

Retrospective Study

Endoscopic mucosal resection of colorectal adenomas > 20 mm: Risk factors for recurrence

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Abstract

AIM: To evaluate risk factors for local recurrence after endoscopic mucosal resection of colorectal adenomas > 20 mm.

METHODS: Retrospective data analysis of 216 endoscopic mucosal resections for colorectal adenomas > 20 mm in 179 patients (40.3% female; median age 68 years; range 35-91 years). All patients had at least 1 follow-up endoscopy with a minimum control interval of 2 mo (mean follow-up 6 mo/2.0-43.4 mo). Possible factors associated with local recurrence were analyzed by univariate and multivariate analysis.

RESULTS: Median size of the lesions was 30 mm (20-70 mm), 69.0% were localized in the right-sided (cecum, ascending and transverse) colon. Most of the lesions (85.6%) showed a non-pedunculated morphology and the majority of resections was in piecemeal technique (78.7%). Histology showed carcinoma or high-grade intraepithelial neoplasia in 51/216 (23.6%) lesions including 4 low risk carcinomas (pT1a, L0, V0, R0 - G1/G2). Histologically proven recurrence was observed in 33/216 patients (15.3%). Patient age > 65 years, polyp size > 30 mm, non-

pedunculated morphology, localization in the right-sided colon, piecemeal resection and tubular-villous histology were found as associated factors in univariate analysis. On multivariate analysis, only localization in the right-sided colon (HR = 6.842/95%CI: 1.540-30.394; $P = 0.011$), tubular-villous histology (HR = 3.713/95%CI: 1.617-8.528; $P = 0.002$) and polyp size > 30 mm (HR = 2.563/95%CI: 1.179-5.570; $P = 0.017$) were significantly associated risk factors for adenoma recurrence.

CONCLUSION: Meticulous endoscopic follow-up is warranted after endoscopic mucosal resection of adenomas localized in the right-sided colon larger than > 30 mm, with tubular-villous histology.

Key words: Colorectal adenoma; Endoscopic mucosal resection; Piecemeal resection; Local recurrence rate; Tubular-villous adenoma

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Core tip: Endoscopic mucosal resection of larger adenomas is burdened with relatively high rates of local recurrence. In this retrospective analysis, size > 30 mm, non-pedunculated morphology, right-sided localization, piecemeal resection and histology were all associated with local recurrence. In addition, right-sided localization, tubular-villous histology and size > 30 mm were independently associated with local recurrence. These findings emphasize the necessity of meticulous endoscopic follow-up, they might also argue in favor of *en bloc* resection of larger colorectal lesions, in particular in the right-sided colon.

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INTRODUCTION

Screening colonoscopy and removal of detected adenomas is now recognized as an effective measure to prevent colorectal cancer^[1-3]. However, efficacy of screening endoscopy is hampered not only by a low adenoma detection rate but also by incomplete removal of advanced adenomas^[4].

Endoscopic mucosal resection (EMR) is the current standard for the treatment of colorectal adenomas in Western countries^[5-7]. While widely used, EMR is burdened by incomplete adenoma resections even for smaller lesions up to 20 mm^[8]. The technique is also used for lesions > 20 mm where it is performed in piecemeal technique, *i.e.*, the adenoma is removed in fragments. As a consequence of fragmentation it is impossible to histologically confirm the completeness of

resection. Endoscopic control is therefore recommended after 2-6 mo by current guidelines^[9-12]. Reported recurrence rates during endoscopic follow-up vary from 5%-27% in retrospective studies^[13-23]. In a recently published well-conducted prospective study the recurrence rate was 32%^[24]. Since the majority of colorectal lesions harbors only low-grade intraepithelial neoplasia, local recurrence is usually not viewed as a treatment failure^[22,25]. Nevertheless, all patients need close endoscopic observation and those with recurrences often need several EMR interventions during follow-up^[26]. Moreover, there is a concern about late local recurrences and even subsequent cancer after a negative first control endoscopy^[13,22,24,27]. Many of these problems could be overcome by the use of endoscopic submucosal dissection (ESD) - which allows *en bloc* resection of larger adenomas, but colorectal ESD is still largely considered an experimental therapy in the Western world^[11].

Several risk factors for local recurrence after EMR (*e.g.*, lesion size, localization, morphology, resection in piecemeal technique, histological features) have been reported in retrospective studies^[18,22,28-30]. The purpose of this study was to analyze risk factors in a cohort of larger colorectal adenomas with preferentially right-sided localization. The results of this study should have an impact on the choice of the resection strategy (*e.g.*, EMR vs ESD vs laparoscopic surgery) as well as on the intensity of endoscopic follow-up.

MATERIALS AND METHODS

Patients and data collection

A single experienced interventional endoscopist (FLD) performed 688 EMRs over a five-year period (03/2008-03/2013). Of these, 216 EMRs in 179 patients, 87 female (40.3%) and 129 male (59.7%), with a median age of 68 years (35-91) met the inclusion criteria of polyp size > 20 mm, at least one endoscopic control 2-6 mo after EMR and sufficient data of follow-up examinations. The median follow-up time was 6 mo (range: 2-43.4 mo).

EMR procedure

EMRs were carried out under conscious sedation with propofol (B Braun Melsungen, Melsungen, German) and occasionally midazolam (Roche Pharma AG, Basel, Switzerland) using standard endoscopes (GIF 1-TQ160, CF-H180 AL, PCF 180 AL; Olympus Europe, Hamburg Germany). After detailed endoscopic inspection, lesions were classified according to the Paris classification^[31] and the size of the lesion was estimated by comparison to an opened snare. Submucosal injection of normal saline with 0.01% indigo carmine (Novaplus, Lake Forrest, IL, United States) was performed with a small bore injector needle (25G, Olympus Europe, Hamburg, Germany). EMR was then carried out with different snare types according to the size and shape of the lesions (Snaremaster®, Olympus Europe, Hamburg,

Table 1 Characteristics of the resected lesions *n* (%)

| No. of polyps | <i>n</i> = 216 |
|--|-------------------|
| Size (median/range) | 30 mm (20.0-70.0) |
| Localization | |
| Right-sided colon (cecum, ascending, transverse) | 149 (69.0) |
| Left-sided colon (descending, sigmoid) or rectum | 67 (31.0) |
| Morphology of polyps (Paris classification ^[31]) | |
| Pedunculated (0-Ip) | 31 (14.4) |
| Non-pedunculated (0-Is; 0-IIa/b/c) | 185 (85.6) |
| Resection in piecemeal technique | 170 (78.7) |
| Final histology | |
| Low-risk invasive adeno-carcinoma | 4 (1.9) |
| Tubular-villous adenoma | 102 (47.2) |
| Tubular adenoma | 65 (30.1) |
| Serrated adenoma | 45 (20.8) |

Germany; Acusnare®, Cook Medical Germany, Mönchengladbach, Germany) using standard power settings on an Erbe VAI0 200S electrosurgical unit (Erbe Elektromedizin, Tübingen, Germany). Careful APC coagulation of resection bed or margins was performed if deemed necessary. Resected specimens were retrieved and fixed in phosphate buffered formaldehyde solution for histopathology. To prevent delayed bleeding hemoclips (EZ clip; Olympus Europe, Hamburg, Germany) were used in most procedures.

Endoscopic follow-up after EMR

According to the German S3 guideline on colorectal carcinoma^[11] control endoscopies were done 2-6 mo after EMR. If longer follow-up endoscopies without signs of recurrence were available the longest follow-up interval was counted.

Statistical analysis

Univariate (Kaplan Meier) analysis was carried out to describe the distributions of baseline variables. Cox regression analysis was then used to evaluate various combinations and interactions of prognostic variables in a multivariate manner. Data analysis was done using the SPSS package (student's edition; SPSS Inc. Somers, NY, United States). A *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 216 adenomas with a median size of 30 mm (range 20-70 mm) were resected. Most adenomas were localized in the right-sided colon (69%), had a flat or sessile morphology (85.6%) and were resected in piecemeal technique (78.7%). Histological analysis revealed tubular adenoma (30.1%), tubular-villous adenoma (47.2%), serrated adenoma (20.8%) and invasive cancer in four lesions (1.9%). High-grade intraepithelial neoplasia was detected in 47 lesions (21.8%). While piecemeal fragments did show lateral margins with adenoma tissue, positive vertical margins were not detected. All four colorectal cancers were low risk (pT1a, L0, V0, R0 - G1/G2) and did not recur

Table 2 Histology by localization of the lesions *n* (%)

| Histology | Right-sided colon (<i>n</i> = 149) | Left-sided colon (<i>n</i> = 67) |
|-----------------------------------|--|--------------------------------------|
| Low-risk invasive adeno-carcinoma | 1 (0.7) | 3 (4.5) |
| Tubular-villous adenoma | 63 (42.3) | 39 (58.2) |
| Tubular adenoma | 42 (28.2) | 23 (34.3) |
| Serrated adenoma | 43 (28.9) | 2 (3.0) |

during follow-up (Tables 1 and 2).

After a median follow-up interval of 6 mo (range 2-43.4) a total number of 33 recurrences were detected, resulting in a local recurrence rate of 15.3%. All recurrences showed the same histology as the initially resected lesion and by the time of writing all patients with recurrences had been treated endoscopically by EMR and/or argon plasma coagulation. Univariate (Kaplan-Meier) analysis (Table 3) detected significant differences in the recurrence rates for age group (< 65 years: 11.4%/> 65 years: 19.2%), adenoma size (< 30 mm: 12.4%/> 30 mm: 22.2%), localization (left-sided colon: 3.0%/right-sided colon: 20.8%), morphology (pedunculated: 0%/non-pedunculated: 17.8%), resection technique (*en bloc*: 6.5%/piecemeal: 17.6%) and histology (tubular, serrated, carcinoma: 7.1%/ tubular-villous 24.3%) but not for time interval of follow-up or histology of serrated adenoma. On multivariate (Cox regression) analysis only localization in the right-sided colon (HR = 6.842), histology of tubular-villous adenoma (HR = 3.713) and size > 30 mm (HR = 2.563) were independently associated with local recurrence. We did not detect an association of recurrence with high-grade intraepithelial neoplasia (OR = 0.549/95%CI: 0.193-1.562; *P* = 0.279) (Table 4).

DISCUSSION

In this retrospective analysis of EMRs for 216 large colorectal adenomas (median size 30 mm) with preferential proximal localization (69% right-sided colon) we observed a recurrence rate of 15.3% after a median follow-up of 6 mo. Univariate analysis showed significantly higher recurrence rates for patient age > 65 years, adenoma size > 30 mm, proximal localization, non-pedunculated morphology, resection in piecemeal technique and tubular-villous histology. Multivariate analysis revealed only adenoma size > 30 mm, right-sided localization and tubular-villous histology as risk factors independently associated with local recurrence.

Many of the above mentioned factors have been described in the literature (Table 5). Interestingly, and in contrast to most other reports, the strongest risk factor for adenoma recurrence identified in this study was a right-sided localization (HR = 6.842). These findings are in line with data from Cipolletta *et al*^[30] who reported a similar association for lesions with predominantly right-sided localization. In the present study, 69% of the lesions were located in the right-sided colon and the

Table 3 Risk factors for recurrence (univariate analysis)¹

| Variable | Recurrence (fraction/%) | OR (95%CI) | P value ² |
|---|-------------------------|------------------|----------------------|
| Age | | | |
| < 65 yr | 10/96 (11.4%) | 2.492 | 0.011 |
| > 65 yr | 23/120 (19.2%) | (1.182-5.252) | |
| Size | | | |
| < 30 mm | 19/153 (12.4%) | 2.472 | 0.005 |
| > 30 mm | 14/63 (22.2%) | (1.233-4.957) | |
| Morphology | | | |
| Paris 0-Ip (pedunculated) | 0/31 (0%) | 26.386 | 0.018 |
| Paris 0-Is, 0-II a, b, c (sessile/flat) | 33/185 (17.8%) | (0.473-1472.565) | |
| Localization | | | |
| Right-sided colon | 31/149 (20.8%) | 7.475 | 0.002 |
| Left-sided colon or rectum | 2/67 (3.0%) | (1.787-31.264) | |
| Resection technique | | | |
| Piecemeal (fragmented) | 30/170 (17.6%) | 3.741 | 0.01 |
| <i>En bloc</i> | 3/46 (6.5%) | (1.139-12.292) | |
| Histology | | | |
| Tubular-villous adenoma | 25/103 (24.3%) | 3.417 | 0.002 |
| Tubular, serrated, carcinoma | 8/113 (7.1%) | (1.533-7.614) | |

¹The overall recurrence rate was 33/216 (15.3%); ²As calculated with the Kaplan-Meier method.

recurrence rate was 20.9% (vs 3.0% for localization in left-sided colon or rectum). Our interpretation is, that this association is driven by the higher technical difficulty for the treatment of right-sided lesions, resulting in lower complete resection rates, in particular since all pedunculated lesions were localized in the left-sided colon. Since relatively high recurrence rates have been reported after resection of serrated lesions^[8] it is tempting to speculate on a correlation of a serrated histology with local recurrence rates but in the current study we did not find any statistically significant association. Interestingly, contradictory findings with higher recurrence rates for left-sided rather than right-sided localization have been reported from a retrospective study with predominantly left-sided adenomas^[28]. Thus, the diverging findings most probably reflect a difference in the study population, in particular with respect to adenoma characteristics (size, localization, morphology, *en bloc* resection rate), rather than true differences.

In addition, a larger size of the lesion^[14,22,23,30] and resection in piecemeal technique^[19,23,29,30] or a resection in more than 5 fragments^[18] have been reported as risk factors for recurrence. Our findings of a significant association of piecemeal resection (univariate analysis only) and of adenoma size > 30 mm (multivariate) with local recurrence after EMR are in complete agreement with the aforementioned studies.

Finally, we identified tubular-villous histology as a risk factor for local recurrence. Since tubular-villous adenoma represents a more advanced neoplastic lesion these data are in line with Lim *et al.*^[28] who reported an association of recurrence with high-grade intraepithelial neoplasia (not significantly associated in our dataset). Such associations could reflect biological

Table 4 Risk factors for recurrence (multivariate analysis)¹

| Variable | HR (95%CI) | P value |
|-----------------------------------|----------------------|---------|
| Size > 30 mm | 2.563 (1.179-5.570) | 0.017 |
| Localization right-sided colon | 6.842 (1.540-30.394) | 0.011 |
| Histology tubular-villous adenoma | 3.713 (1.617-8.528) | 0.002 |

¹The factors age, morphology, resection technique were not significant in multivariate analysis.

Table 5 Reported associations with adenoma recurrence from the literature

| Ref. | Lesions (n) | Size | Localization | Piecemeal resection |
|--|-------------|---------|--------------|---------------------|
| Luigiano <i>et al.</i> ^[14] | 148 | > 40 mm | | |
| Lim <i>et al.</i> ^[28] | 239 | | Left-sided | |
| Mannath <i>et al.</i> ^[29] | 121 | | | Yes |
| Sakamoto <i>et al.</i> ^[18] | 222 | | | Yes |
| | | | | (> 5 pieces) |
| Woodward <i>et al.</i> ^[19] | 423 | | | Yes |
| Cipolletta <i>et al.</i> ^[30] | 1012 | > 30 mm | Right-sided | Yes |
| Moss <i>et al.</i> ^[22] | 799 | > 40 mm | | |
| Oka <i>et al.</i> ^[23] | 1029 | > 40 mm | | Yes |
| Briedigkeit <i>et al.</i> (this study) | 216 | > 30 mm | Right-sided | Yes |
| | | | | (univariate only) |

differences between the different types of histology (serrated vs tubular vs tubular-villous) but the study size was probably too small to definitively address such differences in greater detail. The same holds true for age, morphology and resection technique with significant associations only on univariate but not on multivariate analysis.

The presented study has several limits. In particular, the retrospective design and the relatively short follow up interval (which results from the current guideline in our country^[11]) might have underestimated the true recurrence rate. In addition, the relatively low number of adenoma recurrences could have reduced the probability of correctly identifying associated risk factors. Nevertheless, the data underscore the necessity of meticulous endoscopic follow-up, in particular after EMR of larger adenomas with right-sided localization and tubular-villous histology, and probably also for adenomas resected in piecemeal technique. In these situations alternative procedures with higher *en bloc* resection rates such as colorectal ESD^[23,32] or laparoscopic surgery should be considered.

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COMMENTS

Background

Endoscopic mucosal resection of colorectal adenomas is the standard treatment in the Western world. However, the effectiveness for endoscopic mucosal resection (EMR) is limited for larger adenomas with reported recurrence rates of more than 30%.

Research frontiers

The identification of risk factors associated with local adenoma recurrence may be useful to identify patients in need for a more intensive follow-up and - possibly - to guide treatment methods.

Innovations and breakthroughs

This study shows an increased risk for recurrence after EMR of adenomas with proximal localization, larger size (> 30 mm) and tubular-villous histology.

Applications

The results can be used to determine the follow-up strategy, which should be more stringent for adenomas with the above-mentioned criteria. Moreover, resection strategy for colorectal adenomas with particular high recurrence risk should preferably be an *en bloc* resection (either by endoscopic submucosal dissection or laparoscopic surgery).

Peer-review

The study is a well written paper, addressing an important issue regarding treatment of these borderline lesions.

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