Efficacy and Safety of Endoscopic Resection Therapies for Rectal Carcinoid Tumors: A Meta-Analysis

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Purpose: Several endoscopic resection therapies have been applied for the treatment of rectal carcinoid tumors. However, there is currently no consensus regarding the optimal strategy. We performed a meta-analysis to compare the efficacy and safety of endoscopic mucosal resection (EMR) or modified EMR (m-EMR) versus endoscopic submucosal dissection (ESD) for the treatment of rectal carcinoid tumors.

Materials and Methods: PubMed, Web of Science, Medline, Embase and CNKI were searched up to the end of January 2014 in order to identify all studies on the effects of EMR (or m-EMR) and ESD on rectal carcinoid tumors.

Results: A total of fourteen studies involving 782 patients were included. The pooled data suggested a significantly higher rate of pathological complete resection among patients treated with ESD or m-EMR than those treated with EMR [odds ratio (OR)=0.42, 95% confidence interval (CI): 0.25–0.71; OR=0.10, 95% CI: 0.03–0.33, respectively], while there was no significant difference between the m-EMR group and ESD group (OR=1.19, 95% CI: 0.49–2.86); The procedure time of ESD was longer than EMR or m-EMR groups [mean differences (MD)=-11.29, 95% CI: -14.19 – -8.38, MD=-10.90, 95% CI: -18.69 – -3.11, respectively], but it was insignificance between the EMR and m-EMR groups. No significant differences were detected among the treatment groups with regard to complications or recurrence.

Conclusion: The results of this meta-analysis suggest that treatment of rectal carcinoid tumors with ESD or m-EMR is superior to EMR, and the efficacy of m-EMR is equivalence to ESD treatment. However, more well-designed studies are needed to confirm these findings.

Key Words: Endoscopic submucosal dissection, endoscopic mucosal resection, rectal carcinoid tumor, meta-analysis

INTRODUCTION

Rectal carcinoid tumors are uncommon neuroendocrine neoplasms and they account for approximately 10% to 17% of all carcinoid tumors.1,2 Generally, they are found incidentally during colonoscopy as submucosal tumors covered with yellow-discolored mucosa. The number of incidence of carcinoid tumors of the gastrointestinal tract has increased over the past five decades, due in part to rapid advances in screening endoscopy.3,4 Approximately 80% of rectal carcinoid tumors are smaller than 1 cm in diameter, without invasion or metastasis at the time of di-
Endoscopic Resection Therapy for Rectal Carcinoid Tumor

Materials and Methods

Search Strategy
A literature search was conducted using PubMed, Web of Science, Medline, Embase and CNKI up to January 2014 without language restrictions. Relevant studies were identified using the following terms: “endoscopic submucosal dissection or ESD”, “endoscopic mucosal resection or EMR”, and “rectal carcinoid tumor or rectal neuroendocrine tumor”. The search was restricted to human subjects. Additional studies were identified using a hand search of references of original or review articles and international conferences on this topic, primarily including Asian Pacific Digestive Week, United European Gastroenterology Week and American Gastroenterological Association Digestive Disease Week.

Inclusion and Exclusion Criteria
Studies were included if they met the following criteria: 1) including patients with rectal carcinoid tumors, 2) including a comparison of EMR or m-EMR therapy with ESD for rectal carcinoid tumors, and 3) presenting detailed outcomes of two groups or including such data for calculation in the article text. Meanwhile, the major exclusion criteria were: 1) an unclear study population or trial size, 2) study without extractable data, and 3) case reports, editorials, commentaries, reviews or abstracts only.

Data Extraction
Two investigators (He L and Deng T) independently extracted the data and reached a consensus for all items. If the investigators generated different results, they checked the data again and had a discussion in order to reach an agreement. If they were unable to reach an agreement, an expert was invited to join the discussion. The following data were extracted from the selected studies: the first author’s name, year of publication, country of origin, treatment, patients in the two groups, age, gender, tumor size limit, mean size of the tumor (endoscopic and pathological), numbers of complete resections (endoscopic and pathological), procedure time, numbers of bleeding, perforation, recurrence, and follow-up time.

Statistical Analysis
The efficacy and safety of ESD therapy compared with EMR or m-EMR for the treatment of rectal carcinoid tumors was estimated for each study using the odds ratio (OR) and 95% confidence interval (95% CI). The mean differences (MD) with 95% CI were used for continuous variables (tumor size and procedure time). The Z-test-based Q statistic test was performed to assess the between-study heterogeneity. We also quantified the effect heterogeneity according to the F test. When a significant Q test (p<0.05) or F >50% indicated heterogeneity across studies, the random effects model was used. Otherwise, the fixed effects model was applied. An analysis of sensitivity was performed in order to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg’s funnel plot and Egger’s regression test. A p value of <0.05 was regarded as being statistically significant.

All statistical analyses were performed using the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study Characteristics
A total of 637 citations were identified in the search. Accord-
Compete resection rate and pooled data suggested a significantly higher rate of complete resection among patients treated with ESD or m-EMR than among those treated with EMR (OR = 0.42, 95% CI: 0.25–0.71; OR = 0.10, 95% CI: 0.03–0.33, respectively), while there was no significant difference between the m-EMR group and ESD group (OR = 1.19, 95% CI: 0.49–2.86) (Table 2, Fig. 1).

Twelve studies with available data reported endoscopically complete resection rate. The results showed that the complete resection rates were significantly higher in the ESD or m-EMR group compared with the EMR group (OR = 0.28, 95% CI: 0.11–0.70; OR = 0.33, 95% CI: 0.14–0.76, respectively).

### Quantitative data synthesis

#### Complete resection rate

Ten studies with available data reported pathologically complete resection rate and pooled data suggested a significantly higher rate of complete resection among patients treated with ESD or m-EMR than among those treated with EMR (OR = 0.42, 95% CI: 0.25–0.71; OR = 0.10, 95% CI: 0.03–0.33, respectively), while there was no significant difference between the m-EMR group and ESD group (OR = 1.19, 95% CI: 0.49–2.86) (Table 2, Fig. 1).

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### Table 1. Characteristics of the Included Studies

| Study       | Yr  | Country | Treatment          | Patients | No. of treated tumors | Age, mean±SD, yr | Gender (male/female) | Size limit (mm) | Mean size of the tumor, mean±SD, mm |
|-------------|-----|---------|-------------------|----------|-----------------------|------------------|---------------------|----------------|-------------------------------------|
|             |     |         |                   |          |                       |                  |                     |                | Endoscopic                         |
|             |     |         |                   |          |                       |                  |                     |                | Pathological                       |
| Back        | 2010 | Korea   | EMR               | 9        | 9                     | 47.6 (32–64)     | 7/2                 | 10             | 8.8 (5–13)                         |
|             |     |         | ESD               | 3        | 3                     |                  | 2/1                 |                |                                     |
| Choi, et al.| 2013 | Korea   | EMR-B             | 29       | 29                    | 47.75±11.73      | 15/14               | 10             | 4.3±1.75                            |
|             |     |         | ESD               | 31       | 31                    | 48.29±14.44      | 20/11               | 5.2±2.09        |
| Dou, et al. | 2013 | China   | EMR               | 24       | 26                    | 49.0±8.3         | 15/9                | 20             | 5.6±1.2                            |
|             |     |         | ESD               | 19       | 20                    | 48.6±9.0         | 10/9                | 7.4±5.3         |
| Kim, et al. | 2008 | Korea   | EMR               | 6        | 6                     | 46.7±10.8        | 3/3                 | 15             | 5.5±2.3                            |
|             |     |         | ESD               | 2        | 2                     | 46.0±11.3        | 1/1                 |                | 6.5±4.9                            |
| Kim, et al. | 2012 | Korea   | EMR               | 55       | 55                    | 48.8±13.9        | 35/20               | 10             | 6.3±2.5                            |
|             |     |         | ESMR-L             | 45       | 45                    | 53.5±10.4        | 31/14               | 5.9±2.0         |
| Kim, et al. | 2013 | Korea   | EMR               | 31       | 31                    | 47.74±11.52      | 20/11               | 10             | 6.77±1.75                         |
|             |     |         | ESMR-L             | 40       | 40                    | 48.15±8.87       | 23/17               | 6.33±1.75       |
|             |     |         | ESD               | 44       | 44                    | 47.18±10.22      | 32/12               | 5.91±1.83       |
|             |     |         |                   |          |                       |                  |                     |                | 4.27±1.88                         |
| Lee, et al. | 2010 | Korea   | EMR               | 28       | 28                    | 49.0±10.3        | 14/14               | 15             | NR                                  |
|             |     |         | ESD               | 46       | 46                    | 48.6±12.0        | 21/25               | 6.4±2.7         |
|             |     |         |                   |          |                       |                  |                     |                | NR                                  |
|             |     |         |                   |          |                       |                  |                     |                | 6.2±3.1                            |
| Lee, et al. | 2013 | Korea   | EMR               | 44       | 44                    | 51.4±12.3        | 25/19               | 16             | 6.4±2.7                            |
|             |     |         | ESD               | 26       | 26                    | 47.4±10.6        | 22/4                | 6.2±4.1         |
|             |     |         |                   |          |                       |                  |                     |                | NR                                  |
| Niimi, et al.| 2012 | Japan   | EMR               | 11       | 11                    | 45.5±10.6        | 8/3                | 10             | 5.7±2.05                           |
|             |     |         | ESD               | 13       | 13                    | 55.3±8.6         | 9/4                | 5.4±1.4         |
| Onozato, et al. | 2010 | Japan  | Two-channel EMR   | 24       | 26                    | 58.3 (31–87)     | 18/6               | 10             | 6.6±2.1                            |
|             |     |         | ESD               | 9        | 9                     | 7/2               |                     | 6.7±1.0         |
| Park, et al. | 2010 | Korea   | EMR               | 62       | 62                    | 51±12             | 42/20               | 16             | 7±2.2                              |
|             |     |         | ESD               | 31       | 31                    | 50±8              | 18/13               | 6.8±2.4         |
| Sung, et al. | 2012 | Korea   | Two-channel EMR   | 58       | 58                    | 52.3±12.0        | 48/29*              | 15             | 7±2.8                              |
|             |     |         | ESD               | 5        | 5                     |                  |                     |                | NR                                  |
| Zhao, et al. | 2012 | China   | EMR               | 10       | 10                    | 54.04±11.58      | 21/9*               | 10             | NR                                  |
|             |     |         | EMR-C              | 10       | 10                    |                  |                     |                | NR                                  |
| Zhou, et al. | 2010 | China   | EMR               | 23       | 23                    | 50.3±13.6        | 14/9               | 10             | 6.7±2.1                            |
|             |     |         | ESD               | 20       | 20                    | 47.6±18.5        | 12/8               | 7.2±1.9         |

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EMR-B, EMR using a band-ligation device; EMR-C, EMR using a transparent cap; EMR-D, EMR using a dual-channel endoscope; EMR-L, EMR with a ligation device; ESMR-L, endoscopic submucosal resection with a ligation device; NR, not reported.

*No. of all groups.
## Table 2. Efficacy and Safety of ESD or EMR (m-EMR)

| Study          | Year | Country | Treatment | Patients | No. of treated tumors | No. of complete resections, n (%) | Margin involvement, n (%) | Procedure time (mins) |
|----------------|------|---------|-----------|----------|-----------------------|-----------------------------------|--------------------------|----------------------|
|                |      |         |           |          | Endoscopic Pathological | Lateral Vertical Both |                       |                      |
| Baek          | 2010 | Korea   | EMR       | 9        | 9                     | NR 9 (100) 0 (0) 0 (0) | NR                     | 32.6±10.5            |
|               |      |         | ESD       | 3        | 3                     | NR 3 (100) 0 (0) 0 (0) | NR                     |                      |
| Choi, et al.  | 2013 | Korea   | EMR       | 29       | 29                    | NR 24 (82.8) 2 (6.9) 1 (3.4) 2 (6.9) | 6.3±3.52               | 15.09±5.73          |
|               |      |         | ESD       | 31       | 31                    | NR 25 (80.6) 0 (0) 6 (19.4) 0 (0) | NR                     |                      |
| Dou, et al.   | 2013 | China   | EMR       | 24       | 26                    | 26 (100) 0 (0) 0 (0) 0 (0) | 8.9±6.3                |                      |
|               |      |         | ESD       | 19       | 20                    | 20 (100) 19 (95) 0 (0) 1 (5) 0 (0) | NR                     | 32.6±10.5            |
| Kim, et al.   | 2008 | Korea   | EMR-C     | 6        | 6                     | 6 (100) NR 1 (16.7) - - | -                      | 5.0±0.8              |
|               |      |         | ESD       | 2        | 2                     | 2 (100) NR 1 (50) - - | -                      |                      |
| Kim, et al.   | 2012 | Korea   | EMR       | 55       | 55                    | 50 (91) 36 (65.5) 3 (5.5) 19 (34.5) | 4.8±0.9                |
|               |      |         | ESMR-L    | 45       | 45                    | 45 (100) 42 (93.3) 1 (2.2) 2 (4.4) | -                      |                      |
| Kim, et al.   | 2013 | Korea   | EMR       | 31       | 31                    | 24 (77.4) 24 (77.4) 1 (3.2) 7 (22.6) | 3.50±2.06              |
|               |      |         | ESMR-L    | 40       | 40                    | 38 (95) 40 (100) 0 (0) 0 (0) | -                      | 11.7±4.58            |
|               |      |         | ESD       | 44       | 44                    | 43 (97.7) 43 (97.7) 0 (0) 1 (2.3) | -                      | 9.38±4.09            |
| Lee, et al.   | 2010 | Korea   | EMR       | 28       | 28                    | 25 (89.3) 18 (64.3) 2 (7.1) 8 (28.6) | 12.0±12.9             |
|               |      |         | ESD       | 46       | 46                    | 46 (100) 38 (82.6) 0 (0) 7 (15.2) | -                      | 18.9±7.3             |
| Lee, et al.   | 2013 | Korea   | EMR       | 44       | 44                    | 44 (100) 38 (86.3) 1 (2.3) 4 (9.1) 1 (2.3) | 9.75±7.11             |
|               |      |         | ESD       | 26       | 26                    | 26 (100) 23 (88.4) 0 (0) 3 (11.5) 0 (0) | 22.38±7.56            |
| Niimi, et al. | 2012 | Japan   | EMR-L     | 11       | 11                    | 11 (100) 11 (100) 0 (0) 0 (0) 0 (0) | -                      | 17.4±4.4             |
|               |      |         | ESD       | 13       | 13                    | 13 (100) 12 (92.3) 0 (0) 1 (7.7) 0 (0) | -                      | 28.6±16.2            |
| Onozato, et al.| 2010 | Japan   | ESD       | 9        | 9                     | 7 (77.8) NR 0 (0) 2 (22.2) | -                      | 25.6±8.8             |
| Park, et al.  | 2010 | Korea   | EMR       | 62       | 62                    | 59 (95.2) 44 (71) 0 (0) 15 (24.2) 3 (4.8) | 4.2±3.2               |
|               |      |         | ESD       | 31       | 31                    | 31 (100) 28 (90.3) 0 (0) 2 (6.5) 1 (3.2) | 11.4±3.7              |
| Sung, et al.  | 2012 | Korea   | EMR       | 14       | 14                    | 10 (71.4) NR 4 (28.6) - - | -                      | NR                   |
|               |      |         | ESMR-L    | 58       | 58                    | 58 (100) NR 15 (25.9) - - | -                      |                      |
| Zhao, et al.  | 2012 | China   | EMR       | 10       | 10                    | 8 (80) NR 2 (20) - - - | 13.4±17.1             |
|               |      |         | ESMR-C    | 10       | 10                    | 10 (100) NR 0 (0) - - - | 5.2±0.78              |
| Zhou, et al.  | 2010 | China   | EMR       | 23       | 23                    | 20 (87) 12 (52.2) 0 (0) 8 (34.8) 3 (13.0) | 12.3±15.4             |
|               |      |         | ESD       | 20       | 20                    | 20 (100) 20 (100) 0 (0) 0 (0) 0 (0) | 28.4±17.2             |

| Study          | Year | Country | Treatment | Patients | No. of treated tumors | No. of bleedings | No. of perforations | No. of recurrence | Follow-up time (month) |
|----------------|------|---------|-----------|----------|-----------------------|-----------------|-------------------|-------------------|------------------------|
| Baek          | 2010 | Korea   | EMR       | 9        | 9                     | 0 0 0 | 0 | 0 | 28 (15–45)          |
|               |      |         | ESD       | 3        | 3                     | 0 0 0 | 0 | 0 |                      |
| Choi, et al.  | 2013 | Korea   | EMR-B     | 29       | 29                    | 0 0 NR | 0 | NR |                      |
|               |      |         | ESD       | 31       | 31                    | 1 0 NR | 0 | NR |                      |
| Dou, et al.   | 2013 | China   | EMR       | 24       | 26                    | 4 0 0 | 0 | 0 | 3–27                  |
| Kim, et al.   | 2008 | Korea   | EMR-C     | 6        | 6                     | NR NR 0 | 0 | NR | 6.8±3.3              |
|               |      |         | ESD       | 2        | 2                     | NR NR 0 | 0 | NR | 5.0±2.8              |
| Kim, et al.   | 2012 | Korea   | EMR       | 55       | 55                    | 0 0 NR | 0 | NR |                      |
|               |      |         | ESMR-L    | 45       | 45                    | 2 0 NR | 0 | NR |                      |
| Kim, et al.   | 2013 | Korea   | EMR       | 31       | 31                    | 0 0 0 | 0 | 0 | 13.1 (6–59)          |
|               |      |         | ESMR-L    | 40       | 40                    | 0 1 0 | 0 | 0 |                      |
|               |      |         | ESD       | 44       | 44                    | 0 0 0 | 0 | 0 |                      |
and m-EMR group (MD=0.80, 95% CI: 0.09–1.51).

**Procedure time**

Eleven studies reported the procedure time of various treatments. The procedure time of ESD was longer than that of EMR or m-EMR groups (MD=-11.29, 95% CI: -14.19–-8.38; MD=-10.90, 95% CI: -18.69 ‒ -3.11, respectively), but the procedure time was not different between the EMR and m-EMR groups (MD=-1.36, 95% CI: -8.66‒5.94) (Table 2, Fig. 2).

**Complications**

Eleven studies reported available data of complications (bleeding and perforation). Of those, bleeding occurred in 11 cases in the EMR group (11/349), 2 cases in the m-EMR group (2/160), and 6 cases in the ESD group (6/253), while perforation occurred in 2 cases in the EMR group (2/349), 1 case in the m-EMR group (1/160), and 4 cases in the ESD group (4/253). The pooled data showed no significant difference in all comparisons among the three groups (EMR vs. ESD: bleeding: OR=1.39, 95% CI: 0.54‒3.57; perforation: OR=0.51, 95% CI: 0.14–1.92, m-EMR vs. ESD: bleeding: OR=0.64, 95% CI: 0.14–2.87; perforation: OR=3.38, 95%}

**Table 2. Continued**

| Study          | Yr  | Country | Treatment       | Patients | No. of treated tumors | No. of bleedings | No. of perforations | No. of recurrence | Follow-up time (month) |
|----------------|-----|---------|----------------|----------|-----------------------|------------------|--------------------|---------------------|------------------------|
| Lee, et al.    | 2010| Korea   | EMR            | 28       | 28                    | 1                | 0                  | 1                   | 23 (3–63)              |
|                |     |         | ESD            | 46       | 46                    | 2                | 1                  | 0                   |                        |
| Lee, et al.    | 2013| Korea   | EMR-D          | 44       | 44                    | 1                | 0                  | 0                   | 8 (1–58)               |
|                |     |         | ESD            | 26       | 26                    | 2                | 0                  | 0                   |                        |
| Niimi, et al.  | 2012| Japan   | EMR-L          | 11       | 11                    | 1                | 0                  | 1                   | 24.0±32.5              |
|                |     |         | ESD            | 13       | 13                    | 0                | 0                  | 0                   | 65.1±57.0              |
| Onozato, et al.| 2010| Japan   | Two-channel EMR| 24       | 26                    | 0                | 0                  | 0                   | 70.1±30.7              |
|                |     |         | ESD            | 9        | 9                     | 0                | 0                  | 0                   |                        |
| Park, et al.   | 2010| Korea   | EMR            | 62       | 62                    | 4                | 1                  | 0                   | 33 (3–117)             |
|                |     |         | ESD            | 31       | 31                    | 1                | 1                  | 0                   | 12.6 (6–24)            |
| Sung, et al.   | 2012| Korea   | EMR            | 14       | 14                    | NR               | NR                 | NR                  | 18.5 (5–107)           |
|                |     |         | Two-channel EMR| 58       | 58                    | NR               | NR                 | NR                  |                        |
|                |     |         | ESD            | 5        | 5                     | NR               | NR                 | NR                  |                        |
| Zhao, et al.   | 2012| China   | EMR            | 10       | 10                    | 0                | 0                  | 0                   | 18.43±9.76             |
|                |     |         | EMR-C          | 10       | 10                    | 0                | 0                  | 0                   |                        |
|                |     |         | ESD            | 10       | 10                    | 0                | 0                  | 0                   |                        |
| Zhou, et al.   | 2010| China   | EMR            | 23       | 23                    | 0                | 0                  | 0                   | 42.6±26.1              |
|                |     |         | ESD            | 20       | 20                    | 0                | 1                  | 0                   | 18.7±10.6              |

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EMR-B, EMR using a band-ligation device; EMR-C, EMR using a transparent cap; EMR-D, EMR using a dual-channel endoscope; EMR-L, EMR with a ligation device; ESD-L, endoscopic submucosal resection with a ligation device; NR, not reported.

However, we failed to detect any difference between the ESD and m-EMR groups (OR=0.65, 95% CI: 0.18–2.34).

In addition, margin involvement was found in 84 cases in the EMR group (84/427), in 31 cases in the m-EMR group (31/224) and in 25 cases in the ESD group (25/260). The pooled data showed that the residual tumor positive rate in EMR group was higher than that in m-EMR or ESD group (EMR vs. ESD: OR=2.24, 95% CI: 1.38–3.63, EMR vs. m-EMR: OR=5.21, 95% CI: 1.17–23.18); whereas there was no obvious difference between the m-EMR group and ESD group (OR=0.89, 95% CI: 0.43–1.85).

**Tumor size**

Ten studies with available data reported endoscopic mean sizes of the tumor. There was no significant difference in all comparisons among the three groups (EMR vs. ESD: MD=0.11, 95% CI: -0.51–0.30, m-EMR vs. ESD: MD=-0.23, 95% CI: -0.70–0.24, EMR vs. m-EMR: MD=-0.42, 95% CI: -0.18–1.02). Five studies reported pathological mean sizes of the tumor, and similar results were found between EMR or m-EMR and ESD treatment (MD=0.24, 95% CI: -0.36–0.85; MD=0.45, 95% CI: -1.18–0.29, respectively), however, significant difference was detected between EMR and m-EMR group (MD=0.80, 95% CI: 0.09–1.51).
Sensitivity analysis and publication bias

The sensitivity analysis performed using sequential excluding of one study at a time did not alter the results. Then, Begg’s funnel plot and Egger’s test were performed to assess the potential publication bias in the available literature. The shape of the funnel plots did not reveal any evidence of asymmetry (data not shown). Egger’s test also showed no statistical significance in evaluation of publication bias (endoscopic complete resection: $p=0.276$; pathological complete resection: $p=0.895$).

DISCUSSION

Carcinoid tumors of the rectum are rare, representing only 0.13–85.37, EMR vs. m-EMR: bleeding: OR=0.16, 95% CI: 0.01–3.35; perforation: OR=0.42, 95% CI: 0.02–10.62) (Table 2, Fig. 3A and B).

Recurrence

Eleven studies reported available data of recurrence during the follow-up time. Recurrence occurred in 5 cases in the EMR group (5/326), 1 case in the m-EMR group (1/137), and none in the ESD group (0/224), and the differences were not statistically significant (EMR vs. ESD: OR=5.39, 95% CI: 0.86–33.61, m-EMR vs. ESD: OR=3.86, 95% CI: 0.14–104.65) (Table 2, Fig. 3C). With regard to EMR vs. m-EMR, two studies listed the data and showed no recurrence in both EMR group and m-EMR group, and there was no significant difference between them (Table 2).
Table: Mean difference in treatment outcomes for rectal carcinoid tumors

| Study or subgroup | EMR (Mean, SD, Total) | ESD (Mean, SD, Total) | Weight (%) | Mean difference (IV, random, 95% CI) |
|------------------|-----------------------|-----------------------|------------|-------------------------------------|
| Choi 2013        | 6.37, 3.52, 29        | 15.09, 5.73, 31      | 12.5       | -8.72 [-11.11, -6.33]               |
| Dou 2013         | 8.9, 6.3, 26          | 10.5, 10.5, 20       | 10.1       | -23.70 [-28.90, -18.50]             |
| Kim 2013         | 3.5, 2.06, 31         | 9.38, 4.09, 44       | 14.4       | -5.88 [-7.29, -4.47]                |
| Lee 2010         | 12, 12.9, 28          | 18.9, 7.3, 46        | 10.1       | -9.60 [-12.12, -1.68]               |
| Lee 2013         | 9.75, 7.11, 44        | 22.38, 7.56, 26      | 12.1       | -12.63 [-16.22, -9.04]              |
| Niimi 2012       | 17.4, 4.4, 11         | 28.6, 16.2, 13       | 6.0        | -11.20 [-20.38, -2.02]              |
| Onozato 2010     | 9.3, 2.2, 26          | 25.6, 8.8, 9         | 9.3        | -16.30 [-22.11, -10.49]             |
| Park 2010        | 4.2, 3.2, 62          | 11.4, 3.7, 31        | 14.3       | -7.20 [-8.73, -5.67]                |
| Zhao 2012        | 13.4, 17.1, 10        | 24.9, 5.78, 10       | 4.6        | -11.50 [-22.69, -0.31]              |
| Zhou 2010        | 12.3, 15.4, 23        | 28.4, 17.2, 20       | 5.5        | -16.10 [-25.92, -6.28]              |
| Total (95% CI)   | 290                   | 250                  | 100.0      | -11.29 [-14.19, -8.38]              |

Heterogeneity: Tau²=14.69; Chi²=62.98, df=9 (p<0.00001); I²=98%

Test for overall effect: Z=7.62 (p<0.00001)

Fig. 2. Forest plots comparing treatment of rectal carcinoid tumors with ESD or EMR (or m-EMR) in terms of the procedure time. (A) ESD vs. EMR. (B) ESD vs. m-EMR. (C) EMR vs. m-EMR. ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; m-EMR, modified EMR; CI, confidence interval.

1.8% of anorectal neoplasms, and present a special therapeutic problem. Most rectal carcinoid tumors are small, with 66% being less than 1 cm in diameter. As for the small tumor (<1 cm), the risk of metastatic disease is very low and local treatment is thus thought to be curative. Up to now, various endoscopic resection procedures, such as an endoscopic polypectomy, EMR, ESD, and m-EMR (such as EMR-B, EMR-C, EMR-D, EMR-L, and ESMR-L) have all been described as effective treatments for rectal carcinoid tumors. However, there are no specific recommendations for treatment choices in rectal carcinoid tumors.

The ESD technique was developed for en bloc resection of mucosal tumors of the gastrointestinal tract and has been applied specifically to early gastric cancer. It has also been applied to resecting tumors extending to a portion of the submucosal layer because both the horizontal margin and the submucosal layer beneath the tumors can be visualized directly during the procedure. However, ESD is difficult for several reasons, including technical difficulty, lack of surgeon expertise, and the need for specific devices. Compared to ESD, EMR is simple, useful and safe for small and superficial neoplasms confined to the mucosa or superficial submucosa in the colorectum. However, its feasibility is still uncertain because of potential problem of incomplete excision. To improve resectability, various modified EMR have been utilized and could provide wider and deeper resection.

In this study, a total of fourteen studies involving 782 patients were included. Complete resection is crucial in guaranteeing a curative treatment for rectal carcinoid tumors. We
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| Study or subgroup | Events | Total | Weight (%) | Odds ratio M-H, fixed, 95% CI |
|-------------------|--------|-------|------------|-----------------------------|
| Baek 2010         | 0      | 9     |            | Not estimable               |
| Choi 2013         | 0      | 29    |            | Not estimable               |
| Dou 2013          | 4      | 26    |            | 6.3  [0.20, 161.83]         |
| Kim 2013          | 0      | 71    |            | Not estimable               |
| Lee 2010          | 1      | 28    |            | 19.6  [0.81, 4.92]          |
| Lee 2013          | 1      | 44    |            | 32.9  [0.28, 3.24]          |
| Niimi 2012        | 1      | 11    |            | 5.4  [0.36, 104.65]         |
| Onozato 2010      | 0      | 26    |            | Not estimable               |
| Park 2010         | 4      | 62    |            | 16.7  [2.07, 19.34]         |
| Zhao 2012         | 0      | 20    |            | Not estimable               |
| Zhou 2010         | 0      | 23    |            | Not estimable               |
| Total (95% CI)    | 349    | 253   | 100.0      | 1.39  [0.54, 3.57]          |

Total events 11

Heterogeneity: Chi²=4.39; df=5 (p=0.49); I²=0%

Test for overall effect: Z=0.68 (p=0.50)

Fig. 3. Forest plots comparing treatment of rectal carcinoid tumors with ESD or EMR in terms of the complications or recurrence. (A) Bleeding. (B) Perforations. (C) Recurrence. ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; CI, confidence interval.
found significantly higher rate of pathologically complete resection among patients treated with ESD or m-EMR than among those treated with EMR, while there was no significant difference between the m-EMR and ESD group; similarly, endoscopically complete resection rates were significantly higher in the ESD or m-EMR group compared with the EMR group, and we failed to detect any difference between ESD and m-EMR groups. We also observed that residual tumor positive rate in EMR group was higher than that in m-EMR or ESD group, and no obvious difference was detected between m-EMR and ESD groups. In addition, the mean tumor sizes (both pathological and endoscopic) before resection were not significantly different among these groups. In general, it has been demonstrated that ESD is a time consuming procedure. In this study, the procedure time in ESD group was longer than EMR or m-EMR groups, but there was no difference between EMR and m-EMR groups. The above results were in line with two previous meta-analyses. However, in the current meta-analysis, we conducted a comprehensive literature search in different databases and included several additional studies, which allowed for a larger number of subjects and more precise risk estimation.

Bleeding and perforation are main complications of endoscopic resection, especially for ESD. In this study, we found no significant differences among the treatment groups. These results can be explained as follows: first, most rectal carcinoid tumors are smaller than 1 cm in diameter, without invasion or metastasis at the time of diagnosis, therefore, the resection size is relatively small; second, rectal carcinoid tumors usually present as small solitary nodules in the lower rectum, where the wall is significantly thicker and supported by surrounding connective tissue. Third, an endoscope is easily manipulated in the rectum because the rectum is fixed to the retroperitoneum. Besides, recurrence is another indicator to determine the therapeutic effect. Similarly, no significant differences among the treatment groups were detected in the follow-up time.

The sensitivity analysis using sequential exclusion of one trial at a time did not alter the results, thus indicating that our results were statistically robust. Nevertheless, some limitations of this meta-analysis should be addressed. First, all the articles included were retrospective studies, and the quality of the studies was relatively low, which might have influenced the results. Second, various types of modified EMR might have produced a small amount of bias. Third, there was conspicuous heterogeneity between studies included due to differences in procedure time, which may influence the results.

In conclusion, this meta-analysis showed that treatment of rectal carcinoid tumors with ESD or m-EMR is superior to EMR, and the efficacy of m-EMR is equivalent to ESD treatment. However, more well-designed trials are needed to confirm these findings.

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