during manipulation of the colonoscopy is considered to cause errors within plus or minus 5 cm. In addition, endoscopists in our hospital described how far the polyps were from the anal verge when defining the location of the polyps. We believe that this criteria can be used as a new index in evaluating the recurrence of polyps.

In our study, we found that age of patients was a statistically significant cause of recurrence. The mechanism for this has not been fully elucidated. However, as there have been reports showing that age is a risk factor for the prevalence of colorectal adenoma[19,20] and that the recurrence increased among older patients on the follow-up colonoscopy after endoscopic removal of adenoma,[21,22] we can presume a similar mechanism for a possible increase in local recurrence. For this, we think that the prospective study using big data should be supplemented in the near future.

In conclusion, this study shows that age of more than 70 years and sessile polyps are significant predictors for recurrence of incompletely resected advanced colorectal adenoma. Moreover, we showed that rescue therapy, such as APC, can reduce the recurrence rate. We recommend that in patients of older age with incompletely resected advanced colorectal adenomas or in patients with sessile-type adenomas, strict monitoring is necessary, and if incomplete resection of adenoma is suspected in these patients, rescue therapy should be considered. However, for elderly patients over the age of 70, life expectancy should be considered when planning for follow-up colonoscopy.

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