Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis

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Background and study aims: Local recurrence has been observed after endoscopic mucosal resection (EMR) of nonpedunculated colorectal lesions. The indications for follow-up colonoscopy and the optimal time interval are currently unclear. The aims of this systematic review were to assess the frequency of local recurrence after EMR, to identify risk factors for recurrence, and to provide follow-up recommendations.

Methods: A literature search was performed in PubMed, EMBASE, and the Cochrane Library. EMR was defined as endoscopic snare resection after submucosal fluid injection for removal of nonpedunculated adenomas and early carcinomas. Local recurrence was subdivided into early recurrence (detected at the first follow-up colonoscopy) and late recurrence (detected after ≥ 1 previous normal colonoscopy). A random effects meta-analysis was performed to calculate the pooled estimate of risk of recurrence.

Results: A total of 33 studies were included. The mean recurrence risk after EMR was 15 % (95 % confidence interval [CI] 12 % – 19 %). Recurrence risk was higher after piecemeal resection (20 %; 95 %CI 16 % – 25 %) than after en bloc resection (3 %; 95 %CI 2 % – 5 %; $P < 0.0001$). In 15 studies that differentiated between early and late recurrences, 152/173 recurrences (88 %) occurred early. In four studies with follow-up at 3, 6, and ≥ 12 months, 19/25 (76 %) recurrences were detected at 3 months, increasing to 24 (96 %) at 6 months. In multivariable analysis, only piecemeal resection was associated with recurrence (3 of 3 studies).

Conclusion: Local recurrence after EMR of nonpedunculated colorectal lesions occurs in 3 % of en bloc resections and 20 % of piecemeal resections. Piecemeal resection was the only independent risk factor for recurrence. As more than 90 % of recurrences are detected at 6 months after EMR, we propose that 6 months is the optimal initial follow-up interval.

Introduction

Removal of colorectal adenomas during colonoscopy reduces the incidence of colorectal carcinoma (CRC) and CRC-related mortality [1 – 4]. Despite surveillance of patients after resection of adenomas [5] the risk of developing CRC remains higher than in the general population [6]. Moreover, it is known that CRC can be detected in the interval between scheduled surveillance colonoscopies [7].

One of the important causes for interval carcinomas is incomplete removal of the original adenoma [8 – 10]. As residual adenomatous tissue has been shown to be capable of rapid regeneration [11, 12], incomplete resection may result in local recurrence [13]. Several studies have indicated that incomplete removal contributes to a higher subsequent incidence of CRC [5, 9, 14 – 16].

Concerns regarding local recurrence exist mostly for lesions with nonpedunculated morphology, which are often removed by endoscopic mucosal resection (EMR) with submucosal fluid injection. The issue of residual tissue seems to be more pronounced after piecemeal resection, which is at least in part due to the difficult histologic evaluation of resection margins when lesions are resected in pieces.

To reduce the risk of interval carcinomas secondary to local recurrence after EMR, international guidelines recommend that follow-up colonoscopy is performed 2 – 12 months after endoscopic resection of flat and sessile lesions [5, 17]. The recommended time interval for the first follow-up colonoscopy varies within and between guidelines, depending on size, morphology, and resection method used. Currently, there is no strong evidence pointing to specific risk factors for local

recurrence, nor is advice for appropriate intervals of follow-up available.

By performing a systematic review and meta-analysis we aimed to assess the magnitude of the problem of local recurrence after EMR of flat and sessile adenomas and minimally invasive carcinomas. Secondary aims were to identify risk factors for local recurrence and to determine the optimal timing for the first follow-up endoscopy after EMR, in order to individualize recommendations for surveillance.

Methods

This systematic review was conducted and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [18].

Eligibility criteria and definitions

Studies were eligible for inclusion if they were prognostic or therapeutic follow-up studies that reported on local recurrence after EMR of nonpedunculated colorectal lesions. Study designs included both prospective and retrospective cohort studies, case–control studies, and therapeutic clinical trials. Feasibility studies for new removal techniques were only included if the technique resembled conventional EMR. Conventional EMR was defined as snare resection after submucosal fluid injection for nonpedunculated lesions. Resected lesions included adenomas with low grade dysplasia (LGD) or high grade dysplasia (HGD) or minimally invasive mucosal or submucosal carcinomas, particularly Sm1 (invasion of submucosa < 1 mm). As in situ carcinoma of the colorectum is not always considered a distinct entity, no distinction was made between HGD and in situ carcinoma.

Local recurrence as an outcome implies that patients were followed up by undergoing at least one colonoscopy after the index procedure. Local recurrence was defined by the criteria of Higaki et al. [19]: lesions reappearing at the site that was previously treated endoscopically, lesions with convergent folds, and lesions with no convergent folds but with a clear polypectomy ulcer scar nearby were regarded as locally recurrent tumors. Local recurrence was divided into early recurrence (found at first follow-up colonoscopy) and late recurrence (found after at least one previous normal colonoscopy). Successful treatment was defined as complete clearance of all adenomatous or carcinomatous tissue, allowing for an unlimited number of endoscopic treatments but not surgery.

Information sources and search strategy

The electronic databases of PubMed, EMBASE, and Cochrane were searched for articles published in the English language between January 2000 and September 2012. The search term comprised synonyms for "colonoscopic resection of colorectal lesions" as domain and "local recurrence" as outcome (see **Appendix e1**, available online).

Study selection

After removing duplicate studies, titles and abstracts were screened for study design and domain. If full texts were available, articles were subsequently assessed in more detail for descriptions of domain and outcome (**Fig. 1**).

Selected full text articles were critically appraised for relevance and validity. In order for articles to be considered relevant, at least 80% of the reported procedures had to be EMRs performed using submucosal fluid injection, or resections without submucosal fluid injection had to be reported separately. Furthermore, studies were only deemed relevant if separate recurrence rates were given or derivable for nonpedunculated vs. pedunculated lesions, adenomas and minimally invasive carcinomas vs. deep submucosal carcinomas (≥ Sm2), and en bloc vs. piecemeal resections (see **Table e1**, available online). For the latter, it was also sufficient for the ratio of en bloc and piecemeal resected lesions in follow-up to be reported. If outcomes were not reported or were unclear, authors were contacted by email. If no additional information was provided, studies were excluded from the review and meta-analysis.

Studies were scored for validity based on potential biases, according to the criteria adapted from Hayden et al. (see **Table e2**, available online) [20]. As this review comprised both prognostic and therapeutic studies, the focus was on study participation, study attrition, and outcome reporting.

Data extraction and statistical analyses

The risk of recurrence of nonpedunculated colorectal adenomas or minimally invasive carcinomas was extracted from the selected articles.

A meta-analysis for the risk of recurrence was performed using a random effects model. Cochran's *Q* test was performed to test for heterogeneity between studies and between recurrence rates after en bloc and piecemeal resections. A P value of < 0.05 was considered significant. All statistical analyses were conducted using R version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection

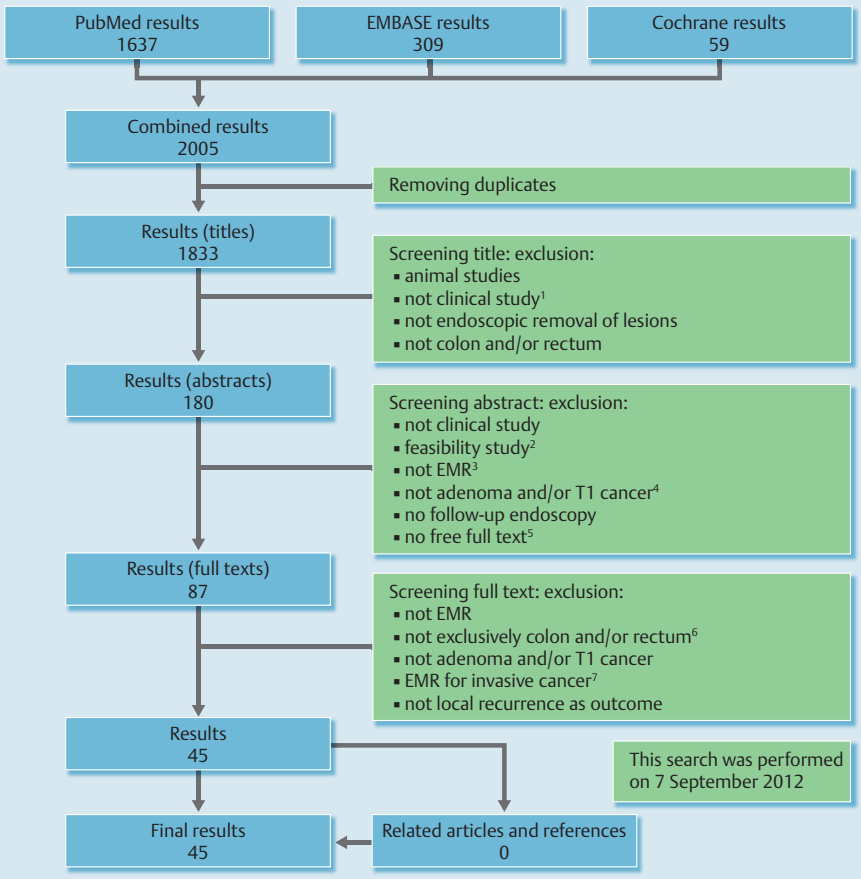
After screening titles, abstracts, and full text articles, 45 eligible studies were identified (**Fig. 1**) [19, 21–24] and assessed for relevance (see **Table e1**, available online). Of these studies, a total of 12 were excluded, either because no separate assessment of recurrences was made for nonpedunculated vs. pedunculated lesions [21–25], deep submucosal lesions vs. non- or minimally invasive lesions [24–27] or en bloc vs. piecemeal resections [21–31], or because submucosal fluid injection was not reported to be used for more than 80% of resections [27,31,32]. One study reported no separate recurrence rates for en bloc and piecemeal resections but instead provided the ratio of en bloc and piecemeal lesions at follow-up [33].

Risk of bias in each study

A total of 33 relevant studies were critically appraised for potential bias in relation to the outcome of interest (see **Table e2**, available online). For six studies, the risk of bias was found to be very small. The risk of bias was considered small in 11 studies and moderate in 16 studies. As there were no relevant studies with a high risk of bias, none of these studies were excluded based on validity.

Study characteristics

The 33 included studies comprised 28 cohort studies and case series (8 prospective [19,40,41,43,45,46,48,50] and 20 retrospective [34–38,42,44,47,49,51,52,54–56,58–60,62–64]), 3 retrospective case–control studies [53,57,61], and 2 therapeutic trials [33,39]. The retrospective cohort studies included six stud-



[1] Clinical studies comprised cohort studies, case-control studies or therapeutic studies. Case reports, reviews, meta-analyses or other publication types were excluded. As this could not always be deduced from the title, abstracts were also used to select articles.
[2] A feasibility study was defined as a study in which a novel therapeutic technique (not similar to conventional EMR) was used.
[3] As this could not always be deduced from the abstract, full texts were also used to select articles.
[4] Studies had to include adenomas and optionally T1 carcinomas. As this could not always be deduced from the abstract, full texts were also used to select articles.
[5] Studies were excluded if full texts were not freely available through institutional access.
[6] Studies were excluded if several gastrointestinal locations were taken into account, not specifically looking at considerable samples of lesions in colon and/or rectum
[7] Studies focussing on resectability of invasive carcinomas and/or predicting invasiveness or lymph node metastasis were excluded.

Fig. 1 Flow chart of the selection of studies eligible for data extraction and analysis.

ies for which it was not clear whether these were prospective or retrospective. Relevant sample sizes for this review are not the baseline populations but the numbers of patients and lesions at follow-up. These samples varied between 19 and 419 lesions. Seven studies were considered to be small (< 50 lesions), thirteen moderate (50 – 100 lesions), seven moderate to large (100 – 150 lesions), and six large (> 150 lesions).

Two studies included rectal lesions only, whereas all other studies included all colorectal locations. Inclusion criteria were lesion size above 40 mm (1 study) or 30 mm (1 study), 20 mm (15 studies), 15 mm (3 studies), or 10 mm (8 studies). Five studies did not report inclusion criteria regarding the size of the lesions. Seven studies included only sessile lesions and eight studies included only flat lesions. A total of 11 studies included both sessile and flat lesions and 7 studies did not report inclusion criteria regarding the type of lesion. All studies included adenomatous lesions, with or without HGD. A total of 22 studies also included mucosal or submucosal invasive lesions, which formed a minority of the lesions in all but one study [46].

A total of 22 studies reported separate results for en bloc and piecemeal resections, and 10 studies focussed on piecemeal resection. One study reported combined results, but provided the ratio of en bloc and piecemeal resected lesions at follow-up. Additional use of argon plasma coagulation (APC) to complete EMR was reported in 17 studies.

As histologic assessment of resection margins after piecemeal resection is practically infeasible if not impossible, information on resection margins was generally not given for piecemeal resected lesions. Of the 23 studies taking into account both en bloc and piecemeal resections, 9 reported on the resection margins, of which only 5 reported this specifically for lesions at follow-up. Almost all en bloc resections appeared to have been radical (**Table 3**).

Follow-up

In most studies the initial follow-up interval was 3 – 6 months. A total of 10 studies allowed the first follow-up colonoscopy to be performed at a later stage. In 23 studies providing a mean and/or a median follow-up, the overall mean was 23 months.

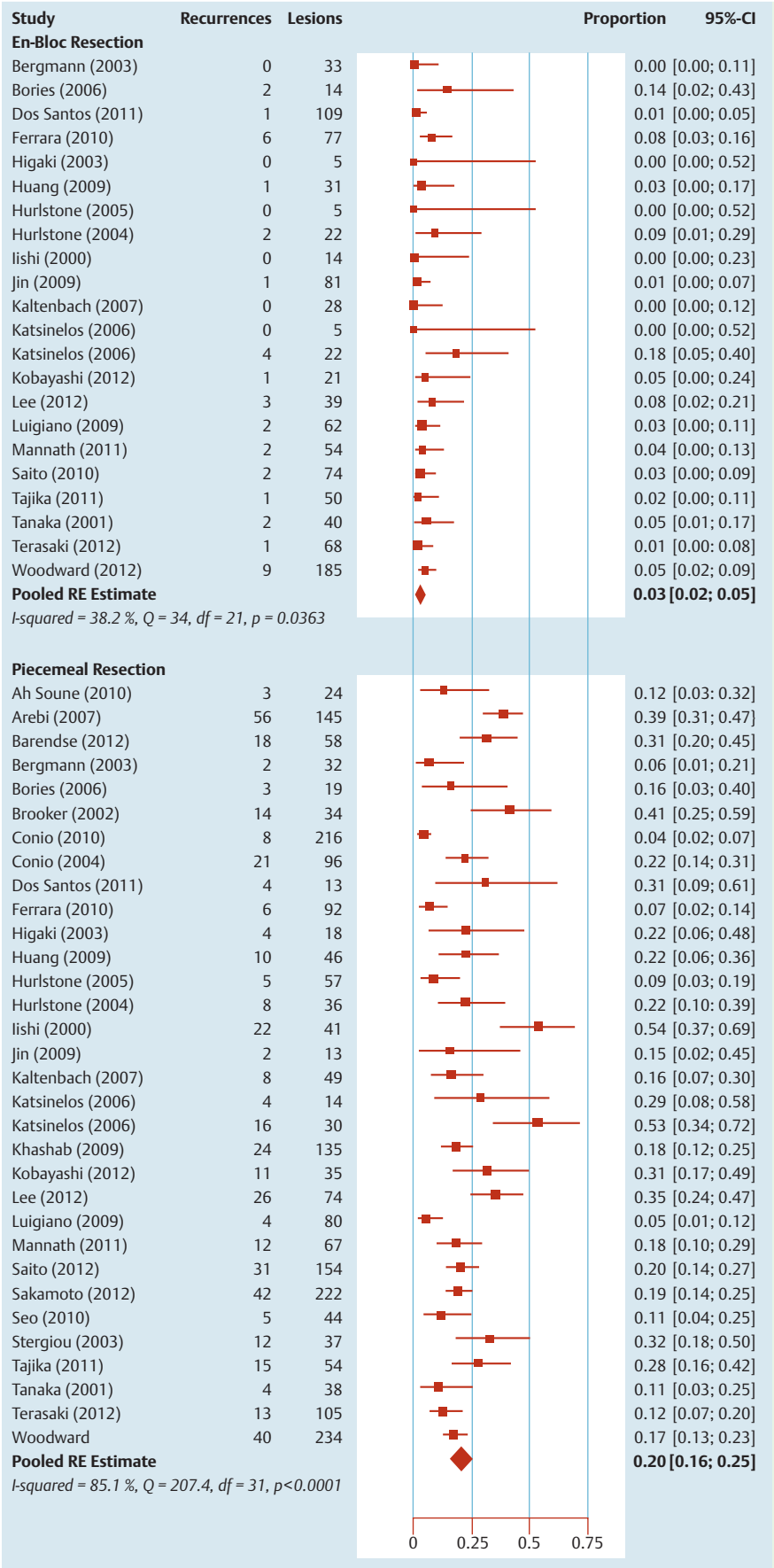


Fig. 2 R-plot showing the individual and pooled estimates of the proportion of lesions with recurrence among 22 studies in which en bloc resection was performed and 32 studies in which piecemeal resection was performed. The study performed by Moss et al. [33] is not included in this figure, as it was not clear how many of the recurrences were found after en bloc vs. piecemeal resection.

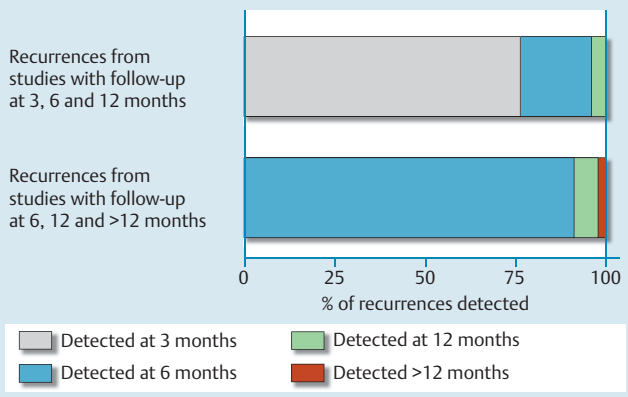


Fig. 3 Cumulative detection of recurrences.

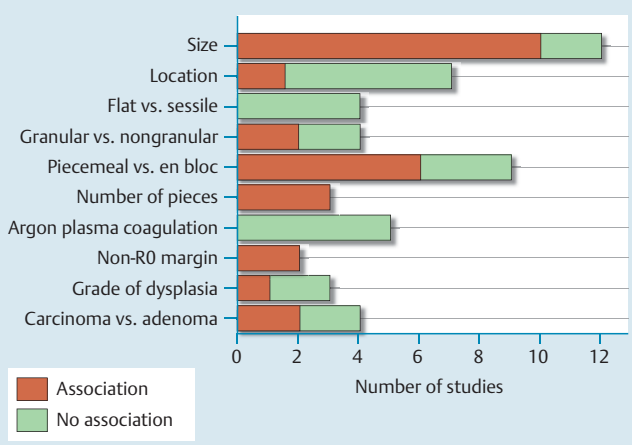


Fig. 4 Number of studies performing univariable analysis for different possible risk factors and the proportion of studies finding an association with recurrence. For further specification of risk factors, see **Table 4**.

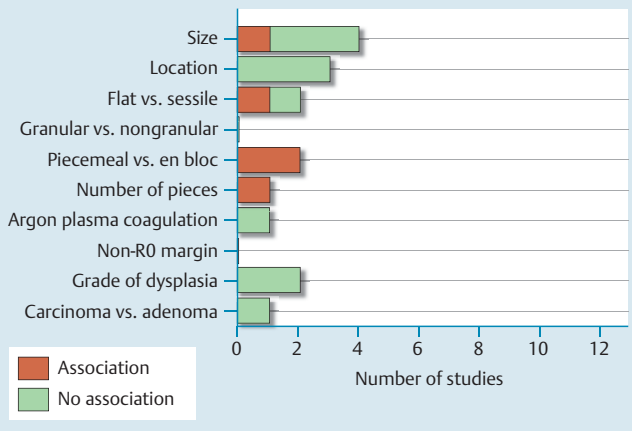


Fig. 5 Number of studies performing multivariable analysis for different possible risk factors and the proportion of studies finding an association with recurrence. For further specification of risk factors, see **Table 4**.

Risk of recurrence and treatment success

Overall, the mean risk of recurrence after EMR in the 33 studies was 15% (95% confidence interval [CI] 12%–19%). In these studies, 31% of lesions had been resected en bloc. The pooled estimate of recurrence risk was significantly higher for piecemeal resections (20%; 95%CI 16%–25%) than for en bloc resections (3%; 95%CI 2%–5%; Cochran's *Q* test $P<0.0001$) (**Fig. 2**).

Of the 351 recurrences that were reported to be re-treated at follow-up endoscopy, 75 (21%) recurred again. Modalities used for retreatment were APC and/or EMR. After a mean of 1.2 endoscopic re-treatments, successful eradication was achieved in 91.4% of recurrences. Overall, endoscopic treatment was successful for 99% of all lesions for which EMR was initially considered adequate, meaning that for 1% of these lesions surgical resection was eventually necessary. The mean number of endoscopic treatments needed to eradicate index lesions was also 1.2.

Early and late recurrence and optimal follow-up interval

In 15 studies that differentiated between early and late recurrences [34,36,42,45,46,48,49,52–55,59,61–63], 152/173 recurrences (88%) were found during the first follow-up colonoscopy and 21 (12%) after at least one previous normal colonoscopy.

In only four studies did all patients undergo follow-up at 3, 6, and ≥12 months. A total of 19 of 25 recurrences (76%) were detected at 3 months, increasing to 24 (96%) at 6 months. In six studies, including the abovementioned four, follow-up was performed before or at 6 months, at 12 months, and after 12 months. Cumulative recurrences were 43 (91%) at 6 months, 46 (98%) at 12 months, and 47 after 12 months (**Fig. 3**).

Recurrence in relation to pathology grade

Risk of recurrence for LGD (two studies, 57 lesions [45,51]), HGD (three studies, 53 lesions [38,45,51]), mucosal carcinomas (three studies, 70 lesions [42,53,61]), and Sm1 carcinomas (five studies, 25 lesions [45,48,53,61,62]) were 7.0%, 18.9%, 15.7%, and 12.0%, respectively (Fisher's exact test $P=0.28$). Only two studies [45,51] reported recurrence risks for both LGD (57 lesions) and HGD (20 lesions), which differed significantly (7.5% vs. 25.0%, Fisher's exact test: $P=0.046$). In nine studies reporting recurrences for both adenomas and carcinomas [37,42,45,48,53,58,61–63], the rates were 8.2% (53/648) and 17.9% (55/307), respectively (Fisher's exact test: $P<0.001$). These risks were not adjusted for size and resection technique.

Risk factor analysis

In studies performing univariable analysis, size, piecemeal resection, and non-R0 resections were reported to be associated with local recurrence in 10 of 12 studies, 6 of 9 studies, and 2 of 2 studies, respectively (**Table 4**; **Fig. 4**). Of the 12 studies that univariably assessed the association between size and recurrence, three used a continuous variable and nine used varying categories with thresholds between 20 and 40 mm. Three studies showed that an increasing number of resected fragments per lesion correlated with the risk of recurrence in univariable analysis. Two studies reported that in case of free resections margins, the risk of recurrence was indeed very small.

Apart from size, lesion characteristics were not found to affect the recurrence risk. Location was not associated with recurrence in any of the studies. Four studies showed that recurrence was not found more often after resection of flat lesions compared with sessile lesions. For laterally spreading tumors (LSTs), the granular form was associated with recurrence in two of four studies in univariable analysis. Classification of lesions at histology was not uniformly tested in different studies and was rarely associated with recurrence.

APC had a protective effect in one study when applied routinely after endoscopically complete EMR [39]. Additional APC treatment for macroscopic residual tissue was not a risk factor for recurrence in five studies.

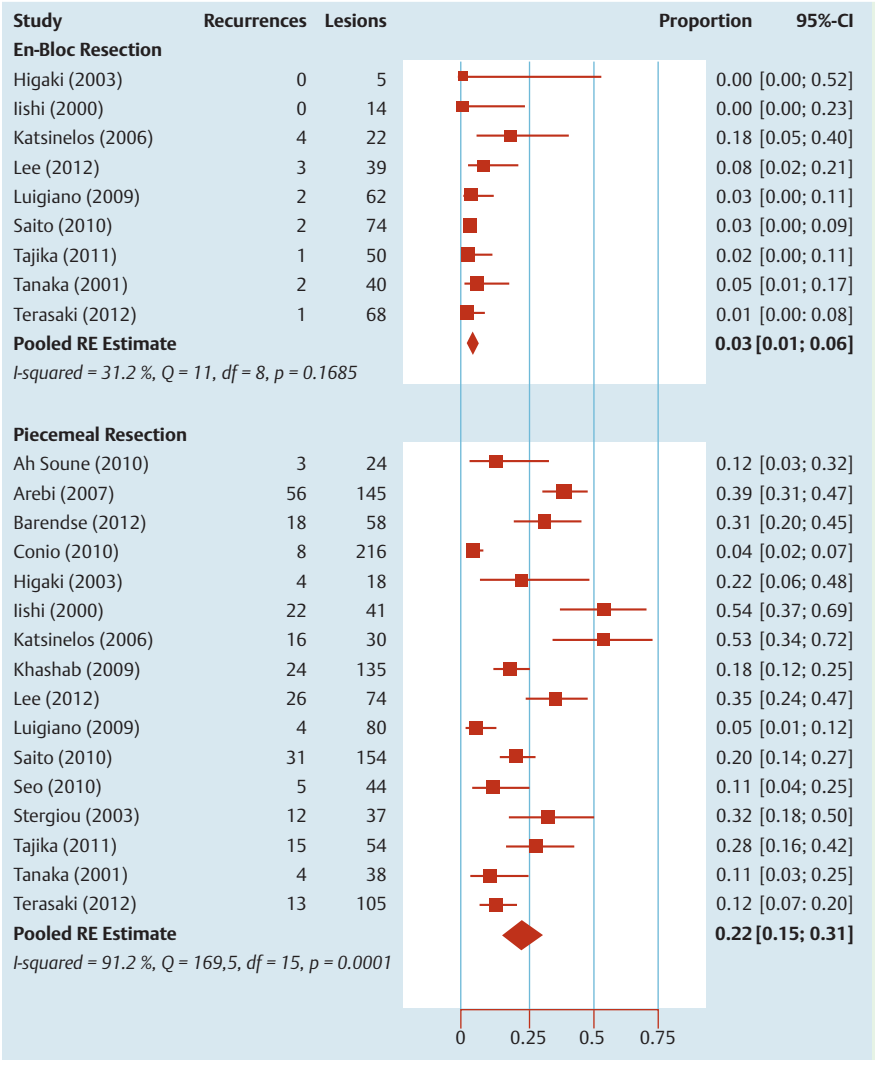


Fig. 6 Meta-analysis of recurrence, subdivided into en bloc and piecemeal resections of lesions >20 mm.

In multivariable analysis, only piecemeal resection was found to be associated with recurrence (in 3 of 3 studies) (**Fig. 5**). Size remained a risk factor in only one of four studies that reported a multivariate analysis. One of two studies reported that flat morphology was associated with recurrence.

Discussion

The results of this systematic review and meta-analysis show that recurrence after piecemeal EMR occurs in 20% of lesions compared with only 3% after en bloc EMR. Most recurrences were found during the first follow-up colonoscopy, irrespective of timing. In the few studies performing follow-up colonoscopy at regular intervals, three-quarters of recurrences were found at 3 months, increasing to more than 90% at 6 months. Piecemeal resection was the only risk factor that was associated with recurrence in multivariable analysis.

A difference in recurrence rates between en bloc and piecemeal resections was anticipated. The decision by the endoscopist to perform the resection in piecemeal fashion is dependent on the difficulty of the resection. Reasons for performing piecemeal EMR instead of en bloc EMR are size above 20–30 mm, location near colonic folds, or a lesion covering a large part of the lumen circumference. The outcome of this meta-analysis therefore must not be interpreted as a comparison between the two techniques, but as an indication that en bloc and piecemeal resected lesions are indeed different with regard to recurrence risk and therefore require different follow-up strategies.

As there is an intrinsic association between larger size and piecemeal resection, an attempt was made to determine the extent to which lesion size might have influenced the high recurrence rate after piecemeal resection. Ideally, raw data would have been used to see whether both size above 20 mm and resection in multiple fragments are independent risk factors for recurrence. However, this was not possible, so instead a meta-analysis was performed on lesions larger than 20 mm (**Fig. 6**), and this showed that the recurrence rate for piecemeal resections (22%) was still higher than for en bloc resections (3%; Cochran's *Q* test $P<0.001$). It seems that piecemeal resection is a more useful clinical predictor for recurrence than size >20 mm.

When analyzing three different categories of mean or median lesion size (10–20 mm, 20–30 mm, and >30 mm) with regard to recurrence after piecemeal resection, no significant differences were found (18%, 19%, and 19%, respectively; Cochran's *Q* test $P=0.88$). Studies with inclusion of lesions >20 mm had no significantly higher risk of recurrence compared with studies that also included smaller lesions (22% vs. 18%; Cochran's *Q* test $P=0.37$). Results in the en bloc group were heterogeneous. However, the only studies finding recurrence risks above 10% were considered

Table 3 Results of individual studies.

Study First author, year [Ref.]	En bloc or piecemeal[1]	R0[2]	Schedule of follow-up, months	Length of follow-up mean (±SD) median (range), months	Recurrences, n						Success
					Overall	After en bloc	After piecemeal	Time to recurrence mean (±SD) median (range), months	Early[3]	Late[4]	
Ah Soune, 2010 [34]	Piecemeal	N/A	3 – 6, 1, 3	12 (NR) NR (3 – 37)	3/24	N/A	3/24	4 (NR) 3 (3 – 6)	3	0	23/24
Arebi, 2007 [35]	Piecemeal	N/A	3 – 12	9 (NR) NR (1 – 48)	60/145	N/A	60/145	NR	60	NR	141/145
Barendse, 2012 [36]	Piecemeal	N/A	NR[5]	NR 12 (1 – 46)	18/58	N/A	18/58	NR	16	2	NR
Bergmann, 2003 [37]	Both	65/65	3 – 6, 12, 18, 24, 30	18 (NR) NR (6 – 30)	2/65	0/33	2/32	NR	NR	NR	NR
Bories, 2006 [38]	Both	14/14	1 – 3, 6, 1, 3, 5	17 (NR) NR (6 – 57)	5/33	2/14	3/19	NR	NR	NR	NR
Brooker, 2002 [39]	Piecemeal 85 %	N/A	3[6], 12	15 (NR) NR	14/34	N/A	14/34	NR	14	NR	27/29
Conio, 2010 [40]	Piecemeal	N/A	3, 6, 12, yearly	NR 12 (6 – 71)	8/216	N/A	8/216	NR	NR	NR	210/210
Conio, 2004 [41]	Piecemeal	N/A	3, 6, 12, yearly	NR 12 (3 – 50)	21/96	N/A	21/96	NR	NR	NR	≥ 91/93
Dos Santos, 2010 [42]	Both	151/158[7]	6, 12, 18	18 (NR) 18 (NR)	5/122	1/109	4/13	NR	5	0	122/122
Ferrara, 2010 [43]	Both	NR	3[8], 6, 12, 24[8], 36	20 (±11) NR (6 – 36)	12/169	6/77	6/92	NR 6 (3 – 12)	NR	NR	169/169
Higaki, 2003 [19]	Both	NR	3, 6, 12, 24	24 (NR) 24 (NR)	4/23	0/5	4/18	NR	NR	NR	21/23
Huang, 2009 [44]	Both	NR	NR[9]	NR[10] NR	11/77	1/31	10/46	NR NR	11	NR	77/77
Hurlstone, 2005 [45]	Both	5/5	3, 6, 12, 24	NR 14 (3 – 24)	5/62	0/5	5/57	NR	5	0	61/62
Hurlstone, 2004 [46]	Both	21/22	3, 6, 12, 24	24 (NR) 24 (NR)	10/58	2/22	8/36	NR	8	2	56/58
Iishi, 2000 [47]	Both	NR	3, 6, ≥12	NR 34 (12 – 84)	22/55	0/14	22/41	NR	NR	NR	49/53
Jin, 2009 [48]	Both	NR	3, 6, 12, 24	25 (±7) NR (3 – 36)	3/94	1/81	2/13	NR	NR	NR	NR
Kaltenbach, 2007 [49]	Both	NR	6	NR NR	8/77	0/28	8/49	NR	8	0	77/77
Katsinelos, 2006 [50]	Both	NR	3, 6, 12, yearly	23 (±16) NR	20/52	4/22	16/30	NR	20	0	51/52
Katsinelos, 2006 [51]	Both	NR	3, 6, ≥12	38 (±24) NR	4/19	0/14	4/5	NR	NR	NR	NR
Khashab, 2009 [52]	Piecemeal 82 %	N/A	3 – 6, ≥12	NR NR (12 – NR)	24/135	N/A	24/135	NR	18	6	≥ 132/135

Table 3 (Continuation)

Study First author, year [Ref.]	En bloc or piecemeal[1]	R0[2]	Schedule of follow-up, months	Length of follow-up mean (±SD) median (range), months	Recurrences, n						Success
					Overall	After en bloc	After piecemeal	Time to recurrence mean (±SD) median (range), months	Early[3]	Late[4]	
Kobayashi, 2012 [53]	Both	NR	3 – 12, yearly	NR 38 (3 – 111)	12/56	1/21	11/35	NR 8 (2 – 49)	10	2	55/56
Lee, 2012 [54]	Both	46/140[11]	6 – 12, yearly	NR 26 (IQR 13 – 41)	29/113	3/39	26/64	NR	29	0	112/113
Luigiano, 2009 [55]	Both	NR	3, 6, 12, 24, 36, 48, 60	30 (± 16) NR (6 – 60)	6/142	2/62	4/80	NR	2	4	141/142
Mannath, 2011 [56]	Both	NR	3 – 12	NR 12 (IQR 8 – 24)	14/121	2/54	12/67	NR	NR	NR	121/121
Moss, 2010 [33]	Both	NR	3	3 (NR) 3 (NR)	7/71	NR/16	NR/55	NR	7	NR	NR
Saito, 2010 [57]	Both	NR	6 – 12	26 (± 17) NR (6 – 68)	33/228	2/74	31/154	6 (NR) NR (2 – 18)	NR	NR	225/228
Sakamoto, 2012 [58]	Piecemeal	N/A	3 – 6, 12	NR 32 (IQR 11 – 53)	42/222	N/A	42/222	NR	NR	NR	219/222
Seo, 2010 [59]	Piecemeal	N/A	3 – 6, 12	NR 37 (3 – 72)	5/44	N/A	5/44	5 (NR) NR (3 – 14)	4	1	41/44
Stergiou, 2003 [60]	Piecemeal	N/A	3 – 12, yearly	NR NR (3 – NR)	12/37	N/A	12/37	NR	12	NR	37/37
Tajika, 2011 [61]	Both	41/104[12]	3 – 12	54 (± 45) NR (3 – 191)	16/104	1/24	15/80	13 (NR) NR (3 – 50)	10[13]	6	99/102
Tanaka, 2001 [62]	Both	18/81[14]	6 – 12, yearly	61 (± 20) NR	6/78	2/40	4/38	5 (NR) NR	5[15]	1	78/78
Terasaki, 2012 [63]	Both	176/178	6 – 12	22 (± 14) NR	14/173	1/68	13/105	13 (NR) NR (3 – 40)	9	5	173/173
Woodward, 2012 [64]	Both	NR	3 – 6	NR NR (3 – 6)	49/419[16]	9/185	40/234	NR NR (3 – 6)	49	NR	NR

IQR, interquartile range; N/A, not applicable; NR, not reported or unclear.

[1] 'Both' means that en bloc and piecemeal resections were performed within the study. The percentage of lesions for which submucosal fluid injection was used is only given if it was not 100 %.

[2] En bloc resection with free margins at first endoscopic resection.

[3] Early: early recurrence, at first follow-up colonoscopy

[4] Late: late recurrence, after at least one previous normal follow-up colonoscopy

[5] The first follow-up colonoscopy was performed in 86 % of patients within 6 months.

[6] In some cases of more advanced disease, first follow-up at less than 3 months.

[7] Of 158 en bloc resected lesions at baseline, 151 had been resected completely.

[8] Follow-up at these moments was only performed for lesions containing high grade dysplasia or cancer, or lesions resected in piecemeal fashion.

[9] First follow-up after mean of 8 ± 6 months.

[10] Length of follow-up was only reported for the recurring lesions: 27 ± 18 months (range 13 – 69).

[11] At baseline there were 140 en bloc and piecemeal resections, of which 46 showed free resection margins.

[12] No distinction was made between en bloc and piecemeal. 50 margins were unidentified.

[13] 10 recurrences were found between 3 and 9 months, 6 were found after 12 months.

[14] No distinction was made between en bloc and piecemeal resections. For at least 31 piecemeal resections margins were not free, as opposed to at least 9 en bloc resections.

[15] 5 recurrences were found between 1 and 5 months, 1 was found after 12 months.

[16] The total number of lesions in follow-up was 423, but the sum of en bloc and piecemeal resections is 419. No reason was given for this discrepancy.

Table 4 Risk factors for recurrence in univariable and multivariable analysis.

Study First author, year [Ref.]	Analysis	Risk factor for recurrence (variable)[1]						
		Size	Location[2]	Form	Piecemeal resection vs. en bloc resection	APC[3]	R1[4]	Histology
Arebi, 2007 [35]	Univariable	+ (categorical variable)	No correlation (categorical variable)	No correlation (flat vs. sessile)				No correlation (dysplasia as categorical variable)
Brooker, 2002 [39]	Univariable					–[5]		
Conio, 2004 [41]	Univariable	No correlation (continuous variable)				No correlation		NR
	Multivariable	+ (> 35 mm)						No correlation (tubulous, villous, HGD)
Conio, 2010 [40]	Univariable					No correlation		
Dos Santos, 2011 [42]	Univariable	+ (> 20 mm)[6]	No correlation (distal)		+			+ (advanced neoplasia)[7]
Ferrara, 2010 [43]	Univariable	No correlation (≥ 30 mm)		No correlation (flat vs. sessile)	No correlation	No correlation		
Hurlstone, 2004 [46]	Univariable (P<0.1)			+ (granular vs. nongranular)	+			
Jin, 2009 [48]	Univariable	+ (> 20 mm)	No correlation (categorical variable)		+			No correlation (tubulous / villous / tubulovillous / T1-carcinoma)
Katsinelos, 2006 [51]	Univariable	+ (> 25 mm)						+ (HGD vs. LGD)
Khashab, 2009 [52]	Univariable	+ (continuous variable)						
Lee, 2012 [54]	Univariable		No correlation (categorical variable)					
Luigiano, 2009 [55]	Univariable	+ (≥ 40 mm)		No correlation (flat vs. sessile)	No correlation	No correlation		
Mannath, 2011 [56]	Multivariable	No correlation (≥ 20 mm)	No correlation (right)	+ (flat vs. sessile)	+	No correlation		No correlation (HGD/ carcinoma vs. LGD)
Sakamoto, 2011 [58]	Univariable	+ (≥ 30 mm)	No correlation (rectal)	No correlation (flat vs. sessile)	+ (≥ 5 pieces)			No correlation (carcinoma)
	Multivariable	No correlation (≥ 30 mm)	No correlation (rectal)	No correlation (flat vs. sessile)	+ (≥ 5 pieces)			No correlation (carcinoma)
Seo, 2010 [59]	Univariable							+ (carcinoma)

Table 4 (Continuation)

Study First author, year [Ref.]	Analysis	Risk factor for recurrence (variable)[1]						
		Size	Location[2]	Form	Piecemeal resection vs. en bloc resection	APC[3]	R1[4]	Histology
Tajika, 2011 [61]	Univariable	+ (continuous variable)	No correlation (categorical variable)	No correlation (granular vs. nongranular and depressed vs. protruded)	+ (and number of pieces)		+[8]	No correlation (adenoma, mucosal and superficial submucosal carcinomas)
Tanaka, 2001 [62]	Univariable	No correlation (NR)		No correlation (granular vs. nongranular)	No correlation		+[9]	No correlation (HGD vs. LGD)
Terasaki, 2012 [63]	Univariable	+ (≥ 40 mm)		+ (granular vs. nongranular)	+ (and 3 vs. ≤ 2 pieces)			
Woodward, 2012 [64]	Univariable	+ (categorical variable)	No correlation (categorical variable)		+			
	Multivariable	No correlation[10] (categorical variable)	No correlation (categorical variable)		+[6]			

APC, argon plasma coagulation; HGD, high grade dysplasia; LGD, low grade dysplasia; NR, not reported.
[1] + association with recurrence; – inverse association with recurrence; empty cells = variable not tested.
[2] Distal = distal vs. proximal; right = right-sided vs. left-sided; rectal = rectal vs. colonic.
[3] Use of APC to complete endoscopic resection.
[4] Resection margins not free at histological assessment.
[5] Only when used in addition to endoscopically complete EMR.
[6] Size over 20 mm was reported to be directly related to piecemeal resection.
[7] Advanced neoplasia was either advanced adenoma or carcinoma.
[8] High negative predictive value (NPV) of free resection margins.
[9] High NPV of free resection margins.
[10] When size was analyzed in subgroups of piecemeal and en bloc it was a significant risk factor, as was piecemeal in 3 categories of size (1 – 3, 2 – 3, and > 3 cm).

to be small [38, 50]. Bories et al. [38] included only lesions with HGD at follow-up, which may partly explain the high proportion of residual lesions. It is not possible to clarify reasons for the high recurrence risk in the study by Katsinelos et al. [50], other than chance. The overall risk of recurrence after en bloc EMR was very low, and when the Katsinelos study [50] was excluded, the results within the en bloc group were indeed homogeneous.

Results within the piecemeal group were also clearly heterogeneous. A multivariable Poisson regression analysis was performed to identify which study- and population-related factors might explain this heterogeneity. This analysis showed a significant trend towards a decrease in recurrence rates over time, as indicated by the year of the studies. Prospective studies showed lower recurrence rates than retrospective studies. These findings provide a partial explanation for the variation in recurrence rates after piecemeal resection and may indicate an improvement of the endoscopic piecemeal resection technique over time and a lower recurrence rate when performed with a predetermined focus on complete removal.

One other systematic review has reported on early and late recurrence after piecemeal EMR for colorectal lesions [65]. Barendse et al. found an early recurrence rate of 11.2%, which is comparable to our overall recurrence of 15%. In a recent study by Pohl et al., biopsies taken from the resection margins after macroscopically complete hot snare resection showed residual tissue in 10% of cases [66]. Although the intervention and outcome measure in that study were not completely the same as in the current meta-analysis, the results indicate a comparable risk of residual tissue after endoscopic resection.

The high percentage of lesions successfully eradicated by performing an unlimited number of additional endoscopic procedures proves that most recurrences do not require surgical treatment. However, this treatment success was calculated for lesions for which attempted endoscopic treatment was considered sufficient for eradication in the first place. Therefore, the outcome is highly dependent on the endoscopist making the decision to perform only follow-up colonoscopy or additional surgical treatment after the first endoscopic treatment.

Data on the earliest possible detection of recurrence are scarce and therefore strong recommendations regarding timing of follow-up colonoscopy cannot be made. However, it is clear from the current results that recurrences are not always detected at the first follow-up colonoscopy. Anecdotal evidence shows that it is not unusual for recurrences to be found after a normal follow-up colonoscopy at 3 months. Therefore, we recommend not to solemnly rely on the outcome of a colonoscopy at 3 months, but to perform follow-up colonoscopy at 6 and/or 12 months in all cases.

Risk factors were only assessed in a descriptive way because a complete set of raw data was not available. A convincing majority of studies showed that size was associated with recurrence in univariable analysis. However, the previously discussed association between size and piecemeal resection has probably resulted in confounding. This is supported by the fact that only one of four studies found size to be associated with risk of recurrence in multivariable analysis. On the other hand, the study by Woodward et al. [64] showed that within categories of en bloc and piecemeal resected lesions, size was still a risk factor. Conversely, piecemeal resection was a risk factor in all three size categories in that study. In addition, Longcroft-Wheaton et al. [67] recently reported that lesion size above 60 mm was a risk factor for recurrence after piecemeal resections.

There is no indication that flat lesions recur more often than sessile lesions, but this may be true for granular vs. nongranular LSTs. The two studies finding no association between granular morphology and recurrence were small compared with the two larger studies that did report an association. However, none of the studies performed multivariable analyses.

Piecemeal resection was the only risk factor that was clearly associated with recurrence in multivariable analysis. The risk for recurrence after en bloc resected lesions is indeed small, especially if the pathologist confirms complete resection. As use of APC – in the case of an endoscopically incomplete resection – was no risk factor for recurrence in the current study, additional APC treatment seems to reduce the risk of recurrence so that it is comparable to that after a resection that was endoscopically complete without APC. Two previous studies have shown that APC is an effective additional treatment in case of macroscopic residual tissue after polypectomy [68, 69]. However, in a more recent study by Moss et al. [30], which included 328 EMRs with follow-up, APC was identified as an independent risk factor for recurrence. We should therefore be careful not to rely too much on APC for complete eradication of neoplastic tissue.

In conclusion, this systematic review and meta-analysis confirms that the risk of local recurrence after piecemeal EMR is significantly higher than after en bloc EMR. A recurrence rate of 20% justifies performing a follow-up colonoscopy after piecemeal resections, especially because complete clearance can still be achieved in > 90% of local recurrences after only one endoscopic re-treatment. The optimal timing of the first follow-up colonoscopy remains to be determined in well-scheduled prospective studies, but based on the current data an initial interval of 6 months seems to be more adequate for recurrence detection than an interval of 3 months. Thus far, no risk factors other than piecemeal resection have been identified that can be used to guide a personalized follow-up schedule.

Competing interests: None

References

1 *Winawer SJ*, *Zauber AG*, *Ho MN* et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977 – 1981
2 *Zauber AG*, *Winawer SJ*, *O'Brien MJ* et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012; 366: 687 – 696
3 *Citarda F*, *Tomaselli G*, *Capocaccia R* et al. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001; 48: 812 – 815
4 *Jorgensen OD*, *Kronborg O*, *Fenger C* et al. Influence of long-term colonoscopic surveillance on incidence of colorectal cancer and death from the disease in patients with precursors (adenomas). Acta Oncol 2007; 46: 355 – 360
5 *Lieberman DA*, *Rex DK*, *Winawer SJ* et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012; 143: 844 – 857
6 *Cottet V*, *Jooste V*, *Fournel I* et al. Long-term risk of colorectal cancer after adenoma removal: a population-based cohort study. Gut 2012; 61: 1180 – 1186
7 *Leung K*, *Pinsky P*, *Laiyemo AO* et al. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointest Endosc 2010; 71: 111 – 117
8 *Pabby A*, *Schoen RE*, *Weissfeld JL* et al. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc 2005; 61: 385 – 391
9 *Robertson DJ*, *Greenberg ER*, *Beach M* et al. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005; 129: 34 – 41

10 *Huang Y*, *Gong W*, *Su B* et al. Risk and cause of interval colorectal cancer after colonoscopic polypectomy. Digestion 2012; 86: 148 – 154
11 *Matsuda K*, *Masaki T*, *Abo Y* et al. Rapid growth of residual colonic tumor after incomplete mucosal resection. J Gastroenterol 1999; 34: 260 – 263
12 *Kunihiro M*, *Tanaka S*, *Haruma K* et al. Electrocautery snare resection stimulates cellular proliferation of residual colorectal tumor: an increasing gene expression related to tumor growth. Dis Colon Rectum 2000; 43: 1107 – 1115
13 *Fujita M*, *Tsuruta O*, *Ikeda H* et al. Local recurrence of colorectal tumors after endoscopic mucosal resection. Int J Oncol 1997; 11: 533 – 538
14 *Farrar WD*, *Sawhney MS*, *Nelson DB* et al. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006; 4: 1259 – 1264
15 *Loeve F*, *van Ballegooijen M*, *Boer R* et al. Colorectal cancer risk in adenoma patients: a nation-wide study. Int J Cancer 2004; 111: 147 – 151
16 *Atkin WS*, *Morson BC*, *Cuzick J*. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992; 326: 658 – 662
17 *Cairns SR*, *Scholefield JH*, *Steele RJ* et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010; 59: 666 – 689
18 *Moher D*, *Liberati A*, *Tetzlaff J* et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006 – 1012
19 *Higaki S*, *Hashimoto S*, *Harada K* et al. Long-term follow-up of large flat colorectal tumors resected endoscopically. Endoscopy 2003; 35: 845 – 849
20 *Hayden JA*, *Cote P*, *Bombardier C*. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006; 144: 427 – 437
21 *Ahlawat SK*, *Gupta N*, *Benjamin SB* et al. Large colorectal polyps: endoscopic management and rate of malignancy: does size matter? J Clin Gastroenterol 2011; 45: 347 – 354
22 *Lim TR*, *Mahesh V*, *Singh S* et al. Endoscopic mucosal resection of colorectal polyps in typical UK hospitals. World J Gastroenterol 2010; 16: 5324 – 5328
23 *Salama M*, *Ormonde D*, *Quach T* et al. Outcomes of endoscopic resection of large colorectal neoplasms: an Australian experience. J Gastroenterol Hepatol 2010; 25: 84 – 89
24 *Buchner AM*, *Guarner-Argente C*, *Ginsberg GG*. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc 2012; 76: 255 – 263
25 *Tamura S*, *Nakajo K*, *Yokoyama Y* et al. Evaluation of endoscopic mucosal resection for laterally spreading rectal tumors. Endoscopy 2004; 36: 306 – 312
26 *Fasoulas K*, *Lazaraki G*, *Chatzimavroudis G* et al. Endoscopic mucosal resection of giant laterally spreading tumors with submucosal injection of hydroxyethyl starch: comparative study with normal saline solution. Surg Laparosc Endosc Percutan Tech 2012; 22: 272 – 278
27 *Kao KT*, *Giap AQ*, *Abbas MA*. Endoscopic excision of large colorectal polyps as a viable alternative to surgical resection. Arch Surg 2011; 146: 690 – 696
28 *Arezzo A*, *Pagano N*, *Romeo F* et al. Hydroxy-propyl-methyl-cellulose is a safe and effective lifting agent for endoscopic mucosal resection of large colorectal polyps. Surg Endosc 2009; 23: 1065 – 1069
29 *Mahadeva S*, *Rembacken BJ*. Standard "inject and cut" endoscopic mucosal resection technique is practical and effective in the management of superficial colorectal neoplasms. Surg Endosc 2009; 23: 417 – 422
30 *Moss A*, *Bourke MJ*, *Williams SJ* et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 2011; 140: 1909 – 1918
31 *Seitz U*, *Bohnacker S*, *Seewald S* et al. Long-term results of endoscopic removal of large colorectal adenomas. Endoscopy 2003; 35: 41 – S44
32 *Hotta K*, *Fujii T*, *Saito Y* et al. Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 2009; 24: 225 – 230
33 *Moss A*, *Bourke MJ*, *Metz AJ*. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. Am J Gastroenterol 2010; 105: 2375 – 2382
34 *Ah Soune P*, *Menard C*, *Salah E* et al. Large endoscopic mucosal resection for colorectal tumors exceeding 4 cm. World J Gastroenterol 2010; 16: 588 – 595
35 *Arebi N*, *Swain D*, *Suzuki N* et al. Endoscopic mucosal resection of 161 cases of large sessile or flat colorectal polyps. Scand J Gastroenterol 2007; 42: 859 – 866
36 *Barendse RM*, *van den Broek FJ*, *van Schooten J* et al. Endoscopic mucosal resection vs transanal endoscopic microsurgery for the treatment of large rectal adenomas. Colorectal Dis 2012; 14: e191 – 196
37 *Bergmann U*, *Beger HG*. Endoscopic mucosal resection for advanced non-polypoid colorectal adenoma and early stage carcinoma. Surg Endosc 2003; 17: 475 – 479
38 *Bories E*, *Pesenti C*, *Monges G* et al. Endoscopic mucosal resection for advanced sessile adenoma and early-stage colorectal carcinoma. Endoscopy 2006; 38: 231 – 235
39 *Brooker JC*, *Saunders BP*, *Shah SG* et al. Treatment with argon plasma coagulation reduces recurrence after piecemeal resection of large sessile colonic polyps: a randomized trial and recommendations. Gastrointest Endosc 2002; 55: 371 – 375
40 *Conio M*, *Blanchi S*, *Repici A* et al. Cap-assisted endoscopic mucosal resection for colorectal polyps. Dis Colon Rectum 2010; 53: 919 – 927
41 *Conio M*, *Repici A*, *Demarquay JF* et al. EMR of large sessile colorectal polyps. Gastrointest Endosc 2004; 60: 234 – 241
42 *Dos Santos CEO*, *Malaman D*, *Pereira-Lima JC*. Endoscopic mucosal resection in colorectal lesion: a safe and effective procedure even in lesions larger than 2 cm and in carcinomas. Arquivos de Gastroenterologia 2011; 48: 242 – 247
43 *Ferrara F*, *Luigiano C*, *Ghersi S* et al. Efficacy, safety and outcomes of 'inject and cut' endoscopic mucosal resection for large sessile and flat colorectal polyps. Digestion 2010; 82: 213 – 220
44 *Huang Y*, *Liu S*, *Gong W* et al. Clinicopathologic features and endoscopic mucosal resection of laterally spreading tumors: experience from China. Int J Colorectal Dis 2009; 24: 1441 – 1450
45 *Hurlstone DP*, *Sanders DS*, *Cross SS* et al. A prospective analysis of extended endoscopic mucosal resection for large rectal villous adenomas: an alternative technique to transanal endoscopic microsurgery. Colorectal Dis 2005; 7: 339 – 344
46 *Hurlstone DP*, *Sanders DS*, *Cross SS* et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. Gut 2004; 53: 1334 – 1339
47 *Iishi H*, *Tatsuta M*, *Iseki K* et al. Endoscopic piecemeal resection with submucosal saline injection of large sessile colorectal polyps. Gastrointest Endosc 2000; 51: 697 – 700
48 *Jin HY*, *Wu K*, *Ye H* et al. Size over 20mm is an independent risk factor of endoscopic mucosa resection (EMR) for colorectal lateral spread tumor (LST): A prospective study and multivariate analysis. Cancer Therapy 2009; 7: 27 – 30
49 *Kaltenbach T*, *Friedland S*, *Maheshwari A* et al. Short- and long-term outcomes of standardized EMR of nonpolypoid (flat and depressed) colorectal lesions > or = 1 cm (with video). Gastrointest Endosc 2007; 65: 857 – 865
50 *Katsinelos P*, *Kountouras J*, *Paroutoglou G* et al. Endoscopic mucosal resection of large sessile colorectal polyps with submucosal injection of hypertonic 50 percent dextrose-epinephrine solution. Dis Colon Rectum 2006; 49: 1384 – 1392
51 *Katsinelos P*, *Paroutoglou G*, *Beltsis A* et al. Endoscopic mucosal resection of lateral spreading tumors of the colon using a novel solution. Surg Laparosc Endosc Percutan Tech 2006; 16: 73 – 77
52 *Khashab M*, *Eid E*, *Rusche M* et al. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. Gastrointest Endosc 2009; 70: 344 – 349
53 *Kobayashi N*, *Yoshitake N*, *Hirahara Y* et al. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. J Gastroenterol Hepatol 2012; 27: 728 – 733
54 *Lee EJ*, *Lee JB*, *Lee SH* et al. Endoscopic treatment of large colorectal tumors: comparison of endoscopic mucosal resection, endoscopic mucosal resection-precutting, and endoscopic submucosal dissection. Surg Endosc 2012; 26: 2220 – 2230
55 *Luigiano C*, *Consolo P*, *Scaffidi MG* et al. Endoscopic mucosal resection for large and giant sessile and flat colorectal polyps: a single-center experience with long-term follow-up. Endoscopy 2009; 41: 829 – 835
56 *Mannath J*, *Subramanian V*, *Singh R* et al. Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. Dig Dis Sci 2011; 56: 2389 – 2395
57 *Saito Y*, *Fukuzawa M*, *Matsuda T* et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc 2010; 24: 343 – 352

58 *Sakamoto T*, *Matsuda T*, *Otake Y* et al. Predictive factors of local recurrence after endoscopic piecemeal mucosal resection. J Gastroenterol 2012; 47: 635 – 640
59 *Seo GJ*, *Sohn DK*, *Han KS* et al. Recurrence after endoscopic piecemeal mucosal resection for large sessile colorectal polyps. World J Gastroenterol 2010; 16: 2806 – 2811
60 *Stergiou N*, *Riphaus A*, *Lange P* et al. Endoscopic snare resection of large colonic polyps: how far can we go? Int J Colorectal Dis 2003; 18: 131 – 135
61 *Tajika M*, *Niwa Y*, *Bhatia V* et al. Comparison of endoscopic submucosal dissection and endoscopic mucosal resection for large colorectal tumors. Eur J Gastroenterol Hepatol 2011; 23: 1042 – 1049
62 *Tanaka S*, *Haruma K*, *Oka S* et al. Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm. Gastrointest Endosc 2001; 54: 62 – 66
63 *Terasaki M*, *Tanaka S*, *Oka S* et al. Clinical outcomes of endoscopic submucosal dissection and endoscopic mucosal resection for laterally spreading tumors larger than 20 mm. J Gastroenterol Hepatol 2012; 27: 734 – 740
64 *Woodward TA*, *Heckman MG*, *Cleveland P* et al. Predictors of complete endoscopic mucosal resection of flat and depressed gastrointestinal neoplasia of the colon. Am J Gastroenterol 2012; 107: 650 – 654
65 *Barendse RM*, *van den Broek FJ*, *Dekker E* et al. Systematic review of endoscopic mucosal resection versus transanal endoscopic microsurgery for large rectal adenomas. Endoscopy 2011; 43: 941 – 949
66 *Pohl H*, *Srivastava A*, *Bensen SP* et al. Incomplete polyp resection during colonoscopy – results of the complete adenoma resection (CARE) study. Gastroenterology 2013; 144: 74 – 80
67 *Longcroft-Wheaton G*, *Duku M*, *Mead R* et al. Risk stratification system for evaluation of complex polyps can predict outcomes of endoscopic mucosal resection. Dis Colon Rectum 2013; 56: 960 – 966
68 *Zlatanic J*, *Waye JD*, *Kim PS* et al. Large sessile colonic adenomas: use of argon plasma coagulator to supplement piecemeal snare polypectomy. Gastrointest Endosc 1999; 49: 731 – 735
69 *Regula J*, *Wronska E*, *Polkowski M* et al. Argon plasma coagulation after piecemeal polypectomy of sessile colorectal adenomas: long-term follow-up study. Endoscopy 2003; 35: 212 – 218

Tables e1 and e2 and Appendix e1

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Table e2 Critical appraisal of validity of relevant studies.

Study First author, year	Participation	Loss to follow-up, n/N (%)	Attrition	Outcome	Total
Ah Soune, 2010	++	2/26 (7.7)	+	++	++
Arebi, 2007	+	12/157 (7.6)	+	±	±
Barendse, 2012	++	15/73 (20.5)	-	±	±
Bergmann, 2003	+	0/65 (0.0)	±	±	±
Bories, 2006	++	10/43 (20.9)	–	±	±
Brooker, 2002	++	0/34 (0.0)	+	++	++
Conio, 2010	++	16/232 (6.9)	±	+	+
Conio, 2004	++	26/122 (21.3)	±	±	±
Dos Santos, 2011	+	44/166 (26.5)	–	++	±
Ferrara, 2010	++	0/172 (0.0)	+	+	+
Higaki, 2003	++	1/24 (4.2)	++	++	++
Huang, 2009	+	20/99 (20.2)	–	+	±
Hurlstone, 2004	+	0/58 (0.0)	+	++	++
Hurlstone, 2005	++	0/62 (0.0)	+	++	++
Iishi, 2000	++	18/73 (13.7)[1]	–	±	±
Jin, 2009	++	0/94 (0.0)	+	±	+
Kaltenbach, 2007	++	18/95 (18.9)	±	+	+
Katsinelos, 2006	++	0/52 (0.0)	+	±	+
Katsinelos, 2006	+	0/19 (0.0)	+	+	+
Khashab, 2009	++	77/209 (36.8)[2]	±	+	+
Kobayashi, 2012	±	155/373 (41.6)[3]	±	+	±
Lee, 2012	++	16/129 (12.4)	–	+	±
Luigiano, 2009	++	26/174 (14.9)[4]	+	++	++
Mannath, 2011	++	32/137 (23.4)[5]	–	+	±
Moss, 2010	++	0/71 (0.0)	+	±	+
Saito, 2010	+	151/379 (39.8)[6]	±	±	±
Sakamoto, 2012	++	71/293 (24.2)[7]	–	±	±
Seo, 2010	++	2/46 (4.7)	±	++	+
Stergiou, 2003	+	0/40 (0.0)	+	–	±
Tajika, 2011	+	26/130 (20.0)[8]	–	+	±
Tanaka, 2001	±	0/78 (0.0)	+	+	±
Terasaki, 2012	++	0/176 (0.0)	+	±	+
Woodward, 2012	+	0/423 (0.0)	++	±	+

N/A, not applicable.
Potential bias was scored as follows: ++ very small risk; + small risk; ± moderate risk; – high risk.
Studies were scored for potential bias from three sources.
Study participation: adequate description of:
– recruitment, including setting and period
– inclusion and exclusion criteria
– baseline characteristics of patients and lesions.
Study attrition:
– numbers and percentages lost to follow-up
– adequate description of reasons for loss to follow-up
– adequate description of population lost to follow-up and comparison with population in follow-up.
Outcome measurement and data reporting:
– clear definition of outcome measure
– adequate reporting of length of follow-up
– use of a fixed follow-up schedule for all patients
– adequate reporting of outcome.
[1] 18 patients without follow-up were excluded from the study.
[2] 77 patients without follow-up were excluded from the study.
[3] Of 373 consecutive lesions between 2000 and 2009, 155 were lost to follow-up. Of 218 remaining cases, 56 were selected.
[4] 24 patients were excluded from the study, because they were hospitalized in other institutions.
[5] 32 patients (34 lesions) without follow-up were excluded from the study.
[6] 151 lesions without follow-up were excluded from the study.
[7] 54 patients (71 lesions) without follow-up were excluded from the study.
[8] 26 lesions without follow-up were excluded from the study.

Appendix e1
Search strategy for PubMed, EMBASE, and the Cochrane Library

▼

PubMed

(((colon [MESH] OR colon [tiab] OR rectum [MESH] OR rectum [tiab] OR colorectum [tiab] OR colonic [tiab] OR rectal [tiab] OR colorectal [tiab]) AND (adenoma [MESH] OR adenoma [tiab] OR adenomas [tiab] OR adenomatous [tiab] OR adenomata [tiab] OR adenomatous polyps [MESH] OR polyps [tiab] OR polyp [tiab] OR lesion [tiab] OR lesions [tiab] OR tumor [tiab] OR tumors [tiab] OR tumour [tiab] OR tumours [tiab] OR neoplasm [tiab] OR neoplasms [tiab])) OR (colonic polyps [MESH] OR colorectal neoplasms [MESH])) AND (Remov* [tiab] OR resect* [tiab] OR polypectomy [tiab] OR polypectomies [tiab] OR EMR [tiab] OR excision [tiab] OR excisions [tiab]) AND (colonoscopy [MESH] OR colonoscopy [tiab] OR colonoscopic [tiab] OR endoscopy [MESH] OR endoscopy [tiab] OR endoscopic [tiab]) AND (recurrence [MESH] OR neoplasm recurrence, local [MESH] OR recur* [tiab] OR reoccur* [tiab] OR incomplete [tiab] OR incompleteness [tiab] OR complete [tiab] OR completeness [tiab] OR clear* [tiab]) AND English[Language]
Filter: Publication date from 2000/01/01

EMBASE

((('colon'/exp OR colon:ab,ti OR 'rectum'/exp OR rectum:ab,ti OR colorectum:ab,ti OR colonic:ab,ti OR rectal:ab,ti OR colorectal:ab,ti) AND ('adenoma'/exp OR adenoma:ab,ti OR adenomas:ab,ti OR adenomatous:ab,ti OR adenomata:ab,ti OR 'adenomatous polyp'/exp OR polyps:ab,ti OR polyp:ab,ti OR lesion:ab,ti OR lesions:ab,ti OR tumor:ab,ti OR tumors:ab,ti OR tumour:ab,ti OR tumours:ab,ti OR neoplasm:ab,ti OR neoplasms:ab,ti)) OR ('colon tumor'/exp OR 'rectal tumor'/exp)) AND (remov*:ab,ti OR resect*:ab,ti OR polypectomy:ab,ti OR polypectomies:ab,ti OR emr:ab,ti OR excision:ab,ti OR excisions:ab,ti) AND ('colonoscopy'/exp OR colonoscopy:ab,ti OR colonoscopic:ab,ti OR 'endoscopy'/exp OR endoscopy:ab,ti OR endoscopic:ab,ti) AND ('recurrent disease'/exp OR 'tumor recurrence'/exp OR recur*:ab,ti OR reoccur*:ab,ti OR residual:ab,ti OR incomplete:ab,ti OR incompleteness:ab,ti OR complete:ab,ti OR completeness:ab,ti OR clear*:ab,ti)
AND [english]/lim AND [embase]/lim NOT [medline]/lim AND [1-1-2000]/sd NOT [1-1-3000]/sd AND ('article'/it OR 'article in press'/it OR 'review'/it)

The Cochrane Library

(((colon OR rectum OR colorectum OR colonic OR rectal OR colorectal) AND (adenoma OR adenomas OR adenomatous OR adenomata OR polyps OR polyp OR lesion OR lesions OR tumor OR tumors OR tumour OR tumours OR neoplasm OR neoplasms OR "adenomatous polyps")) OR ("colonic polyps" OR "colorectal neoplasms")) AND (remov* OR resect* OR polypectomy OR polypectomies OR EMR OR excision OR excisions):ti,ab,kw AND (colonoscopy OR colonoscopic OR endoscopy OR endoscopic):ti,ab,kw AND (Recur* OR reoccur* OR residual OR incomplete OR incompleteness OR complete OR completeness OR clear* OR "neoplasm recurrence, local"):ti,ab,kw from 2000 – 2012 in Trials