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The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects

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GASTROENTEROLOGY

Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumor: A retrospective study

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Key words
endoscopic mucosal resection, endoscopic submucosal dissection, early rectal cancer, non-invasive rectal tumor, transanal endoscopic microsurgery, transanal resection.

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Abstract

Background and Aim: Endoscopic submucosal dissection (ESD) is an alternative to transanal resection (TAR) in treating rectal adenomas, intramucosal cancers, and superficial submucosal cancers. The purpose of this study is to compare the clinical efficacy between ESD and TAR for non-invasive rectal tumors.

Methods: Between January 1998 and December 2006, 85 patients with preoperative diagnosis of non-invasive rectal tumors were treated by ESD or TAR. En-bloc resection, local recurrence, complication, procedure time, and hospital stay were evaluated retrospectively using a prospectively-completed database.

Results: Mean resection sizes were 40 mm and 39 mm in diameter for the ESD and TAR groups, respectively. En-bloc resections with a negative resection margin were achieved in 67% (35/52) of the ESD group, which was significantly higher than the 42% (14/33) in the TAR group. Sixty-three lesions were diagnosed as curative resection, histopathologically. There was no local recurrence in the ESD group, but five local recurrences developed in the TAR group. Two rectal perforations, one minor delayed bleeding, and one subcutaneous emphysema in the ESD group were successfully managed conservatively. There were one minor delayed bleeding and two anesthesia-related complications in the TAR group. The ESD group had a shorter hospital stay than the TAR group (4.9 days *vs* 7 days), but a longer procedure time (131 min *vs* 63 min).

Conclusion: ESD was more effective than TAR in treating non-invasive rectal tumors, with a lower recurrence rate and shorter hospital stay.

Introduction

Early rectal cancers are now detected more often, therefore local excision with minimal invasiveness and excellent clinical outcome are feasible treatment options. Transanal resection (TAR) and transanal endoscopic microsurgery (TEM) are well-developed surgical procedures for local excision in the rectum and are now widely accepted for managing early-stage rectal cancer. However, high local recurrence rates and severe complications have been reported for both procedures.[1–4]

Endoscopic submucosal dissection (ESD) technique was introduced for non-invasive colorectal neoplastic lesions (adenoma, intramucosal cancer, and superficial submucosal cancer), especially in the rectum as an alternative of TAR as early as 1998.[5,6] The major advantage of ESD is being able to perform en-bloc resections for lesions ≥ 20 mm.

The aim of this retrospective study was to compare the result of ESD with TAR in treating non-invasive rectal tumors, which were unsuitable for conventional endoscopic mucosal resection (EMR).

Methods

Between January 1998 and December 2006 at National Cancer Center Hospital in Japan, a total of 85 rectal adenomas, intramucosal cancers (Tis), and superficial submucosal cancers (T1sm1) in 85 patients were treated by either ESD or TAR after informed written consent.

Before 2003, the indications for TAR were lesions unsuitable for conventional EMR or tumors spreading to the dentate line. Starting from 2003, TAR was performed for only eight lesions in our hospital when it was not difficult to assess the tumor margin, based on the judgement of a consultant surgeon. From 2003 onwards, we introduced ESD as the standard treatment for large

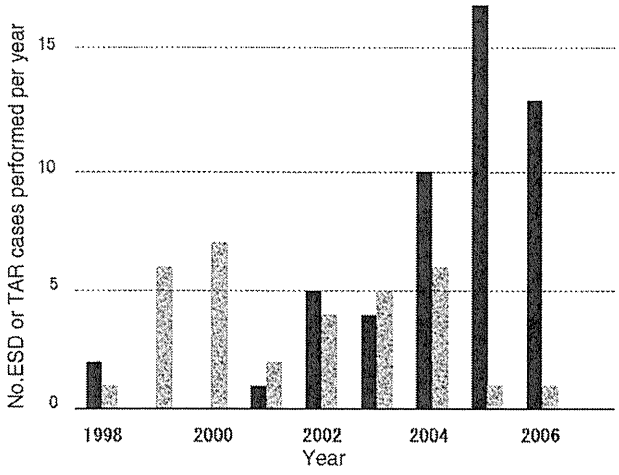

Figure 1 Historical changes between endoscopic submucosal dissection and transanal resection for a lower rectal tumor. ■, ESD; ▩, TAR.

non-invasive rectal tumors and those spreading to the dentate line (Fig. 1).

Data were analyzed using a prospectively-completed database and pathological reports, with respect to en-bloc resection rate, local recurrence rate, early and late complications, histological diagnosis, procedure time, and length of hospital stay in both groups. This study was performed in accordance with the 1989 revised Helsinki Declaration.

ESD procedure

ESD were carried out with a high-magnification endoscope (PCF-Q240ZI or GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) with CO_2 insufflation.[7] All ESD were performed under conscious sedation. For those lesions spreading to the dentate line, we used a local injection of lidocaine solution (0.5%) to reduce anal pain.

Each ESD procedure was performed according to the following steps (Fig. 2): (i) 0.4% indigo carmine dye was sprayed; (ii) glycerol and sodium hyaluronic acid were injected into the submucosal layer; (iii) an initial cut was made with a bipolar current needle knife (B-knife; XEMEX, Tokyo, Japan);[8] (iv) complete a circumferential incision; (v) submucosal dissection was performed using the B-knife and an insulation-tipped knife (IT knife; KD-610L, Olympus Medical Systems, Japan).

TAR procedure

TAR were performed under general or spinal anesthesia, with patients assuming the prone jack knife position or lithotomy position. No indigo carmine dye was applied. Normal saline solution with epinephrine was injected into the submucosal layer. In the case of suspected submucosal deep invasion, a full-thickness excision, including muscularis propria, would be performed (Fig. 3).

Assessment of procedures and histopathology

ESD procedure times were measured from the initial insertion of the endoscope to its removal following resection of the tumor,

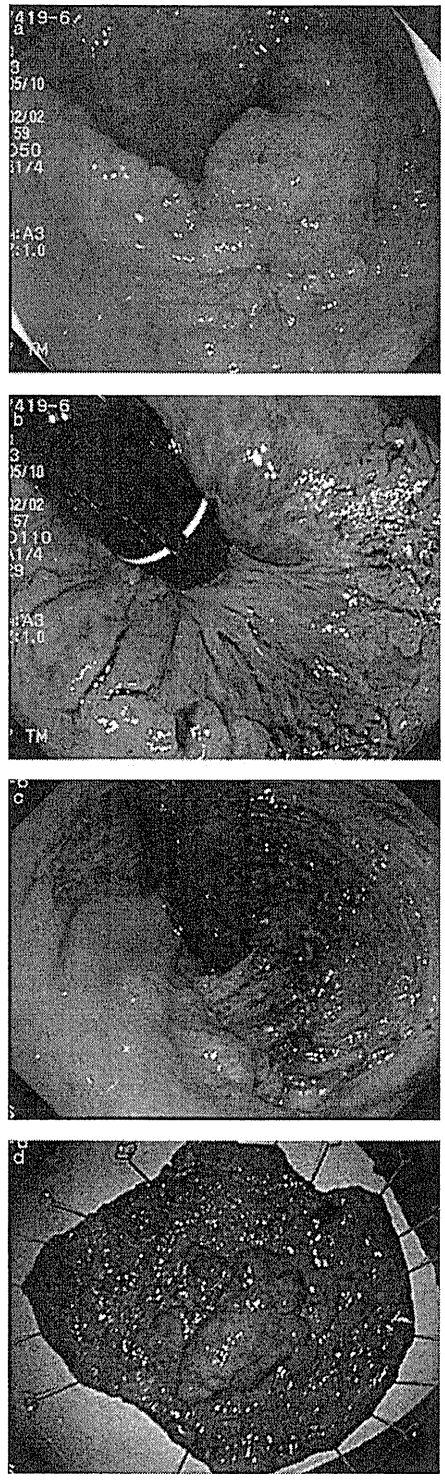

Figure 2 Representative endoscopic submucosal dissection case. (a) Large 0-Is+IIa lesion located in the lower rectum; (b) margins delineated using 0.4% indigo carmine dye spraying; (c) area of rectum following en-bloc resection; (d) resected specimen was 100 mm in diameter, and histological examination revealed well-differentiated adenocarcinoma with tumor-free resected margin.

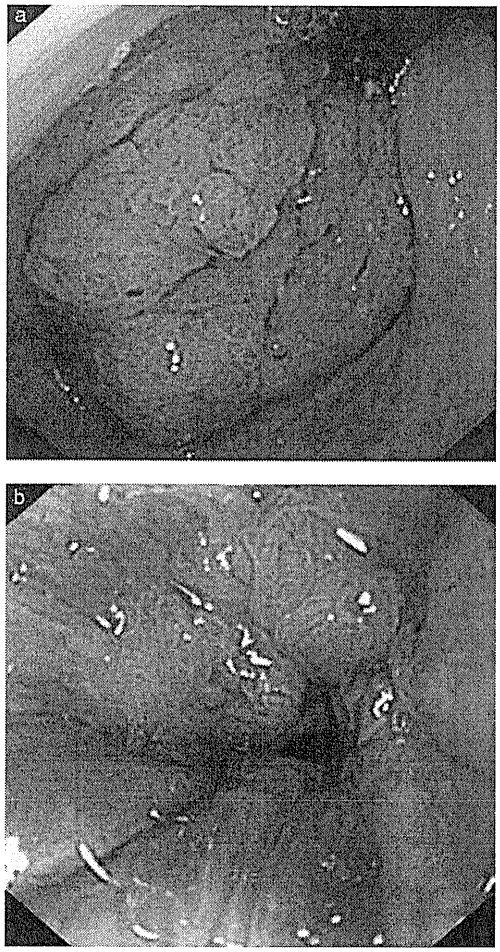

Figure 3 Representative transanal resection case. (a) Large 0–Is lesion located in the lower rectum; (b) tumor spread to anal canal.

while TAR procedure times were measured from the initial incision to the completion of resection and hemostasis, as determined by the individual surgeons. The lateral and vertical margins of specimens resected by ESD and TAR were examined macroscopically for any tumor involvement by endoscopists or surgeons.

An en-bloc R0 resection was successfully achieved when both the lateral and vertical margins of a specimen were free of neoplasm, with resection in one piece. Specimens with deep submucosal (> 1000 μm from the muscularis mucosae) invasion, lymphatic invasion, vascular involvement, or histologically poorly-differentiated component were diagnosed as non-curative.[9] Histological diagnosis was based on the Japanese classification of cancer of the colon and rectum,[10] and the Vienna classification.[11]

Endoscopic and other modality follow up

All patients with curative resection were examined endoscopically 6 months after their original treatment. Indigo carmine dye was sprayed on the previously-resected areas, and high-magnification views were obtained to check for the existence of any recurrence for all patients. One or two biopsies were performed as indicated, with recurrent neoplastic disease identified as type-IIIs, -IIIL, -IV, or -V pit patterns (neoplastic pattern) using high-magnification chromocolonoscopy, according to the criteria established by Kudo and Fujii.[12,13] When a type I or II pit pattern (non-neoplastic pattern) was identified using high-magnification chromocolonoscopy, no biopsy was performed, as there was no evidence of recurrence.[13] Patients with intramucosal cancer and adenoma did not require computed tomography (CT) scan on follow up. Curative resection cases with superficial submucosal invasion (T1sm1) were followed up by annual abdominal and pelvic CT scan.

Statistical analysis

Statistical differences were analyzed using the χ^2-test or *t*-test with a *P*-value less than 0.05, considered as statistically significant. Calculations were made using SPSS version 8.0 for Windows (SPSS Japan, Tokyo, Japan).

Results

Patient characteristics and lesion clinical features

A total of 85 patients were recruited into the study. Fifty-two patients were treated by ESD, and 33 patients were treated by TAR (Table 1). The mean lesion size was 40 mm and 39 mm in diameter for the ESD and TAR groups, respectively. Eleven lesions in the ESD group were located in the upper rectum (Ra; oral side from the middle transverse fold of rectum), 37 in the lower rectum (Rb; anal side from the middle transverse fold of the rectum), and four extended from the Rb to the anal canal (Rb–P). In comparison, none (0%) of the lesions in the TAR group was located in the Ra, 22 lesions were in the Rb, and 11 were in the dentate line (Rb–P).

Histological results of adenoma/intramucosal carcinoma (Tis)/T1sm1/deep submucosal carcinoma (T1sm2) were 9/26/6/11 in the ESD group and 2/18/2/11 in the TAR group, respectively.

The mean procedure time of the ESD group was significantly longer than that of the TAR group (131 *vs* 63 min, $P < 0.001$). The mean length of hospital stay in the ESD group was significantly shorter than that of the TAR group (4.9 days *vs* 7 days, $P < 0.001$).

Histopathological results and local recurrence rates

The macroscopically-clear resection margin rates of ESD and TAR were 100% (Table 2). En-bloc resection with the microscopically-clear resection margin (En-bloc R0 resection) was successfully achieved in 67% of the ESD group, which was significantly higher than the 42% in the TAR group ($P < 0.001$).

Clinical results in the curative resection subgroup

After histological examination, 11 ESD and 11 TAR were found to have deep submucosal invasion, including one TAR with lymphovascular involvement. These 11 ESD and 11 TAR patients

Table 1 Patient characteristics and lesion clinical features

	Endoscopic submucosal dissection	Transanal resection	*P*-value
No. lesions	52	33	
Age (Mean [SD]), years	61 ± 11	64 ± 13	NS
Tumor size, mm	40 ± 21	39 ± 24	NS
Location			
Ra/Rb/Rb–P	11/37/4 (21/71/8%)	0/22/11 (0/67/33%)	< 0.001
Macroscopic type			
Sessile/flat/recurrent	4/44/4 (8/84/8%)	17/16/0 (52/48/0%)	NS
Histological depth			
Adenoma/Tis/T1sm1/T1sm2	9/26/6/11 (17/50/12/21%)	2/18/2/11 (6/55/6/33%)	NS
Procedure time, min (mean ± SD)	131 ± 100	63 ± 54	< 0.001
Hospital stay, days	4.9 ± 0.8	7.0 ± 3.0	< 0.001

NS, not significant; Ra, oral side from the middle transverse fold of rectum; Rb, anal side from the middle transverse fold of the rectum; Rb–P, oral side from the middle transverse fold of rectum to the anal canal; SD, standard deviation; T1sm1, submucosal invasion < 1000 μm; T1sm2, submucosal invasion > 1000 μm; Tis, intramucosal.

Table 2 Comparison of clinical results

	Endoscopic submucosal dissection	Transanal resection	*P*-value
Macro clear resection rate†	100% (52/52)	100% (33/33)	NS
En-bloc resection rate			
All	88% (46/52)	85% (28/33)	NS
Sessile	100% (4/4)	94% (16/17)	NS
Flat	91% (40/44)	75% (12/16)	NS
Recurrent	50% (2/4)	—	
En-bloc R0 resection rate‡			
All	67% (35/52)	42% (14/33)	< 0.001
Sessile	100% (4/4)	65% (11/17)	NS
Flat	66% (29/44)	19% (3/16)	< 0.005
Recurrent	50% (2/4)	—	

†Macroscopically-clear resection margin; ‡en-bloc and negative resection margin. NA, not applicable; NS, not significant.

received additional surgical procedure or chemoradiotherapy. Sixty-three lesions, including 41 lesions treated by ESD and 22 lesions treated by TAR, were diagnosed as curative resections (Table 3). Among the patients who received curative resection, en-bloc R0 resection was successfully achieved in 78% of the ESD group, which was significantly higher than the 27% in the TAR group ($P < 0.001$). There was no recurrence for all these en-bloc R0 resection cases in the ESD group (26 flat lesions, 4 sessile lesions, and 2 recurrent lesions after other resections) over a median follow-up period of 60 months.

In the remaining nine cases of ESD, seven were resected in one piece, but the lateral margins of the resection specimen were histologically positive for neoplastic components, and two cases were resected in two pieces. These nine ESD resections were all flat lesions, but there was also no local recurrence in any of these cases over a median follow-up period of 35 months.

In comparison, six cases of TAR achieved en-bloc R0 resections. In the other 16 cases of TAR, 11 cases were resected in a single piece, but the lateral margins were histologically positive for neoplastic components. These 11 TAR cases were all flat lesions, and three of them developed local recurrences. The other five cases of TAR were resected as piecemeal, and recurrences were present in two of these five lesions.

The overall local recurrence rate was 23% ($P < 0.01$) in the TAR group cases over a median follow-up period of 55 months. The median time interval of local recurrence was 12 months after TAR. All five local recurrences in the TAR group underwent additional treatment: two proceeded with ESD, two repeated TAR, and one received low anterior resection with lymph node dissection. Curative resections were achieved in all five local recurrent cases.

Complications

Three kinds of complications occurred in the ESD group, including rectal perforations in two patients, minor delayed bleeding in one patient, and one case of subcutaneous emphysema. All four patients were successfully managed by conservative means, using endoclips without the need of blood transfusion or any additional procedure. In comparison, two kinds of complications occurred in the TAR group, including one case of delayed bleeding after the

Table 3 Comparison of clinical results for curative resection cases

	Endoscopic submucosal dissection (41 cases)	Transanal resection (22 cases)	*P*-value
En-bloc R0 resection rate†			
All	78% (32/41)	27% (6/22)	< 0.001
Sessile	100% (4/4)	44% (4/9)	NS
Flat	76% (26/34)	15% (2/13)	< 0.001
Recurrent	67% (2/3)	—	
Local recurrence rate			
All	0% (0/41)	23% (5/22)	< 0.01
Sessile	0% (0/4)	22% (2/9)	NS
Flat	0% (0/34)	23% (3/13)	< 0.05
Recurrent	0% (0/3)	—	
Median recurrence period, months	NA	12 (7–17)	NA

†En-bloc and negative resection margin. NA, not applicable; NS, not significant.

Table 4 Comparison of complications

	Endoscopic submucosal dissection	Transanal resection
Perforation	2 (4%)	0
Minor delayed bleeding	1 (2%)	1 (3%)
Subcutaneous emphysema	1 (2%)	0
Temporary delirium	0	1 (3%)
Dental injury	0	1 (3%)

procedure and two complication cases related to the use of general anesthesia in which one patient experienced temporary delirium and the other suffered a dental injury (Table 4).

Discussion

To the best of our knowledge, this is the first study to compare the effectiveness of ESD with TAR in treating non-invasive rectal tumors (adenoma, intramucosal carcinoma, and superficial submucosal carcinoma). In our study, ESD was proven to be a more effective treatment for non-invasive rectal neoplasms than TAR in terms of both curability and shorter hospital stay. ESD achieved a higher en-bloc R0 resection rate and resulted in no local recurrence. It also had no serious complication, despite a longer procedure time.

Various minimally-invasive local excision treatments for early rectal cancer, such as TAR, TEM, and endoscopic resection techniques, including EMR and ESD, are gaining acceptance in many countries.[1–8,14–19] EMR is the least invasive among all these procedures, but it has been technically difficult to perform en-bloc resection for a flat lesion ≥ 20 mm. Therefore, TAR or TEM are usually performed instead of a piecemeal EMR.

In our study, five local recurrences (23%) occurred in the TAR group, in spite of a high macroscopically-clear resection rate. In the subgroup of flat lesions, the en-bloc R0 resection rate was significantly lower, and the recurrence rate was higher in TAR when comparing to ESD. The reason was probably due to poor visualization of the operative field in TAR, thus the margin of flat tumors could not be clearly observed. Technical failure resulted in piecemeal resection in five cases of TAR. Lack of a high-magnification endoscopic view in the TAR procedure was the main reason for the technical failure.

In this study, no TAR was performed for tumors located in Ra, because it is very difficult to perform TAR in upper rectal tumors. However, more TAR than ESD have been performed for tumors in Rb because it is easy for surgeons to reach low rectal tumors in a transanal approach, as is the case with hemorrhoid surgery.

Endoscopic diagnosis and treatment could be performed at the same time using a flexible endoscope, and the tumor margin could be observed clearly using a magnifying colonoscope. The retroflex view was especially useful for the endoscopic diagnosis and treatment of rectal lesions spreading to the dentate line. When TAR was performed, the tumor margins were usually identified directly by the surgeon's eyes, whereas ESD enabled the use of a high-definition magnified view for precise tumor margin determination. In addition, visualization of the operative field during TAR was more difficult in the rectum because air or CO_2 insufflation could not be used as in ESD. When ESD was performed, the tumor margins were recognized clearly by high-magnification chromocolonoscopy, which resulted in a lower recurrence rate.

Although the en-bloc R0 resection rate of curative resection by ESD was 78%, the fact that there was no recurrence in the ESD group was probably because any residual tumor at the lateral margins would have been observed by magnifying endoscopy and removed during the ESD. Sessile-type lesions could be treated completely without chromocolonoscopy, but it was sometimes difficult to ascertain the margins of flat, laterally-spreading tumors without indigo carmine dye spray. This could have been the reason

for the higher local recurrence rate for the TAR procedure, which was performed without the benefit of high-magnification chromocolonoscopy. If TAR is to be performed for flat rectal lesions when ESD cannot be performed because of technical difficulties, we would recommend TAR after marking around the tumor is done using a needle knife under high-magnification chromocolonoscopy view.

In this study, all ESD procedures were performed under conscious sedation, in which patients received 2–4 mg midazolam intravenously. In contrast, all the patients in the TAR group required general or spinal anesthesia that took a long time to administer. Although the total ESD procedure time was significantly longer than that for TAR, the actual amount of time spent in the operating room did not differ much between the two groups, when considering the extra time needed for sedation and anesthesia. In addition, ESD patients could be discharged from the hospital earlier than those patients who underwent TAR.

With the advent of improving ESD technique, it is now possible to perform en-bloc resection for non-invasive rectal tumors of any size, so the indications for ESD and TAR now overlap to a considerable extent. However, there have been reports regarding recurrence after TAR, with the rate varying between 2.8% and 30% in previously-published series;[20–24] this would be considerably higher when compared to ESD.

TEM is a minimally-invasive surgical procedure for the local excision of rectal tumors that enables resection of the entire depth of the rectal wall. However, TEM requires a high level of technical skill, expensive devices, as well as either general or spinal anesthesia.

The minimal distance of the resected tumor from the anal verge by TEM was 5 cm in a previous study, because of the use of rigid rectoscope.[25] Therefore, it will be difficult to perform TEM if the lesion is near to the dentate line.

In comparison, ESD can be performed even if the lesion is located on the dentate line or in the proximal colon using the flexible endoscope.

The limitations of this study are the retrospective study design; single-center, relatively small sample size; and potential selection bias in treatment options.

ESD needs the specialized technical skills of endoscopists, particularly for the proximal colon lesions, but rectal ESD is relatively easy to perform.

In conclusion, ESD is proven to be more effective than TAR in treating non-invasive rectal tumors, with a much lower local recurrence. ESD is particularly recommended for flat rectal lesions.

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CASE REPORT Open Access

Small invasive colon cancer with systemic metastasis: A case report

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ABSTRACT

Background: Recently, especially in Japan, several researchers have suggested that colorectal cancer can develop not only through an adenoma-carcinoma sequence but also from normal mucosa via a *de novo* pathway, and that these *de novo* cancers have more aggressive malignant potential. We report a case of aggressive colon cancer resulting in systemic metastasis despite small tumour size.

Case Presentation: A 35-year-old woman presented at the referring hospital with swelling of the left cervical lymph node. Biopsy of the lymph node revealed metastatic adenocarcinoma; however, CT scan and mammography were unable to identify the site of the primary lesion. She was diagnosed with unknown primary cancer and referred to our hospital for further examination. Immunohistochemical reevaluation showed the cervical lymph node biopsy specimen to be positive for CDX2 and CK20 and negative for CK7 expression, leading us to suspect the presence of a primary colorectal cancer. We performed a total colonoscopy, and detected a small protruding lesion in the transverse colon. The tumour was only 12 mm in diameter, with a central depressed component and a severely thickened stalk, which suggested direct cancer invasion of the deep submucosa. We concluded that this lesion was the site of origin of the metastasis despite the small tumour size, and performed diagnostic endoscopic mucosal resection. The lesion was found to have an intramucosal cancer component, demonstrating that this lesion represented primary colon cancer. The patient was referred to the gastrointestinal oncology division for systemic chemotherapy.

Conclusions: In this case, immunohistochemical findings strongly suggested the existence of a colorectal cancer. The non-polypoid gross appearance of the tumour suggested that it can originate *de novo* , thus providing a valuable case in support of the aggressive malignant potential of a *de novo* colorectal cancer pathway.

Keywords: Nonpolypoid colorectal cancer, CDX2, CK20, CK7, systemic metastasis

Background

Colorectal cancer is the second leading cause of cancer deaths in men and women in Western countries [1], and its incidence is gradually increasing in Japan as well. The most common pathway of colorectal cancer development is thought to be the adenoma-carcinoma sequence, in which carcinoma develops from an adenomatous polyp [2]. The current practice of removing adenomatous polyps of the colon and rectum is based on the belief that this will prevent colorectal cancer [3]. However, recent reports have described small depressed [4], leading to the proposal of an alternative pathway of *de novo* colon carcinogenesis, which involves an aggressive growth phenotype and quick infiltration of neighbouring tissue and lymph nodes [5-7]. The most common site of metastasis of these cancers is the liver, followed by the lung. Herein, we report a rare case of a small colon cancer with a depressed component and aggressive malignant potential with systemic metastasis, where the chief complaint was cervical lymph node swelling.

Case Presentation

In September 2009, a 35-year-old woman presented at the referring hospital with left cervical lymph node

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swelling. Malignant lymphoma (ML) was first suspected, but aspiration cytology and biopsy of the lymph node suggested metastatic adenocarcinoma resulting from breast cancer. However, no evidence of breast cancer was found on ultrasonography and mammography examinations. Whole-body computed tomography (CT) showed systemic lymph node swellings (left supraclavicular and multiple para-aortic lymph nodes) but no primary lesion (Figure 1). Upper Gastrointestinal endoscopy revealed no evidence of malignancy. The patient was diagnosed with unknown primary cancer and referred to our hospital for further examination in November 2009.

We reevaluated the lymph node biopsy specimen obtained by the referring hospital. The tumour cells with oval to round nuclei with prominent nucleoli were found to be showing partial ductal structures, leading us to suspect poorly differentiated adenocarcinoma. Additionally, immunohistochemistry (IHC) studies showed the biopsy specimen to be negative for cytokeratin 7 (CK7), and positive for CDX2, an intestine-specific homeobox transcription factor, and cytokeratin 20 (CK20), a cytoskeletal protein usually found in the colonic epithelium. These IHC results strongly suggested the metastasis from a primary colorectal cancer (Figure 2). We performed a total colonoscopy and detected a small

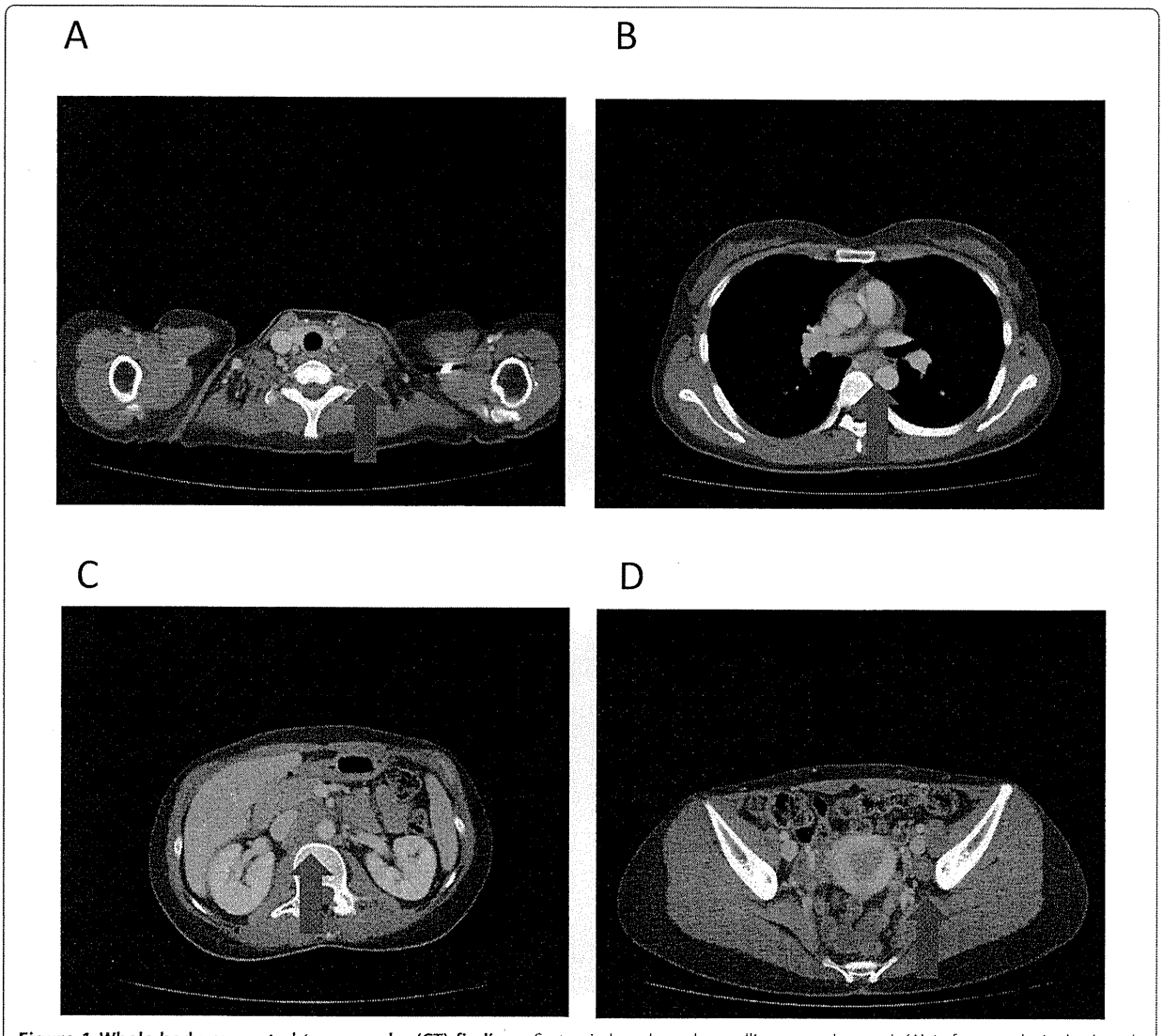

Figure 1 Whole-body computed tomography (CT) findings. Systemic lymph node swelling was observed. (A) Left supraclavicular lymph node metastasis measuring 33 mm in diameter (arrowhead). (B) Middle thoracic para-oesophageal lymph node metastasis measuring 24 mm in diameter (arrowhead). (C) Multiple para-aortic lymph node metastases in the abdomen, the largest one measuring 43 mm in diameter (arrowhead). (D) Left iliac internal lymph node metastasis measuring 18 mm.

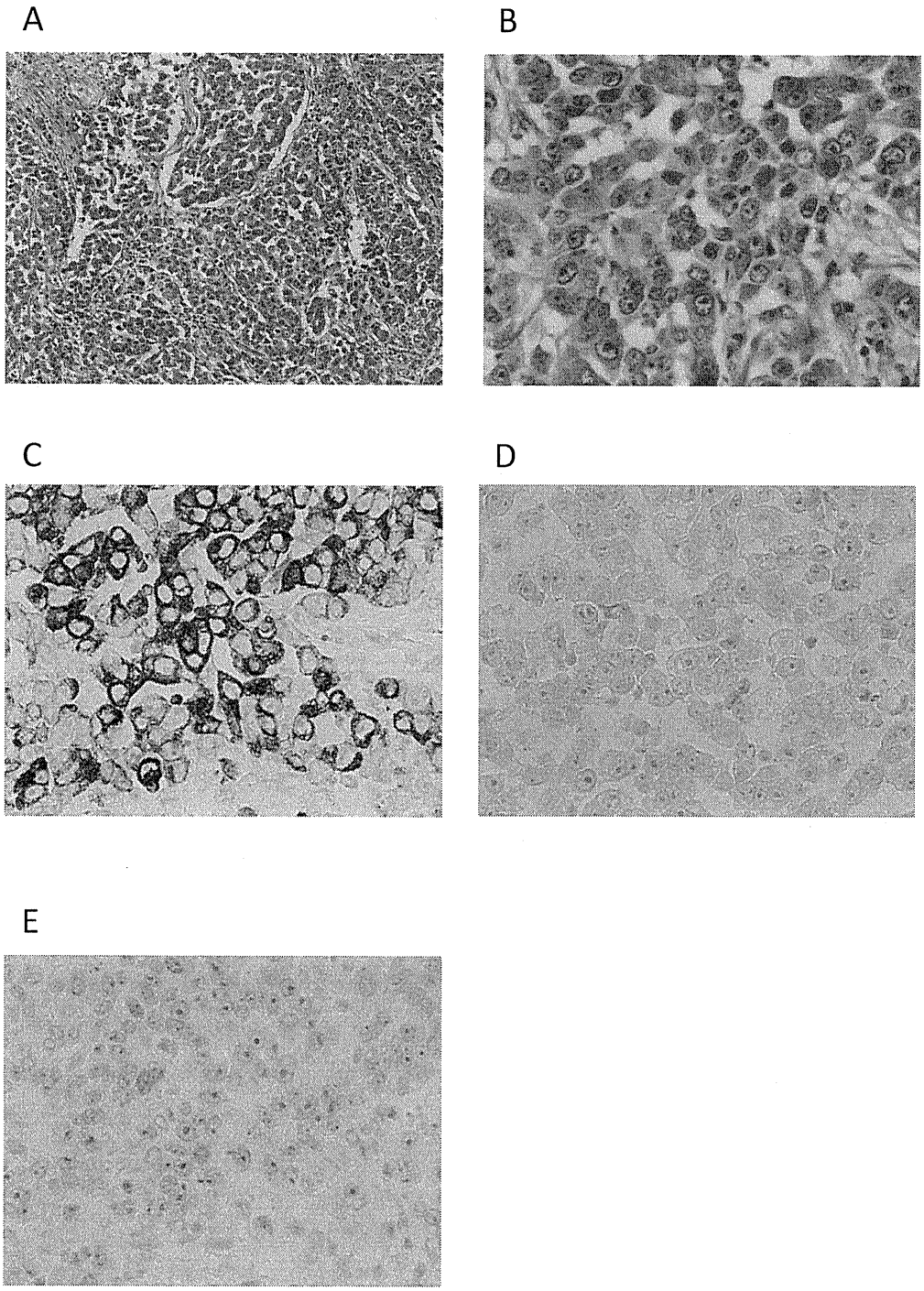

Figure 2 Pathological findings of lymph node metastasis. (A, B) Poorly differentiated adenocarcinoma was observed, with tumour cells spreading into fibrosis stroma in the tumour tissue. Tumour cells contained acidophilic vacuoles and oval nuclear bodies with several clear nucleoluses and partially formed glandular differentiations. (C) Immunohistochemical staining for CK20 was positive. (D) Immunohistochemical staining for CK7 was negative. (E) Immunohistochemical staining for CDX2 was weak but diffusely positive.

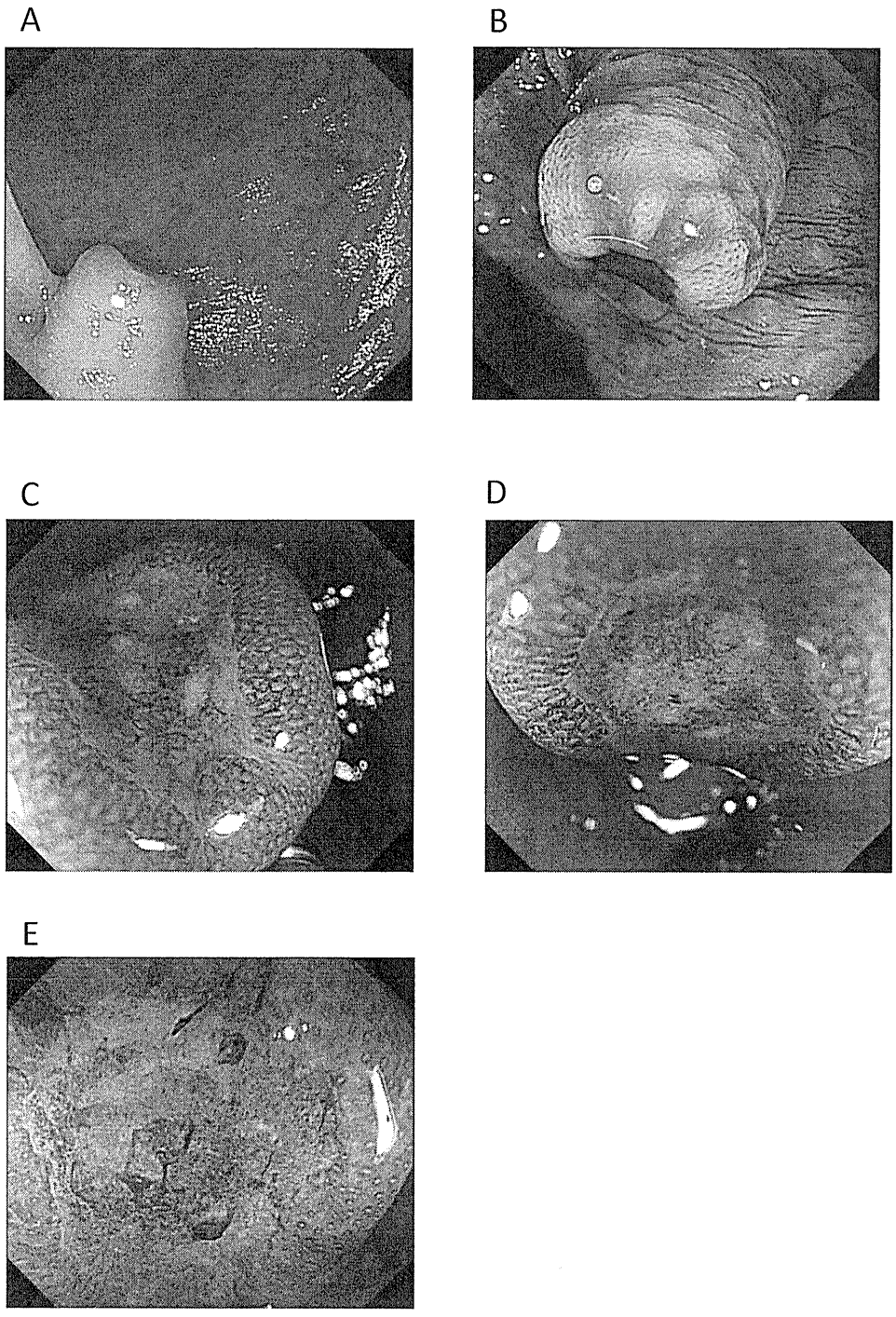

Figure 3 Colonoscopy findings. (A) Conventional colonoscopy showed a protruding lesion with central depression in the transverse colon, 12 mm in diameter. Its stalk was severely thickened, suggesting cancer invasion. (B) Chromoendoscopy with 0.4% indigo-carmine dye clearly showed the depressed area and non-neoplastic mucosa covering the edge of the cancer, suggesting that this tumour followed a non-polypoid growth (NPG)-type pattern. (C, D) Magnified NBI (Narrow Band Imaging) micrograph of the central depressed area, showing loose, irregular capillary vessels. We diagnosed the tumour as type IIIB according to Sano's classification, which suggests the possibility of deep cancer invasion of the submucosal layer. (E) Magnified view with 0.05% crystal violet staining of the surface of the central depression with a severe irregular pit pattern identified in the demarcated area.

protruding lesion in the transverse colon (Figure 3). The tumour was very small, with a diameter of only about 12 mm, and contained a depressed component, leading to a diagnosis of macroscopic type with 0-Is+IIc according to the Paris classification [8]. Furthermore, the severely thickened stalk and irregular pits visible in a magnified image of the depressed area combined to suggest direct invasion of the deep submucosa (Figure 3C) [9]. We concluded that this lesion was the primary site of the metastatic cancer despite its small size.

A diagnostic endoscopic mucosal resection (EMR) was performed and the specimen removed was serially dissected into three sections and examined. The tumour was composed of poorly differentiated adenocarcinoma and signet-ring cell carcinoma (Figure 4). It primarily consisted of solidly proliferated cells, but exhibited some indistinct gland formation. The tumour had a preserved intramucosal component but infiltrated deeply into the submucosal layer, with severe lymphatic and venous invasion detected the submucosal layer. The vertical and horizontal cut ends of the resected tumour were both positive for cancer cells (Figure 4). IHC studies showed strong expression of MUC5AC, and weak expression of MUC2 and CDX2; indicating the tumour having a mixed gastric and intestinal character, with the gastric phenotype being predominant. Patients with advanced colorectal cancer with gastric phenotypes have been reported to frequently exhibit lymphatic permeation and lymph node metastasis [10]. Additionally, the tumour was positive for CK20 and slightly positive for CK7. There was no evidence of differentiation to endocrine tumour or hepatoid adenocarcinoma (Figure 5).

These pathological results suggested that colon cancer was the origin of lymph node metastasis. The patient was referred to the Gastrointestinal Oncology Division, where she underwent combination chemotherapy using capecitabine (Xeloda®) plus oxaliplatin (Elplat®) and bevacizumab (Avastin®), which is one of the standard therapy of metastatic colon cancer. After 4 courses, CT scan showed a significant reduction of tumour volume, but after 10 courses, the tumour marker rapidly increased and peritoneal metastasis progressed. The genomic analysis of KRAS status revealed wild type, so we started the second-line combination chemotherapy using cetuximab (Erbitax®) plus irinotecan hydrochloride (Topotecin®). After the 4 times administration of cetuximab, tumor marker was decreased significantly. Her age, i.e. 35-years, is in accordance with the Guideline, which are used as recommendation criteria for MSI testing. However, she did not agree to undergo MSI testing, because she would like to give top priority to receive the chemotherapy.

Conclusions

In patients with an unknown primary carcinoma, the site remains unidentified in 15~25% of the cases even after autopsy [11,12], although recent advances in clinical examination and diagnostic work-up have decreased this frequency. The median survival of high-risk patients with cancer of unknown primary origin ranges from 3 to 11 months, making prompt diagnosis and treatment very important [13-15]. In this case, 2 months elapsed between the initial consultation at the referring institution and the patient's presentation at our hospital. Pathological and IHC reviews of cervical lymph node tissue were the main tools used to determine the primary site of cancer origin.

When attempting to trace the primary site of a metastatic tumour of unknown origin, clarification of the histological type is indispensable in selecting appropriate treatment. Microscopic features and cell morphologies can be identified with hematoxylin and eosin (HE) staining, and this information can be used to identify the primary site. However, in the evaluation of undifferentiated or poorly differentiated cancers, IHC evaluation is a useful addition to HE staining in locating the tumour site. In particular, a pattern of positive CDX2 or CK20 expression and negative CK7 expression is indicative of primary colorectal cancer [16,17].

In this case, IHC investigation of a lymph node biopsy strongly suggested primary colorectal cancer. In a total colonoscopy examination, we detected one colorectal lesion with the gross appearance of a submucosal tumour. This appearance is relatively rare in primary colon cancer, and thus we should exclude metastatic colon cancer as a possible diagnosis. EMR is more useful than simple biopsy in confirming the existence of a mucosal component, which would lead to a primary cancer diagnosis, but it carries a high risk of bleeding and perforation in cases where deep submucosal invasion is suspected. We performed diagnostic EMR after obtaining proper consent and agreement.

The adenoma-carcinoma sequence hypothesis proposes that colorectal cancers arise from adenomatous polyps. Alternately, several researchers, especially in Japan, have suggested that colorectal cancer can also develop from normal mucosa, in a *de novo* process involving morphological changes from a small superficial-type carcinoma to depressed-type carcinoma. *De novo* cancers are thought to have an aggressive growth phenotype, despite small tumour size, and to quickly infiltrate neighbouring tissue and lymph nodes. In this case, the tumour exhibited a severely thickened stalk, which suggested direct cancer invasion of the deep submucosa, and a clearly demarcated depressed area in the centre of the lesion, suggesting that it can originate *de*

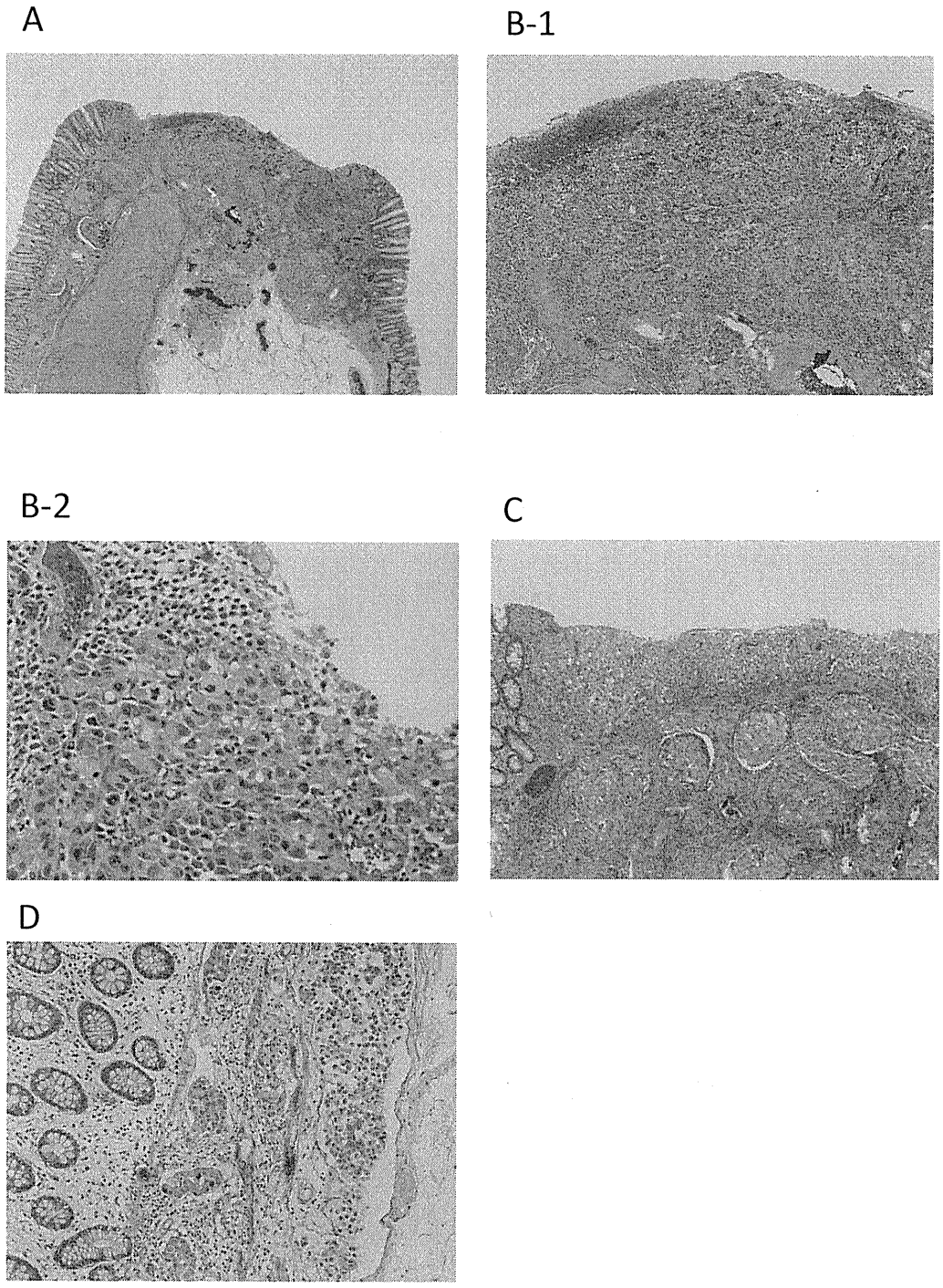

Figure 4 Pathological results of endoscopic mucosal resection. (A) An intramucosal component corresponding to the depressed lesion was observed. The tumour formed a massive invasion below the muscularis propria. (B-1,2) The tumour was composed of poorly differentiated adenocarcinoma and signet-ring cell carcinoma, mostly formed by solidly proliferating cells but with some indistinct gland formation. (C) The tumour had an intramucosal component, but infiltrated deeply into the submucosal layer with severe lymphatic and venous invasion. (D) Extensive lymphatic and venous invasion was detected mainly under the muscularis propria.

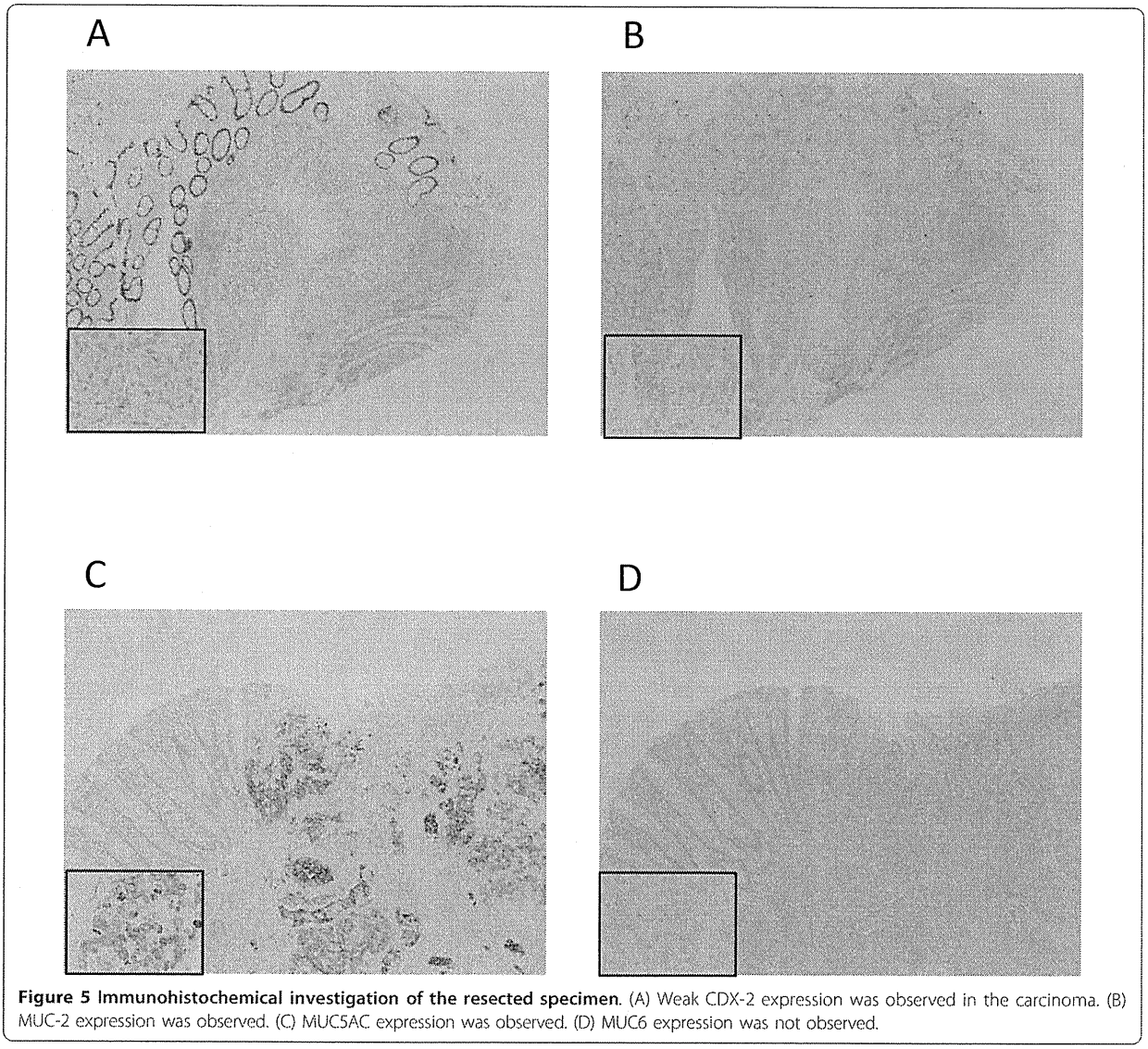

Figure 5 Immunohistochemical investigation of the resected specimen. (A) Weak CDX-2 expression was observed in the carcinoma. (B) MUC-2 expression was observed. (C) MUC5AC expression was observed. (D) MUC6 expression was not observed.

novo simply due to its morphology and clinical behaviour. This case of small primary colon cancer with systemic metastasis provides valuable support for the aggressive malignant potential of the *de novo* pathway in colorectal carcinogenesis.

In conclusion, we have reported a rare case of small primary colon cancer with systemic metastasis

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Abbreviations

CK: cytokeratin, CT: computed tomography, EMR: endoscopic mucosal resection, IHC: immunohistochemistry

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Authors' contributions

MM collected the data and wrote the report, and was involved in drafting the manuscript. TN revised the manuscript critically for important intellectual content. All authors read and approved of the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: A retrospective multicenter study

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Depth of invasion in early invasive colorectal cancer is considered an important predictive factor for lymph node metastasis. However, no large-scale reports have established the relationship between invasion depth of pedunculated type early invasive colorectal cancers and risk of lymph node metastasis. The aim of this retrospective cohort study was to clarify the risk of lymph node metastasis in pedunculated type early invasive colorectal cancers in a large series. Patients with pedunculated type early invasive colorectal cancer who underwent endoscopic or surgical resection at seven referral hospitals in Japan were enrolled. Haggitt's line was used as baseline and the invasion depth was classified into two groups, head invasion and stalk invasion. The incidence of lymph node metastasis was investigated between patients with head and stalk invasion. We analyzed 384 pedunculated type early invasive colorectal cancers in 384 patients. There were 154, 156, and 74 endoscopic resection cases, endoscopic resection followed by surgical operation, and surgical resection cases, respectively. There were 240 head invasion and 144 stalk invasion lesions. Among the lesions treated surgically, the overall incidence of lymph node metastasis was 3.5% (8/230). The incidence of lymph node metastasis was 0.0% (0/101) in patients with head invasion, as compared with 6.2% (8/129) in patients with stalk invasion. Pedunculated type early invasive colorectal cancers pathologically diagnosed as head invasion can be managed by endoscopic treatment alone. (*Cancer Sci* 2011; 102: 1693–1697)

It has been reported that intramucosal colorectal cancers show no lymph node metastasis and are good candidates for endoscopic resection.[1,2] In contrast, 6–12% of early invasive colorectal cancers (i.e. cancer cells invade through the muscularis mucosae into the submucosal layer but do not extend into the muscularis propria) are associated with lymph node metastasis requiring surgical resection including lymph node dissection for curative treatment.[3–7] Recently, increasing evidence suggests that lesions with submucosal invasion limited to <1000 μm without lymphovascular invasion and/or poorly differentiated components do not metastasize to lymph nodes.[8] Endoscopic resection is an appropriate treatment for early stage colorectal cancers, however, the resected specimen must be examined to determine whether there is a clinically significant risk of lymph node metastasis that would warrant additional surgery. Colorectal lesions can be subdivided according to endoscopic appearance using the Paris classification (Fig. S1), whereas Haggitt's classification is frequently used to define the depth of invasion of pedunculated lesions.[9] Haggitt and colleagues stratified the level of cancer invasion according to the following criteria: level 0, carcinoma *in situ* (i.e. has not extended below the muscularis mucosae); level 1, carcinoma invading through the muscularis mucosae but limited to the head of the polyp (i.e. above the junction between the adenoma and its stalk); level 2, carcinoma invading the level of the neck (i.e. the junction between adenoma and its stalk); level 3, carcinoma invading any part of the stalk; and level 4, carcinoma invading into the submucosa of the bowel wall below the stalk (Fig. S2). The authors concluded a low risk of metastasis or local recurrence when the level is <4. Pedunculated lesions can easily be treated endoscopically, however, there are no large-scale reports establishing the risk of lymph node metastasis in this lesion type stratified by depth of invasion. We report the incidence of lymph node metastasis in pedunculated type early invasive colorectal cancers in a large series.

Materials and Methods

Patients. Patients with pedunculated type early invasive colorectal cancers that had been treated by endoscopic resection or surgical resection at seven institutions in Japan (National Cancer Center Hospitals [Tokyo, Kashiwa], Tokyo Medical University Hospital, Okayama University Hospital, Shizuoka Cancer Center, Tochigi Cancer Center, and Okayama Saisei-kai General Hospital) between January 1992 and December 2007 were examined retrospectively. Patients eligible for this study had pathologically proven adenocarcinoma invading through the muscularis mucosae into the submucosal layer but not extending deeply into the muscularis propria. Eligibility also required the lesion to be endoscopically diagnosed as pedunculated type suitable for one-piece resection. Patients with synchronous advanced colorectal cancer, multiple early invasive colorectal cancers, inflammatory bowel disease, hereditary non-polyposis colorectal cancer, and familial adenomatous polyposis were excluded from this study. This study was carried out with the approval of each institution's ethics review board.

Treatment strategy. *Endoscopic resection:* All lesions diagnosed as intramucosal or superficial submucosal invasive cancers at colonoscopy were removed by polypectomy or endoscopic mucosal resection. If the histopathological result did not meet the criteria for complete endoscopic resection, additional surgery was recommended. *Surgical operation:* Patients with endoscopic features suggestive of submucosal invasion into the stalk were referred directly for surgical operation (i.e.

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colectomy with lymph node dissection). Among the lesions treated surgically, the incidence of lymph node metastasis was analyzed. Recurrence was recorded as local, distant, and overall. Recurrent lesions were identified by endoscopic examinations, CT scan, or abdominal ultrasound.

Histopathologic evaluation. Resected specimens were immediately fixed in a 10% buffered formalin solution. Paraffin-embedded samples were then sliced into 3-μm sections and were stained by H&E. Experienced gastrointestinal pathologists blinded to each endoscopic diagnosis evaluated all pathological specimens. The histopathological type and lymphovascular (lymphatic and venous) invasion, poor differentiation, and depth of invasion were examined. Histopathological diagnosis was based on the World Health Organization criteria.[10] The upper limit of level 2 according to Haggitt's classification was used as baseline for all lesions and the invasion depth was classified into two groups (head invasion and stalk invasion).

Definition of terms. *Haggitt's line:* The baseline to distinguish between head invasion and stalk invasion. This imaginary line is drawn according to an upper limit of level 2 invasion by Haggitt *et al.* (Fig. 1). *Head invasion:* The deepest portion of cancer invasion is limited to above the baseline (Haggitt's line), as shown in Figure 1(A). *Stalk invasion:* The cancer has invaded into the submucosal layer deeply beyond Haggitt's line (Fig. 1B).

Statistical analysis. Patients' characteristics were summarized using mean and standard deviation for continuous variables, and percentage for discrete variables. Both the chi squared test and Fisher's exact tests were used to examine the difference in incidence (lymph node metastasis and recurrence) between head invasion and stalk invasion. Risk factors for lymph node metastasis were also examined by chi squared or Fisher's exact tests. All statistical tests were two-sided and the significance level was set at 5%. All statistical analysis was carried out using SPSS statistical software (version 16.0J for Windows; SPSS, Tokyo, Japan).

Results

A total of 384 patients with pedunculated type early invasive colorectal cancer (male, 286 [74%]; female, 98 [26%]; mean age, 62.7 years [range, 29–89 years]; follow-up period [median], 44 months) were enrolled in this study. There were 154 (40%), 156 (41%), and 74 (19%) endoscopic resection cases, endoscopic resection followed by surgical operation, and surgical resection cases, respectively. The mean tumor size was 18.2 ± 8.0 mm (range, 5–60 mm), and location was as follows: sigmoid colon, 304 (79%); ascending colon, 25 (7%); rectum, 23 (6%); descending colon, 18 (5%); and transverse colon, 14 (3%). Three-hundred and forty patients (89%) were followed up and available for recurrence rate analysis. Among them, 159 (72%) patients in the head invasion group and 95 (79%) patients in the stalk invasion group were followed up for more than 36 months. In contrast, 21 (6%) patients were followed up for <12 months as shown in Table 1.

Histopathological characteristics. Among 384 pedunculated type early invasive colorectal cancers, 240 (63%) lesions were diagnosed as head invasion, and 144 (37%) were classified as stalk invasion. There were 54 (14%), 53 (14%), and 52 (14%) positive cases of lymphatic invasion, venous invasion, and poorly differentiated component, respectively (Table 2).

Incidence of lymph node metastasis and recurrence rate. The overall incidence of lymph node metastasis and recurrence rate were 3.5% (8/230; 95% confidence interval CI, 1.5–6.7%) and 0.3% (1/340; 95% CI, 0.01–1.6%), respectively (Table 2). Among lesions diagnosed as head invasion, the incidence of lymph node metastasis and recurrence rate were 0% (0/101; 95% CI, 0.0–3.6%) and 0% (0/219; 95% CI, 0.0–1.7%), as compared with 6.2% (8/129; 95% CI, 2.7–11.9%) and 0.8% (1/121; 95% CI, 0.02–4.50%) in patients with stalk invasion. Head versus stalk invasion: lymph node metastasis, $P = 0.02$; recurrence, $P = 0.72$.

Among lesions diagnosed as head invasion, 29 of 101 (29%) were lymphovascular (lymphatic and/or venous) invasion positive, and 72 of 101 (71%) were negative. There were no cases of lymph node metastasis in either group. In contrast, among stalk invasion lesions, 49 of 129 (38%) were lymphovascular invasion positive, whereas 80 of 129 (62%) were negative. There were three of 49 (6.1%) cases of lymph node metastasis in the lymphovascular invasion positive group, and there were five of 80 (6.3%) cases of lymph node metastasis in the lymphovascular invasion negative group, as shown in Table 3. There was no significant difference between lymph node metastasis and lymphovascular invasion.

Risk factors of lymph node metastasis. Clinicopathological factors were compared between lymph node metastasis positive

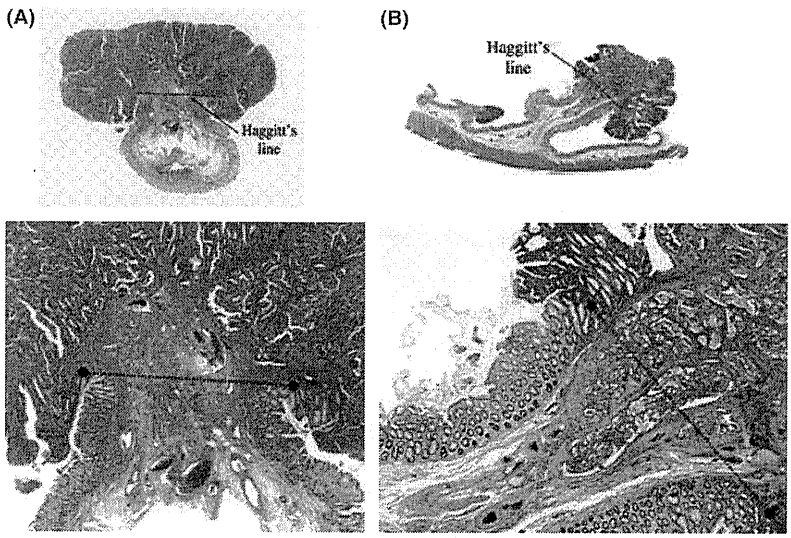

Fig. 1. Definition of head invasion (A) and stalk invasion (B) in pedunculated type early invasive colorectal cancer.

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Table 1. Clinical characteristics of 384 patients with pedunculated type early invasive colorectal cancer

	Head invasion	Stalk invasion	Total
Total number, *n* (%)	240 (63)	144 (37)	384 (100)
Gender (M/F), *n* (%)	183 (76)/57 (24)	103 (72)/41 (28)	286 (74)/98 (26)
Age (years), mean (range)	62.1 (36–87)	63.6 (29–89)	62.7 (29–89)
Size (mm), mean ± SD† (range)	17.5 ± 7.4 (6–60)	19.4 ± 9.0 (5–57)	18.2 ± 8.0 (5–60)
Location, *n* (%)			
Rectum	11 (5)	12 (8)	23 (6)
Sigmoid colon	194 (81)	110 (76)	304 (79)
Descending colon	13 (5)	5 (4)	18 (5)
Transverse colon	10 (4)	4 (3)	14 (3)
Ascending colon	12 (5)	13 (9)	25 (7)
Treatment strategy, *n* (%)			
Endoscopic resection	139 (58)	15 (10)	154 (40)
Endoscopic resection followed by surgical operation	67 (28)	89 (62)	156 (41)
Surgical operation	34 (14)	40 (28)	74 (19)
Follow-up period, median (months)	43	47	44
<12 months, *n* (%)	17 (8)	4 (3)	21 (6)
12–36 months	43 (20)	22 (18)	65 (19)
>36 months	159 (72)	95 (79)	254 (75)

†Standard deviation.

Table 2. Histopathological characteristics of 384 cases of pedunculated type early invasive colorectal cancer

	Head invasion	Stalk invasion	Total
Lymph node metastasis			
n (%)	0/101 (0)	8/129 (6.2)	8/230 (3.5)
95% CI (%)	0.00–3.60	2.70–11.90	1.50–6.70
		*	
Recurrence			
n (%)	0/219 (0)	1/121 (0.8)	1/340 (0.3)
95% CI (%)	0.00–1.70	0.02–4.50	0.01–1.60
		**	
Lymphovascular invasion†, *n* (%)	35/240 (15)	55/144 (38)	90/384 (23)
Lymphatic invasion, *n* (%)	21 (9)	33 (23)	54 (14)
Venous invasion, *n* (%)	16 (7)	37 (26)	53 (14)
Poorly differentiated component, *n* (%)	26/240 (11)	26/144 (18)	52/384 (14)

*P = 0.02; **P = 0.72. †Lymphatic and/or venous invasion.
CI, confidence interval.

Table 3. Lymphovascular invasion among 384 cases of pedunculated type early invasive colorectal cancer with lymph node metastasis

	Head invasion	Stalk invasion	Total
Lymph node metastasis, *n* (%)			
ly (+), v (+)	0/1 (0.0)	0/14 (0.0)	0/15 (0.0)
ly (+), v (–)	0/16 (0.0)	2/17 (11.8)	2/33 (6.1)
ly (–), v (+)	0/12 (0.0)	1/18 (5.6)	1/30 (3.3)
ly (–), v (–)	0/72 (0.0)	5/80 (6.3)	5/152 (3.3)

ly, lymphatic invasion; v, venous invasion.

and negative groups. Regarding the depth of invasion, eight stalk invasion cases were identified in the lymph node metastasis positive group, representing a significant difference compared with the negative group (P = 0.02). No significant differences in any other factors were noted between lymph node metastasis positive and negative groups (Table 4).

Discussion

Advances in endoscopic instruments and techniques have allowed increased detection of early stage colorectal cancer, and endoscopic resection is a safe and effective curative treatment for such lesions when there is no risk of lymph node metastasis.

Kudo[11] was the first to classify submucosal invasion of early invasive colorectal cancer as SM1 (upper third of submucosa), SM2 (middle third of submucosa), and SM3 (lower third of submucosa). Since then, Kikuchi *et al.*[12] have reported lymph node metastasis in 0%, 10%, and 25% of 182 patients with SM1, SM2, and SM3 early invasive colorectal carcinomas, respectively. More recently, Nascimbeni *et al.*[13] showed that SM3 invasion had a significantly higher risk of lymph node metastasis compared to SM1–2 by multivariate analysis (SM1, 3%; SM2, 8%; SM3, 23%). The overall risk of lymph node metastasis in early invasive colorectal cancer is approximately 10%, suggesting that endoscopic removal of the vast majority of lesions without surgical intervention could ultimately be curative. In contrast, the rate of lymph node metastasis in patients who underwent additional surgical excision of the colorectum following endoscopic treatment has been reported to be 2.1–25.0%.[3,14–17] This suggests that a significant percentage of patients may undergo unnecessary additional surgery following endoscopic treatment, and more stringent criteria are required to prevent this. Protruding colorectal neoplasms and, more specifically, pedunculated lesions may be easier than non-pedunculated lesions to detect and remove endoscopically. However, the risk

Table 4. Comparison of clinicopathological factors between lymph node metastasis positive (+) and negative (–) groups among 384 cases of pedunculated type early invasive colorectal cancer

Variables	Lymph node metastasis	*P*-value
Depth of invasion (stalk *vs* head)	(+) 8/0 (–) 121/101	0.02
Lymphovascular invasion (ly and/or v [+] *vs* [–])	(+) 3/5 (–) 75/147	>0.99
Poorly differentiated component	(+) 1/7 (–) 38/184	>0.99
Tumor size† (≥20 mm *vs* <20 mm)	(+) 5/3 (–) 101/108	0.67

†Unknown, 13 cases. ly, lymphatic invasion; v, venous invasion.

of lymph node metastasis and the prognostic significance of this specific subtype of early invasive colorectal cancer have not been sufficiently examined. This is the first large-scale multicenter study in Japan to assess the incidence of lymph node metastasis and recurrence of pedunculated type early invasive colorectal cancer.

Conventional measurement of submucosal invasion using SM1–SM3 was originally devised for examination of surgical specimens where the full thickness of the colonic wall was available to the pathologist. Haggitt's level 2 was used as the baseline to differentiate between head and stalk invasion by Kitajima *et al.*[18] and submucosal invasion depth was measured as the vertical distance from this baseline (Haggitt's line) to the deepest point of invasion. This method of invasion measurement is more appropriate to endoscopically resected specimens where the muscularis propria is not included. According to the data from the Japanese Society for Cancer of the Colon and Rectum, the "so-called 1000 μm rule of submucosal invasion" is applied to not only non-pedunculated type but also pedunculated type early invasive colorectal cancers. In our current study, among lesions diagnosed as "stalk invasion", the incidence of the "<1000 μm group" was under 10%, similar to Kitajima's data.[18] Moreover, all lymph node metastasis positive cases (eight cases) were classified into the "more than 1000 μm group". In this study, however, the number of lymph node metastasis positive cases was limited. Therefore, we concluded that more cases with stalk invasion and more cases with lymph node metastasis are necessary to investigate the feasibility of the present 1000 μm rule.

We devised a straightforward description of cancer invasion to either head (above Haggitt's line) or stalk (below this line) and estimated the risk of lymph node metastasis and recurrence rate for pedunculated type early invasive colorectal cancer according to these groups. In our retrospective study there was no risk of lymph node metastasis in patients with head invasion (0%, 0/101) compared to 6.2% (8/129) of patients with stalk invasion. Furthermore, the recurrence rate during the follow-up period (mean ± SD, 40.7 ± 24.1 months) in patients with head invasion treated by endoscopic resection was also 0% (0/139; 95% CI, 0.0–2.6%).

In the past 20 years investigators have proposed that the presence of submucosal invasion more than 1000 μm, lymphatic invasion, and/or poor differentiation required additional surgery following endoscopic mucosal resection of early invasive colorectal cancer. Conversely, depth of invasion (stalk invasion) was the only predictive factor for lymph node metastasis in our study. Although our results showed that none of the patients in the head invasion group showed lymph node metastasis, lymphovascular invasion was present in 29 cases in this group and these patients underwent additional surgery. Our results are promising and indicate that the risk of lymph node metastasis in these 29 patients is low, however, prospective studies confirming these findings are required before a change in surgical management is implemented.

It is widely recognized that depressed type (0–IIc) lesions invading into the submucosa display a significantly higher rate of lymph node metastasis in comparison to protruded type (0–Ip and 0–Is), superficial elevated (0–IIa), and flat (0–IIb) lesions.[6,18,19] Pan *et al.*[20] also reported that early invasive colorectal cancers at the fold-top or with a long distance from the muscularis mucosae to the muscularis propria have a lower tendency to metastasize to lymph nodes. These studies indicate that the lower rate of lymph node metastasis in pedunculated type early invasive colorectal cancers could be elucidated by the presence of a greater muscularis mucosae to muscularis propria distance. Our study also showed a low rate of lymph node metastasis in pedunculated type lesions, although this data was only available for patients who underwent surgical resection (n = 230).

Some controversies with regard to pedunculated type lesions exist. Haggitt *et al.*[9] stipulated that the presence or absence of a stalk is largely irrelevant histopathologically. Moreover, they commented that the surgeon and pathologist may disagree on stalk length or even existence. Certain factors such as traction force used during removal, retraction of the pedicle following division and shrinkage after fixation could explain this. To avoid contention we imposed strict inclusion criteria in our study allowing only endoscopically diagnosed pedunculated type lesions with an obvious stalk to be eligible.

There are some limitations to our study. First, we retrospectively analyzed the clinical records of all patients who underwent endoscopic resection or surgical resection for pedunculated type colorectal cancers at seven institutes in Japan. The number of examined cases was large compared to previous studies, however, we did not re-evaluate lymphovascular invasion using immunohistochemical staining for all cases. Routine use of immunohistochemistry should be considered in future retrospective studies. Second, several authors have indicated that early invasive colorectal cancers in the rectum have a higher incidence of lymph node metastasis and local recurrence.[9,12,21] We were unable to assess this risk in our patients as 79% (304/384) of the pedunculated type lesions were located in the sigmoid colon. Finally, tumor budding, which has also been referred to as sprouting or dedifferentiation[22,23] was not evaluated in this study. We evaluated the presence or absence of any poorly differentiated adenocarcinoma component, including that found at the most invasive submucosal margin. This is similar to the focal dedifferentiation reported by Tominaga *et al.*,[24] however, Sohn *et al.*[25] argued that tumor budding should be categorized separately.

In conclusion, all cases with lymph node metastasis or recurrence were categorized into the stalk invasion group in this retrospective multicenter study. Our data suggest that pedunculated type early invasive colorectal cancer diagnosed as head invasion could be managed by endoscopic treatment alone.

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