Yukiko Takatsu, Yosuke Fukunaga, Shunsuke Hamasaki, Atsushi Ogura, Jun Nagata, Toshiya Nagasaki, Takashi Akiyoshi, Tsuyoshi Konishi, Yoshiya Fujimoto, Satoshi Nagayama, Masashi Ueno, Gastroenterological Center, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo 135-8550, Japan

Author contributions: Takatsu Y designed, performed research and wrote the paper; Fukunaga Y designed the research and supervised the report; Hamasaki S, Ogura A, Nagata J, Nagasaki T, Akiyoshi T, Konishi T, Fujimoto Y, Nagayama S and Ueno M supervised the report.

Institutional review board statement: An Ethics Committee’s approval is unnecessary for this manuscript in our hospital’s rule because of its retrospective case study.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Dr. Yosuke Fukunaga, Gastroenterological Center, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. yosuke.fukunaga@jfcr.or.jp
Telephone: +81-3-35200111
Fax: +81-3-35200141

Received: July 22, 2015
Peer-review started: July 30, 2015
First decision: September 9, 2015
Revised: September 26, 2015
Accepted: November 30, 2015
Article in press: November 30, 2015
Published online: February 21, 2016

Abstract

AIM: To evaluate the type of recurrence after endoscopic resection in colorectal cancer patients and whether rescue was possible by salvage operation.

METHODS: Among 4972 patients who underwent surgical resection at our institution for primary or recurrent colorectal cancers from January 2005 to February 2015, we experienced eight recurrent colorectal cancers after endoscopic resection when additional surgical resection was recommended.

RESULTS: The recurrence patterns were: intramural local recurrence (five cases), regional lymph node recurrence (three cases), and associated with simultaneous distant metastasis (three cases). Among five cases with lymphatic invasion observed histologically in endoscopic resected specimens, four cases recurred with lymph node metastasis or distant metastasis. All cases were treated laparoscopically and curative surgery was achieved in six cases. Among four cases located in the rectum, three cases achieved preservation of the anus. Postoperative complications occurred in two cases (enteritis).

CONCLUSION: For high-risk submucosal invasive colorectal cancers after endoscopic resection, additional surgical resection with lymphadenectomy is recommended, particularly in cases with lympho-
vascular invasion.

Key words: Colorectal neoplasms; Colorectal surgery; Laparoscopy; Endoscopy; Recurrence

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This is a retrospective study to evaluate the type of recurrence after endoscopic resection in colorectal cancer patients and whether rescue was possible by salvage operation. All cases were treated laparoscopically and curative surgery was achieved in six cases. Among five cases with lymphatic invasion observed histologically in endoscopic resected specimens, four cases recurred with lymph node metastasis or distant metastasis. For high-risk submucosal invasive colorectal cancers after endoscopic resection, additional surgical resection with lymphadenectomy is recommended, particularly in cases with lymphovascular invasion.

Takatsu Y, Fukunaga Y, Hamasaki S, Ogura A, Nagata J, Nagasaki T, Akiyoshi T, Konishi T, Fujimoto Y, Nagayama S, Ueno M. Recurrent colorectal cancer after endoscopic resection when additional surgery was recommended. World J Gastroenterol 2016; 22(7): 2336-2341 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i7/2336.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i7.2336

INTRODUCTION

Following recent advances in endoscopic diagnosis and techniques, the number of T1 [tumor node metastasis (TNM) cancer staging] colorectal cancer cases initially treated by endoscopic resection has been increasing[1]. Lymph node metastasis occurs in approximately 10% of cases with submucosal invasive colorectal cancers[2]. In Japan, according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines[3], when any high-risk findings are observed in histological examination of the endoscopic resected specimen: (1) depth of submucosal invasion ≥ 1000 μm; (2) lymphovascular invasion was positive; (3) signet-ring cell carcinoma, mucinous carcinoma, or poorly differentiated adenocarcinoma; (4) Grade 2/3 budding; and (5) vertical tumor margin was positive. All cases had undergone endoscopic resection at another hospital and were referred to our institution after cancer recurred. The study was approved by our local institutional review board and signed consent was obtained from all patients to use data from their medical records in the study.

We retrospectively reviewed the patient characteristics including age, sex, American Society of Anesthesiologists physical status, body mass index, tumor location, and pathological data. Pathological data in six of eight cases were re-examined in our institution. All specimens from endoscopic resection were examined microscopically for resection margin status and tumor characteristics as identified above. Treatment and analysis information for recurrence after ER included the use of adjuvant therapy, follow-up interval, recurrence pattern, time to recurrence, and treatment to recurrence. Surgical outcome information in our institution included the surgical procedures, harvested lymph nodes, estimated blood loss, operating time, and complications. Postoperative outcome data included pathological findings, therapy after surgery, and survival outcome.

RESULTS

Patients’ demographic data, including the primary cancer, are shown in Table 1. The median age was 60 years (range, 39-76 years) and the proportion of male patients was higher than female (six vs two cases, respectively). The median body mass index of all indicated have been published[4-7], few reports discuss outcomes in these patients[8].

In the present study, we retrospectively reviewed eight recurrent colorectal cancer cases after endoscopic resection, for which additional surgical resection including lymphadenectomy was recommended because of high-risk submucosal invasive cancer. Our aim was to evaluate the type of recurrence and whether the patient could be rescued by a salvage operation.

MATERIALS AND METHODS

Among 4972 patients who underwent surgical resection at our institution for primary or recurrent colorectal cancers at our institution from January 2005 to February 2015, we experienced eight recurrent colorectal cancers after endoscopic resection. Additional surgical resection with lymphadenectomy had been recommended in these patients because of high-risk submucosal invasive colorectal cancer. High-risk submucosal invasive colorectal cancer after ER is defined according to the JSCCR Guidelines, when any of the following findings are observed in histological examination of the endoscopic resected specimen: (1) depth of submucosal invasion ≥ 1000 μm; (2) lymphovascular invasion was positive; (3) signet-ring cell carcinoma, mucinous carcinoma, or poorly differentiated adenocarcinoma; (4) Grade 2/3 budding; and (5) vertical tumor margin was positive. All cases had undergone endoscopic resection at another hospital and were referred to our institution after cancer recurred. The study was approved by our local institutional review board and signed consent was obtained from all patients to use data from their medical records in the study.

We retrospectively reviewed the patient characteristics including age, sex, American Society of Anesthesiologists physical status, body mass index, tumor location, and pathological data. Pathological data in six of eight cases were re-examined in our institution. All specimens from endoscopic resection were examined microscopically for resection margin status and tumor characteristics as identified above. Treatment and analysis information for recurrence after ER included the use of adjuvant therapy, follow-up interval, recurrence pattern, time to recurrence, and treatment to recurrence. Surgical outcome information in our institution included the surgical procedures, harvested lymph nodes, estimated blood loss, operating time, and complications. Postoperative outcome data included pathological findings, therapy after surgery, and survival outcome.
patients was 20.7 (range, 17.0–25.4) and the primary cancer was located in the rectum in six patients. Pathological examination in the previous hospitals showed that all cases indicated a need for additional surgical resection including lymphadenectomy, with the following findings: deep submucosal invasion (6 cases), lymphatic invasion positive (five cases), vascular invasion positive (five cases), vertical margin positive (2 cases), poor differentiation (0 case), and grade 2/3 budding (2 cases).

**Follow-up and recurrence after endoscopic resection**
Adjuvant chemotherapy after ER was performed in only one case. Four patients were followed up once every 3–12 mo after ER but another four cases were not followed up. The recurrence patterns were intramural local recurrence in five cases, regional lymph node recurrence in three cases, and associated with simultaneous distant metastasis in three cases (Table 2). Among five cases with lymphatic invasion observed histologically in the ER specimen, four cases recurred with lymph node metastasis or distant metastasis, and one case receiving adjuvant chemotherapy after ER experienced only local recurrence. Surgical outcomes are shown in Table 3. All cases were treated laparoscopically, curative surgery was achieved in six cases, and there was no conversion to open surgery. The median operating time was 284 min (range, 205–440 min) and the median estimated blood loss was 168 mL (range, 10–285 mL). Among four cases located in the rectum, three cases achieved preservation of the anus. Postoperative complications occurred in two cases (enteritis).

Among three cases with distant metastasis, laparoscopic sigmoidectomy and excision of peritoneal dissemination were performed in one case. The remaining two cases received systemic chemotherapy after staging laparoscopy or laparoscopic sigmoid colostomy.

Postoperative outcomes are shown in Table 4. Macroscopically complete resection was achieved in five cases and no recurrence occurred during the 3–106-mo follow-up. Adjuvant chemotherapy was performed in three patients who had lymph node metastasis.

**DISCUSSION**
Of the eight cases in our study, three experienced recurrence with distant metastasis. Follow-up was not performed for all of the patients for whom additional resection after endoscopic treatment was recommended and some cases presented with distant metastasis at the time of recurrence. Yoshii et al. compared outcomes between patients who underwent additional surgery (ER + SURG) and those who did not (ER only) and reported that the cumulative risks of recurrence were 3.7% (5/180) in the ER + SURG group vs 20.1% (13/96) in the ER only group (P = 0.001). The authors also emphasized 6 of 13 recurrent cases in the ER only group were associated with concurrent distant metastasis. These findings support the JSCCR guidelines that additional surgery should be performed. However, additional surgical resection with lymphadenectomy in cases of rectal cancers can be associated with permanent stoma or some degree of anal dysfunction. Certain risks of surgical complications related to the operation have also been reported. Because of these concerns as well as patient age and comorbid state, some cases were followed up by ER

### Table 1  Characteristics of patients and primary tumors

| Case | Age (yr) | Sex | BMI (kg/m²) | Location | Invasion depth | Differentiation | ly | v | VM | Budding |
|------|----------|-----|------------|----------|---------------|----------------|----|---|----|---------|
| 1    | 39       | F   | 19.7       | Rectum   | sm (< 1000 μm) | Well           | +  | + | -  | Grade 2 |
| 2    | 43       | M   | 19.4       | Rectum   | sm (< 1000 μm) | Well           | +  | + | +  | Unknown |
| 3    | 71       | F   | 17.0       | Rectum   | sm (< 1000 μm) | Well           | +  | - | -  | Unknown |
| 4    | 75       | M   | 25.3       | Transverse | sm (< 1000 μm) | Well           | -  | - | -  | Grade 0 |
| 5    | 76       | M   | 21.7       | Rectum   | un clear      | Moderate       | -  | + | -  | Grade 0 |
| 6    | 42       | M   | 18.8       | Rectum   | sm (< 1000 μm) | Well           | +  | - | -  | Grade 0 |
| 7    | 74       | M   | 25.4       | Sigmoid   | sm (< 1000 μm) | Moderate       | +  | - | -  | Grade 3 |
| 8    | 49       | M   | 22.4       | Sigmoid   | sm (< 1000 μm) | Moderate       | -  | - | -  | Grade 1 |

### Table 2  Follow up and recurrence after endoscopic resection

| Case | After ESD | Follow up interval | Recurrence pattern | Time to recurrence |
|------|-----------|--------------------|--------------------|-------------------|
| 1    | -         | 3 mo               | Distant metastasis (lung, PALN) | 8 mo |
| 2    | -         | Every year         | Local + regional lymph node | 10 mo |
| 3    | -         | No follow           | Distant metastasis (lung, liver) | 7 yr |
| 4    | -         | 8 mo               | Local               | 4 yr |
| 5    | -         | No follow           | Local + regional lymph node | 18 mo |
| 6    | -         | XELOX 6 mo         | No follow           | 2 yr |
| 7    | -         | Every year         | Local + regional lymph node | 4 yr |
| 8    | -         | No follow           | Peritoneal dissemination | 4 yr |

Local: Intra mural; PALN: Para aortic lymphnode.
Oka et al.\[9\] reported that the incidence of lymph node metastasis was only 2.2%, regardless of the degree of submucosal invasion depth. Other studies also reported that patients with deep submucosal invasion only had a low cumulative risk of recurrence even without surgery\[8,10,11\]. Similarly, in our series, one case with deep submucosal invasion only, that experienced intramural local recurrence after ER, underwent curative surgery. Therefore, patients with only the single risk factor of deep submucosal invasion could be rescued by salvage if they are followed up.

In contrast, some studies have reported that lymphatic invasion was an independent risk factor for lymph node metastasis\[2\] and that venous invasion and lymph node metastasis were independent factors for a poor prognosis\[2,12\]. In our series, all cases with lymphovascular invasion in the ER specimen recurred with distant metastasis. In patients with lymphovascular invasion, additional surgical resection is strongly recommended.

All of our cases were treated laparoscopically. Similar to findings in previous randomized clinical trials\[13-15\], laparoscopic surgery had less blood loss and associated with shorter hospital stay, and earlier recovery of bowel function compared with the open surgery. These results indicate that laparoscopic surgery is a feasible procedure with short-term benefits compared with open surgery.

Without additional surgical resection.

Regarding adjuvant therapy after ER, our patient with lymphovascular invasion experienced only local recurrence after adjuvant chemotherapy. Studies of additional alternative therapy in rectal cancers have reported the effectiveness of chemoradiotherapy for patients with high-risk submucosal invasive colorectal cancers who declined additional surgery\[16,17\].

Surveillance after endoscopic resection is important. Some studies have reported recurrence within three to five years after curative ER\[18-21\]; however, the ideal follow-up period after ER with indication for additional surgery has not been determined. Yoshii et al.\[8\] suggested a recommended follow-up period of at least 5 years based on the finding that their 13 cases of recurrence after ER occurred over 69 mo. Because the longest interval to recurrence was seven years in our series, it is difficult to recommend an ideal follow-up period.

In our study, two of three cases with simultaneous distant metastasis were not followed up using any modality. If ER is performed without additional surgery, we recommend monitoring closely for recurrence. Because the shortest interval to recurrence was 8 mo in our study, we recommend a follow-up interval of at least every 6 mo.

In conclusion, for high-risk submucosal invasive colorectal cancers after ER, we recommend additional surgical resection with lymphadenectomy particularly in cases with lymphovascular invasion. Patients with
high-risk submucosal invasive colorectal cancers should be adequately advised of the outcome of recurrence.

REFERENCES

1. Muto T, Oya M. Recent advances in diagnosis and treatment of colorectal T1 cancer. Dis Colon Rectum 2003; 46: S89-S93 [PMID: 14530664 DOI: 10.1097/01.DCR.000083525.97708.B5]
2. Kobayashi H, Mochizuki H, Morita T, Kotake K, Teramoto T, Kameoka S, Saito Y, Takahashi K, Hase K, Oya M, Maeda K, Hirai T, Kameyama M, Shirouzu K, Sugihara K. Characteristics of recurrence after curative resection for T1 colorectal cancer: Japanese multicenter study. J Gastroenterol 2011; 46: 203-211 [PMID: 21152938 DOI: 10.1007/s00535-010-0341-2]
3. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajieoka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kamimata Y, Kodok N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimoto T, Koimina N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takuchi H, Tsunoda O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K. Japanese Society for Cancer of the Colon and Rectum (JSSCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 2012; 17: 1-29 [PMID: 22002491 DOI: 10.1007/s10147-011-0315-2]
4. Ikematsu H, Singh R, Yoda Y, Matsuza T, Saito Y. Follow up after endoscopic resection in submucosal invasive colorectal cancers. Dig Endosc 2013; 25 Suppl 2: 6-10 [PMID: 23617641 DOI: 10.1111/den.12114]
5. Hotta K, Fujii T, Saito Y, Matsuza T. Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 2009; 24: 225-230 [PMID: 18972121 DOI: 10.1007/s00384-008-0596-8]
6. Park JJ, Cheon JH, Kwon JE, Shin JK, Jeon SM, Bok HJ, Lee JH, Moon CM, Hong SP, Kim TI, Kim H, Kim WH. Clinical outcomes and factors related to resectability and curability of EMR for early colorectal cancer. Gastrointest Endosc 2011; 74: 1337-1346 [PMID: 22136778 DOI: 10.1016/j.gie.2011.07.069]
7. Lee EJ, Lee JB, Lee SH, Kim do S, Lee DH, Lee DS, Youk EG. Endoscopic submucosal dissection for colorectal tumors—1,000 colorectal ESD cases: one specialized institute’s experiences. Surg Endosc 2013; 27: 31-39 [PMID: 22729707 DOI: 10.1007/s00464-012-2403-4]
8. Yoshii S, Noinima N, Nosho K, Usunuma T, Okuda H, Tsukagoshi H, Fujita M, Yamamoto H, Hosokawa M. Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 2014; 12: 292-302.e3 [PMID: 23962552 DOI: 10.1016/j.cgh.2013.08.008]
9. Oka S, Tanaka S, Nakadou K, Kanao H, Chayama K. Risk analysis of submucosal invasive rectal carcinomas for lymph node metastasis to expand indication criteria for endoscopic resection. Dig Endosc 2013; 25 Suppl 2: 21-25 [PMID: 23617644 DOI: 10.1111/den.12089]
10. Nakadou K, Tanaka S, Kanao H, Terasaki M, Takata S, Oka S, Yoshida S, Aihiro K, Chayama K. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol 2012; 27: 1057-1062 [PMID: 22142484 DOI: 10.1111/j.1440-1746.2011.07041.x]
11. Ueno H, Mochizuki H, Hashiguchi Y, Shimazaki H, Hida S, Hase K, Matsuoka S, Kani T, Kurihara H, Ozawa K, Yoshikura K, Bekka S. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004; 127: 385-394 [PMID: 15300569]
12. Cooper HS, Deppisch LM, Gourley WK, Kawe EJ, Lev R, bundle PN, Pascal RR, Ozilbash AH, Rickert RR, Silverman JF. Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. Gastroenterology 1995; 108: 1657-1665 [PMID: 7768369]
13. Smith PP. Breast models: a useful tool for instructions. Occup Health Nurs 1985; 33: 513-514 [PMID: 3851244 DOI: 10.1186/71-2482-13.8-S2-112]
14. Fleshman J, Sargent D, Green E, Anvari M, Stryker SJ, Beart RW, Hellinger M, Flanagan R, Peters W, Nelson H. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg 2007; 246: 655-662; discussion 662-664 [PMID: 17893502 DOI: 10.1097/SLA.0b013e31815a762]
15. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013; 14: 210-218 [PMID: 23395398 DOI: 10.1016/S1470-2045(13)70016-0]
16. Nakamura T. Proportionnal hazards model with covariates subject to measurement error. Biometrics 1992; 48: 829-838 [PMID: 1420844]
17. Russell AH, Harris J, Rosenberg P, Sause WT, Fisher B, Hoffman JP, Kraybill WG, Byhardt RW. Anal sphincter preservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol
18 Oka S, Tanaka S, Kanao H, Ishikawa H, Watanabe T, Igarashi M, Saito Y, Ikematsu H, Kobuyashi K, Inoue Y, Yahagi N, Tsuda S, Simizu S, Ishi H, Yamano H, Kudo SE, Tsuruta O, Tamura S, Saito Y, Cho E, Fujii T, Sano Y, Nakamura H, Sugihara K, Muto T. Mid-term prognosis after endoscopic resection for submucosal colorectal carcinoma: summary of a multicenter questionnaire survey conducted by the colorectal endoscopic resection standardization implementation working group in Japanese Society for Cancer of the Colon and Rectum. Dig Endosc 2011; 23: 190-194 [PMID: 21429028 DOI: 10.1111/j.1443-1661.2010.01072.x]

19 Winawer SJ, Zauber AG, O’Brien MJ, Ho MN, Gottlieb L, Sternberg SS, Waye JD, Bond J, Schapiro M, Stewart ET. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med 1993; 328: 901-906 [PMID: 8446136]

20 Fleischer DE, Goldberg SB, Browning TH, Cooper JN, Friedman E, Goldner FH, Keefe EB, Smith LE. Detection and surveillance of colorectal cancer. JAMA 1989; 261: 580-585 [PMID: 2642563]

WINAWER SJ, Zauber AG, Fletcher RH, Stillman JS, O’Brien MJ, Levin B, Smith RA, Lieberman DA, Burt RW, Levin TR, Bond JH, Brooks D, Byers T, Hyman N, Kirk L, Thorson A, Simmang C, Johnson D, Rex DK. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 2006; 56: 143-159; quiz 184-185 [PMID: 16737947]

P- Reviewer: Sipos F, Yu B  S- Editor: Yu J  L- Editor: A  E- Editor: Liu XM
