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Case Report

Isolated Right External Iliac Lymph Node Recurrence from a Primary Cecum Carcinoma: Report of a Case

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Isolated lymph node recurrence in the right external iliac region in cases of cecum carcinoma is extremely rare, and the significance of surgical resection for isolated lymph node recurrence has not been established due to the low number of such cases. We report the first case of isolated right external iliac lymph node recurrence from a primary cecum carcinoma, successfully treated by surgical resection.

Key words: cecum carcinoma – isolated lymph node recurrence – surgical resection

INTRODUCTION

In most carcinomas other than colorectal carcinoma, when recurrence is discovered after resection of the primary lesion, they are treated as systemic disease, and salvage surgery is not usually indicated for the recurrent lesion. However, in colorectal carcinoma, resection of the recurrent lesion may improve patient prognosis. In particular, liver metastasis, pulmonary metastasis, and local recurrence are known to be likely to show improved prognosis with surgical resection (1–8). However, with regard to isolated lymph node recurrence, which occurs relatively rarely, although there are some reports of long-term survival following surgical resection, the significance of surgical resection has not been established due to the low number of such cases (9–13). Recently, we encountered a patient with isolated lymph node recurrence in the right external iliac region after radical resection for cecum carcinoma, who underwent en bloc resection of the external iliac vessels and is surviving disease free 18 months after surgery. Isolated lymph node recurrence in the right external iliac region in cases of cecum carcinoma is extremely rare and has not been reported previously in the literature.

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CASE REPORT

A 67-year-old male was referred to the Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan, in November 2002 for the treatment of cecum carcinoma. There was no evidence of metastasis by chest and abdominal computed tomography (CT) scan, except lymph node swelling near the primary lesion. Open right hemicolectomy with lymph node dissection was performed. Macroscopically, the primary lesion appeared to have invaded the abdominal wall in the lower right abdomen, and therefore we performed resection by scraping part of the transverse muscle of the abdomen. The tumor was staged as Stage IIIC (TNM classification), which refers to a moderately-to-poorly differentiated adenocarcinoma. It measured 45 mm in maximal diameter and extended through the bowel wall to the serosa, but not into the abdominal wall (Fig. 1).

Adjuvant chemotherapy was performed using 5-fluorouracil (5-FU) and l-leucovorin (LV). The administration schedule consisted of a 2-h intravenous infusion of l-LV (250 mg/m^2) and an intravenous bolus injection of 5-FU (600 mg/m^2) given 1 h after the start of l-LV infusion. The regimen was repeated every 7 days for 4 weeks with a 2-week pause. 5-FU and l-LV were administered 16 times over 6 months. The patient was then followed by a periodic check-up until his carcinoembryonic antigen (CEA) level increased to 12.8 mg/dl in April 2004, at which time an induration in the lower right abdominal wall, close to the

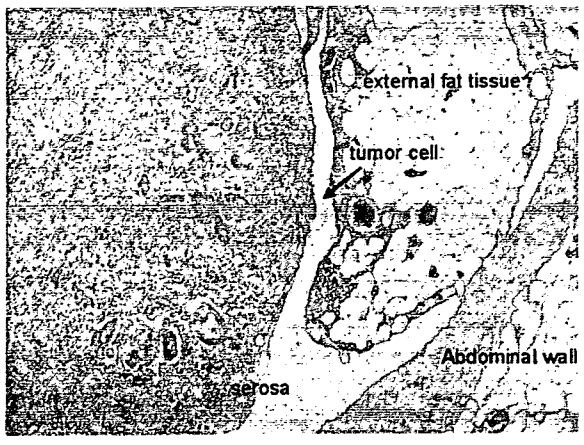

Figure 1. H & E staining of the resected specimen. The tumor cell does not extend into the abdominal wall.

groin, was detected by palpation. The CT scan delineated a mass on the abdominal side of the right external iliac vessels and positron emission tomography (PET) showed a hot spot in the same region. At this point, we considered the possibility of lymph node recurrence, but there were no reported cases of lymph node metastasis occurring in this region after resection of cecum carcinoma and we were also not able to exclude the possibility of peritoneal dissemination. For these reasons, chemotherapy was performed using l-LV, 5-FU and irinotecan. The administration schedule consisted of a 2-h intravenous infusion of l-LV (10 mg/m^2) and an intravenous bolus injection of 5-FU (400 mg/m^2) given 1 h after the start of l-LV infusion, followed by a 1.5 h intravenous infusion of irinotecan (100 mg/m^2). The regimen was repeated every 14 days for 4 weeks with a 1-week pause. l-LV, 5-FU and irinotecan were administered 12 times over 7 months. During this period, the CEA level gradually reduced but chest and abdominal CT performed in October 2004 still showed a mass measuring 23 mm on the abdominal side of the right

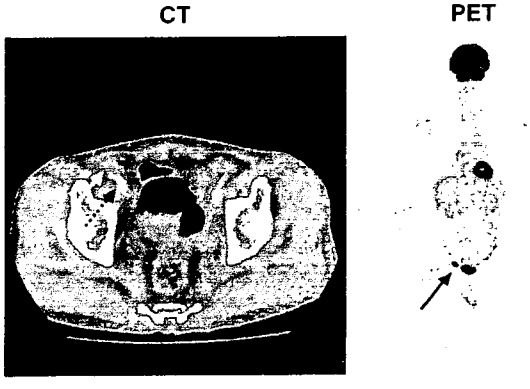

Figure 2. CT and PET findings. Delineated is a mass on the abdominal side of the right external iliac vessels. Solid line, tumor; dotted line, external iliac vessels.

Figure 3. Surgical finding. The mass was fixed to the abdominal side of the right external iliac vessels. En bloc resection with external iliac vessels. Solid line A, tumor; dotted line, external iliac vessels; solid line B, end-to-end anastomosis.

external iliac vessels without a clear boundary with the blood vessels. On both CT and PET, there was no finding of recurrence in other regions (Fig. 2). At this point, we decided to perform surgical resection.

Surgery was performed in November 2004. After laparotomy, there was no finding of metastasis or recurrence in the abdominal cavity, except for the mass in the right external iliac region outside the peritoneum. The mass was fixed to the abdominal side of the right external iliac vessels and in order to increase local radicality, *en bloc* resection with external iliac vessels was performed (Fig. 3). The blood vessels were successfully reconstructed by end-to-end anastomosis. The patient had a favorable post-operative progress and was discharged from the hospital without complications.

In the resected specimen, the cross-section of the tumor showed a smooth margin, uniform interior and clear boundary with the blood vessels. H & E staining of the tumor confirmed the finding of lymph node recurrence of colorectal cancer without invasion into the right external iliac vein, but showed that the capsule of the lymph node came in contact with the blood vessels (Fig. 4). No anti-tumor effect of chemotherapy was observed. Eighteen months after the operation, the patient is surviving recurrence free.

DISCUSSION

There has been no previous report of isolated metastasis in the right external iliac lymph nodes after radical resection for

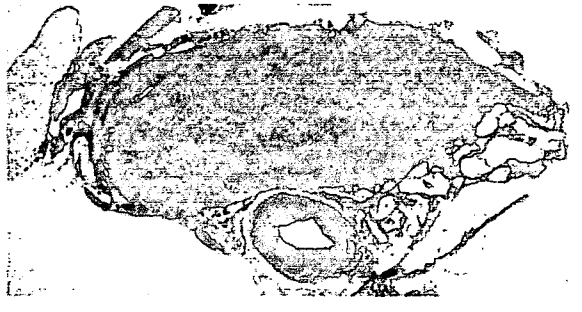

Figure 4. Resected specimen. H & E staining of the tumor confirmed the finding of lymph node recurrence of colorectal cancer without invasion into the right external iliac vein.

cecum carcinoma in the literature. The patient reported underwent surgical resection following chemotherapy and is surviving recurrence free. Generally, lymph node recurrence after colorectal cancer surgery is regarded as systemic disease, and in such cases, chemotherapy, radiotherapy or a combination of both, rather than surgery, is selected. With regard to isolated lymph node recurrence such as this case, there are some reports of resection, but the significance of surgical treatment remains unclear (9–13). Of the previous cases, one patient survived 19 months disease free, one patient survived 36 months although the patient developed hepatic metastasis and was successfully resected, and the other patient died after 18 months as a result of peritoneal dissemination without lymph node recurrence. (9, 11, 12). If there is no finding of recurrence in other regions and surgery is not difficult to perform, then it may be necessary to consider surgery.

An interesting aspect about this particular case is the lymphatic pathway the cecum carcinoma followed to metastasize to the lymph node in the right external iliac region. Most lymphatic pathways run along arteries and it is generally considered that the lymphatic system from cecum carcinoma usually extends to the root of the superior mesenteric artery along the ileocolic artery (14). Lymphatic pathways running to the right external iliac region have not been reported to date. In this case, although obvious tumor invasion into the abdominal wall was not detected histopathologically in the primary lesion, tumor invasion into the abdominal wall was suspected macroscopically at the time of the first operation. One possibility is that the tumor invaded part of the abdominal wall microscopically and then metastasized to the lymph node in the region of the right external iliac artery through a lymphatic pathway along the right inferior epigastric artery.

Isolated lymph node recurrence rarely occurs in colorectal cancer and there is no agreement regarding surgical indication for this condition. However, in surgical treatment for liver and pulmonary metastases, the minimum requirement is local control (1–8). In our case, favorable local control was achieved by initial surgery and, therefore, surgical resection was indicated for recurrent lesion, because of the possibility of achieving long-term prognosis. With regard to *en bloc* resection of blood vessels, it goes without saying that there is a fear of increased risk of complications. However, from the oncological viewpoint, even if the tumor does not invade blood vessels through the capsule of the lymph node, the risk of tumor cell spillage is increased if the dissection maneuver cuts into the lymph node capsule, even to a slight degree. It should of course be avoided. In patients with lateral pelvic lymph node metastasis from rectal carcinoma at our institution, we have reported the favorable effect of lateral lymph node dissection with *en bloc* resection of the internal iliac vessels on local control (15). However, *en bloc* resection of the external iliac vessels requires revascularization and if the range of resection is wide, artificial vessels become necessary. For lymph node recurrence near blood vessels, *en bloc* resection of the vessels may be preferable from the viewpoint of local control, but should be considered only if it can be justified after considering the risks associated with surgery.

CONCLUSION

We encountered a case of right external iliac lymph node recurrence after radical resection for cecum carcinoma, successfully treated by surgical resection. For isolated lymph node recurrence of colorectal carcinoma, surgical resection should be considered, if favorable local control has been achieved. However, further cases need to be accumulated with regard to treatment outcome.

Conflict of interest statement
None declared.

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Diseases of the Colon & Rectum

Minute Depressed-Type Submucosal Invasive Cancer–5 mm in Diameter with Intermediate Lymph-Node Metastasis: Report of a Case

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We report a rare case of colon cancer in which a depressed-type tumor only 5 mm in diameter invaded the submucosal layer and produced intermediate lymph node metastasis. A 47-year-old male received a total colonoscopy for a depressed-type lesion with marginal elevation in the sigmoid colon. The lesion measured 5 mm in diameter. On chromoendoscopic examination, the depression was clearly demarcated and an irregular pit pattern was identified in the demarcated area by magnification suggesting invasion of the submucosal layer requiring surgery. Laparoscopic-assisted sigmoidectomy was performed and the resected specimen demonstrated well-differentiated adenocarcinoma. The depth of invasion was only 900 μm. There was no lymphovascular invasion although not only paracolic, but also intermediate lymph node metastasis was detected. There have been some reports about small depressed-type colorectal cancer invading the submucosal layer; however, intermediate LN metastasis is very rare in submucosal colorectal cancer. In this case, there were two noteworthy points: 1) despite the small size, submucosal invasion could be estimated preoperatively, therefore, a successful lymph node dissection was performed by laparoscopic surgery; and 2) although this depressed-type cancer invaded the submucosal layer only 900 μm and there was no lymphovascular invasion, intermediate lymph node metastasis was detected. [Key words: Early colorectal cancer; Chromoendoscopy; Magnifying colonoscopy]

Reprints are not available.

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Colorectal polypoid-type adenoma is considered the precursor in the majority of colorectal cancer (CRC) cases. The early detection and treatment of these lesions is thought to reduce CRC mortality. Morson[1] estimated that up to two-thirds of CRC develop from adenomatous polyps. Recently, improved endoscopic imaging and advancements in diagnostic technology have led to a higher rate of detection of superficial and small colorectal tumors.[2,3] It has been reported that lesions <10 mm in diameter, whether polypoid or nonpolypoid, were unlikely to be advanced cancer[4]; however, Japanese researchers have reported the existence of advanced cancer lesions <10 mm in diameter.[5,6] Several reports, mostly from Japan, have suggested that some CRC also can develop *de novo* from normal mucosa.[7–9] An alternative explanation is that some carcinomas have an especially aggressive growth pattern that quickly destroys the adjacent adenomatous tissue.

With regard to the pathology, the method of measuring the depth of submucosal (sm) invasion remains controversial. A relative classification system

Figure 1. Conventional colonoscopic views showing a reddish lesion approximately 5 mm in diameter located in the sigmoid colon.

has been used to evaluate sm depth of invasion as follows: sm1, infiltration into the upper third of the submucosal layer; sm2, middle third; and sm3, lower third. Several studies have demonstrated the usefulness of this method for predicting lymph node metastasis[10]; however, this method has not been useful for specimens obtained endoscopically because these specimens do not include the muscularis propria. An absolute classification system, therefore, has become generally accepted to evaluate endoscopic resected specimens. This method classifies the vertical depth of sm invasion from the lowest edge of the muscularis mucosae as follows: sm superficially,

Figure 2. Slightly reddish and depressed lesion detected with marginal elevation (IIa + IIc).

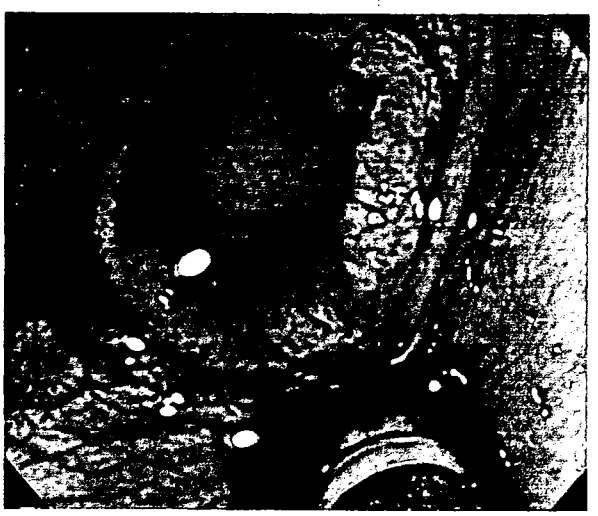

Figure 3. Chromoendoscopy after indigo carmine dye spraying more clearly showed the demarcated depressed area with the center of the depressed area slightly elevated.

<1 mm; and sm deep, ≥1 mm. A standardized method of measuring sm depth has not been established yet. We report a case of small Dukes C colon cancer in which a 5-mm depressed-type tumor was diagnosed endoscopically.

REPORT OF A CASE

A 47-year-old male was referred to our institution for further treatment of a colonic lesion in September 2004. Neither the patient nor the patient's family had a past medical history of cancer. The patient had consulted the previous hospital because of a positive fecal-occult-blood-test. At that time, a total colonoscopy identified a small, depressed lesion in the sigmoid colon. Conventional colonoscopic examination showed a slightly reddish depressed-type lesion with a marginal elevation (IIa+IIc) in the sigmoid colon (Figs. 1 and 2). This lesion measured only 5 mm in diameter and there were no other lesions in the colorectum. After 0.2 percent indigo carmine dye spraying, chromoendoscopic examination showed a clearly demarcated depression (Fig. 3) and crystal violet staining with magnified view (Olympus CF Q 240ZI; Olympus, Tokyo, Japan) identified an irregular pit pattern in the demarcated area corresponding to an invasive pattern (Fig. 4).[11,12] This tumor, therefore, was diagnosed as having invaded the sm layer, resulting in a contraindication for endoscopic mucosal resection (EMR). A biopsy sample demonstrated well-differentiated adenocarcinoma, and there was

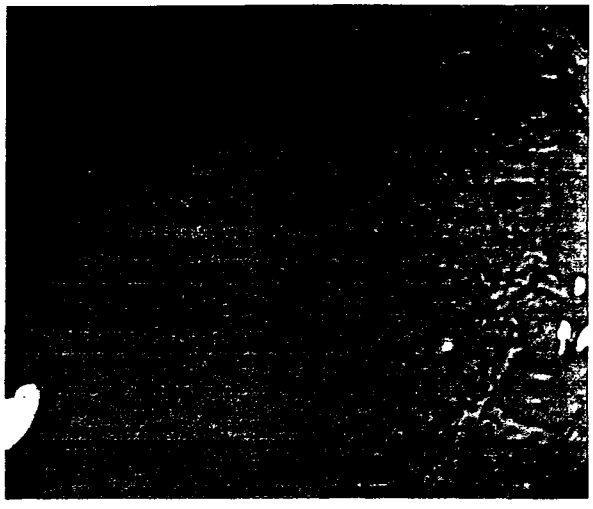

Figure 4. Magnified view with crystal violet staining of the surface of the central depression with an irregular pit pattern identified in the demarcated area.

Figure 6. High-power magnification showing the surface glands of the depressed area were destroyed was consistent with the magnifying colonoscopy findings.

no evidence of metastasis found on computed tomography. A laparoscopic-assisted sigmoidectomy was performed without complication and the resected specimen also demonstrated well-differentiated adenocarcinoma. The depth of invasion was 900 μm and there was no lymphovascular invasion found (Figs. 5 and 6). A deeper cut was performed to evaluate for lymphatic invasion, but there were no findings suggesting such invasion. As for lymph-node metastasis, 14 lymph nodes were examined: two were positive and one of these was intermediate LN (lymph node) metastasis (Fig. 7).

DISCUSSION

There have been some reports about small, depressed-type CRC invading the sm layer; however, intermediate LN metastasis was very rare.[13] In this case, there were two noteworthy points as follows: 1) despite the small size of the lesion, endoscopic findings, including magnifying chromoendoscopy were able to diagnose sm invasion before treatment; and 2) although this depressed-type cancer invaded the sm layer only 900 μm and there was no lymphovascular invasion, intermediate LN metastasis

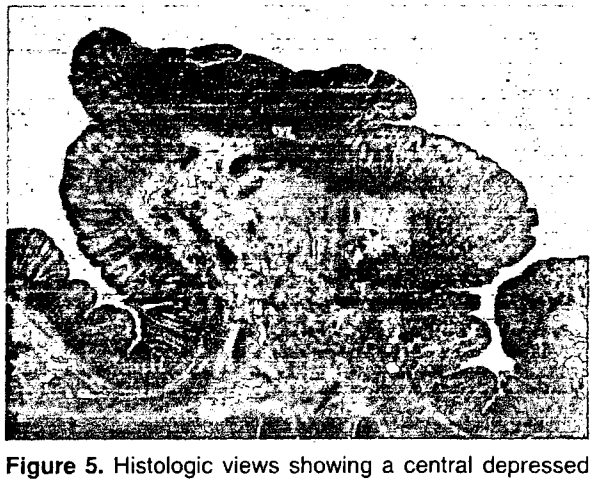

Figure 5. Histologic views showing a central depressed area with a well-differentiated adenocarcinoma invading the submucosa (900 μm). Although there was no lymphovascular invasion, the muscularis mucosa was completely destroyed.

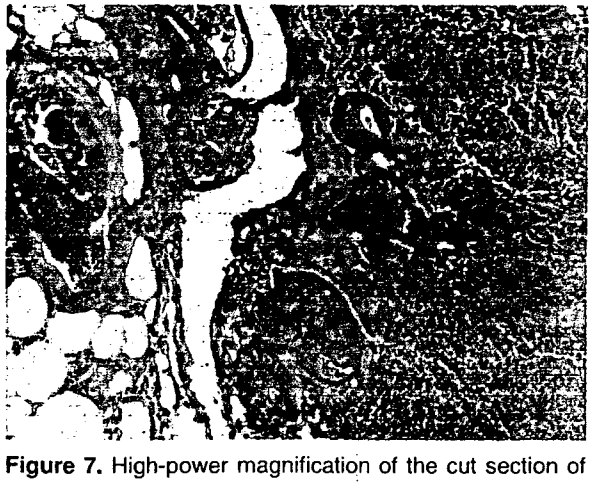

Figure 7. High-power magnification of the cut section of the intermediate lymph node showed focal well-differentiated adenocarcinoma suggesting metastasis.

was detected. After the preoperative diagnosis, successful LN dissection was performed by laparoscopic surgery and this lesion was definitively diagnosed as Dukes C colon cancer.

The adenoma-carcinoma sequence is thought to be the main pathway of CRC carcinogenesis in which carcinoma develops from adenoma.[1] Various oncogenes and tumor suppressor genes, including the APC, K-*ras*, p53, and DCC genes, have been reported to be involved in the carcinogenesis of CRC.[14] In addition, the existence of some depressed-type CRC has been reported, particularly from Japan, raising the possibility that some cancers may develop *de novo* following a different pathway from the adenoma-carcinoma sequence. In fact, a lower frequency of K-*ras* gene mutations is more likely to be found in these lesions, showing a much higher rate of sm invasion despite their small size in contrast to protruding-type lesions.[15,16] Endoscopists, therefore, should pay particular attention to depressed lesions given their higher malignancy potential.

Recently, endoscopic resection has become a generally accepted procedure for superficial or small CRC where the probability of lymph-node metastasis is low and depth of sm invasion is considered an important predictive factor for lymph-node metastasis. According to the Paris workshop guidelines, superficial-type CRC with a depth of invasion <1,000 μm has a very low risk of lymph-node metastasis.[17] The incidence of lymph node metastasis is reported to be approximately 10 percent for CRC with sm invasion, 2 to 3 percent for CRC superficially invading the sm, and 8 to 12 percent for CRC deeply invading the sm.[18] In a recent collaborative Japanese study of nonpedunculated sm invasive CRC, the rate of lymph-node metastasis was 0 percent when the sm depth of invasion was <1,000 μm.[19] In that analysis, 1) an undifferentiated-type tumor, 2) existence of lymphatic or venous infiltration, and 3) a depth of invasion ≥ 1,000 μm from the muscularis mucosae (mm) were independent risk factors for LN metastasis based on multivariate analysis, whereas univariate analysis identified the destruction of the mm as an additional risk factor. Another study conducted at our institution recently[20] used multivariate analysis to show that lymphatic invasion and high-grade focal dedifferentiation at the submucosal invasive front were independent factors predicting lymph-node metastasis.

In this case, only destruction of the mm met these criteria and there were no other risk factors for LN metastasis. The depth of invasion was only 900 μm, and there was no lymphovascular invasion or poorly differentiated component. According to our institution's recent study,[20] univariate analysis showed that the status of the remaining muscularis mucosa had a significant connection with lymph-node metastasis. Physicians should be careful when encountering this type of lesion, because the complete destruction of the mm may be one of the risk factors for LN metastasis. After the preoperative diagnosis, a lymphadectomy was successfully performed by laparoscopic surgery, and there has been no apparent recurrence detected 12 months after surgery.

CONCLUSIONS

We report a rare case of CRC invading the sm layer and showing metastasis to not only the paracolic but also intermediate LN despite the small size of the lesion. For a depressed-type cancer, it is necessary to carefully examine the lesion to establish an accurate diagnosis and perform suitable treatment.

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Original Paper

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Impact of Upward Lymph Node Dissection on Survival Rates in Advanced Lower Rectal Carcinoma

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Key Words
Lymph node dissection · Upward lymph node dissection · Lower rectal carcinoma

Abstract
Background/Aims: This study investigated appropriate level of upward lymph node (LN) dissection in advanced lower rectal carcinoma. ***Methods:*** A total of 285 consecutive patients with stage II/III lower rectal carcinoma were analyzed. LN dissection was classified as follows: division of the root of the superior rectal artery (UD2), division of the root of the inferior mesenteric artery (UD3) and UD3 with para-aortic LN dissection (UD4). ***Results:*** LN metastases at the root of the inferior mesenteric artery were found in 4 patients. Their prognoses were worse than those of the other stage III patients ($p = 0.011$). On the other hand, LN metastases along the superior rectal artery were discovered in 14 patients, whose 5-year overall survival rate was 61.2%. By removing the LNs either UD2 or UD3/4, a similar survival rate was achieved in stage III patients with LN metastases along the superior rectal artery. ***Conclusion:*** Survival of a minority with metastatic LNs at the root of the inferior mesenteric artery was poor. Additionally, survival is no worse in patients with positive LN along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. Low ligation is adequate for advanced lower rectal carcinoma.

Introduction

It is well known that lower rectal carcinoma has two routes of lymphatic spread, i.e. upward and lateral spread. There have been many reports that discuss the significance of lateral pelvic lymph node dissection for advanced lower rectal carcinoma [1–4]. However, there have not been any definitive conclusions and various opinions have been expressed around the world. On the other hand, the impact of upward lymph node dissection for sigmoid colon or upper rectal carcinoma has been discussed in several reports [5–7], and yet few studies have focused on this issue in advanced lower rectal carcinoma. Although Pezim et al. [8] reported that high ligation of the inferior mesenteric artery had no survival advantage for rectal carcinoma patients, no counterarguments have been published and it remains difficult to generalize about the impact of upward lymph node dissection. The appropriate extent of upward lymph node dissection for advanced lower rectal carcinoma remains an unsolved issue and guidelines need to be established.

This study presents a detailed estimation of how the level of upward lymph node dissection affects survival rates following curative resection in advanced lower rectal carcinoma.

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Patients and Methods

Between 1990 and 2002, a series of 303 consecutive patients at the National Cancer Center Hospital, Tokyo, underwent curative surgery for stage II or III lower rectal carcinoma. Lower rectal carcinoma was defined as a tumor with a distal margin 7 cm or less from the dentate line by digital examination and/or proctoscopy. Five patients with a history of malignancy (sigmoid colon carcinoma in 3 and bladder carcinoma in 2), who previously underwent lymph node dissection along the inferior mesenteric artery or in the lateral pelvis, were excluded, because the routes of lymphatic spread seemed to be changed in these cases. Two patients with synchronous advanced rectosigmoid carcinoma were excluded. Three stage II patients and 8 stage III patients did not undergo lymph node dissection along the inferior mesenteric artery but only in the mesorectum (UD1), because of preoperative underestimation. These 11 patients were also excluded. Consequently, 285 patients were eligible for this study. The mean (SD) distance from the dentate line of the tumor was 2.4 (1.0) (range 0.0–7.0) cm. No patients received preoperative radiotherapy and/or chemotherapy. All patients were evaluated before surgery by total colonoscopy, barium enema and computed tomography. To evaluate comorbid conditions, cardiopulmonary function and renal function tests were performed. In our study, lateral pelvic lymph nodes were regarded as regional lymph nodes according to the Japanese classification of colorectal carcinoma [9], although lateral pelvic lymph node metastases are regarded as distant metastases in the TNM classification system [10]. Clinical stage II or III middle or lower rectal carcinoma, located at or below the peritoneal reflection, is an indication for lateral pelvic lymph node dissection in our hospital [2, 3]. Postoperative adjuvant chemotherapy using oral or intravenous fluoropyrimidines was administered for 6 months to 27 stage III patients. Two stage III patients received postoperative radiotherapy and another underwent concomitant chemoradiotherapy.

The incidence of upward lymph node metastases based on histopathological data from the resected specimen, recurrence sites and survival rate were retrospectively analyzed and the appropriate extent of upward lymph node dissection for advanced lower rectal carcinoma was evaluated.

Classification of the Level of Upward Lymph Node Dissection

Standard surgical procedures at our institution were previously reported in detail [11, 12]. The extent of upward lymph node dissection was classified as follows: UD1 is defined as resection of the mesorectum, UD2 as division of the root of the superior rectal artery with lymph node dissection below that level, UD3 as division of the root of the inferior mesenteric artery with lymph node dissection below that level and UD4 as UD3 with the addition of para-aortic lymph node dissection (fig. 1) [12]. The level of upward lymph node dissection was determined by preoperative and intraoperative findings. When a patient was diagnosed as stage I, UD1 to UD2 lymph node dissection was performed. UD2 to UD4 lymph node dissection was performed for patients with stage II or III tumor. UD4 was performed until the first half of the 1990s, but has not been performed thereafter because of excessive operative time, blood loss and a high incidence of postoperative sexual dysfunction, especially in males [11, 13, 14].

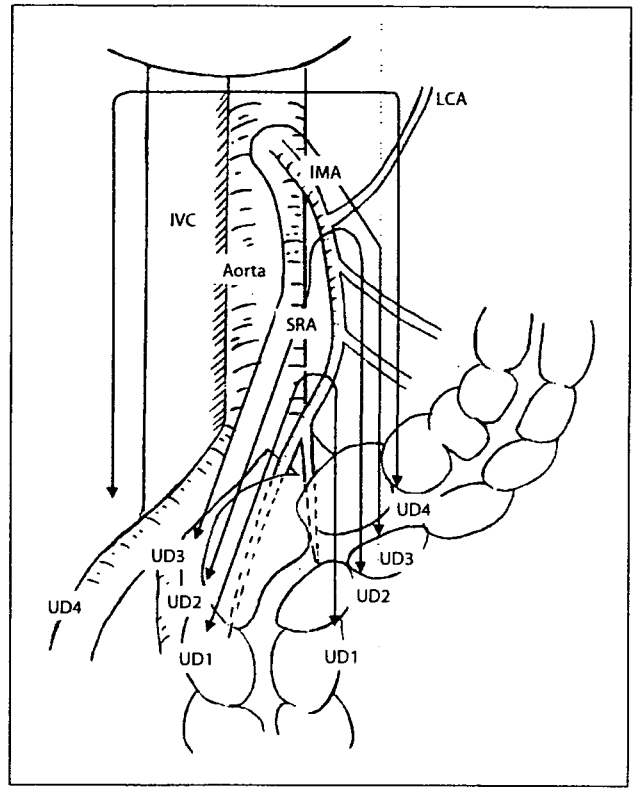

Fig. 1. Classification of the level of upward lymph node dissection. UD1 is defined as resection of the mesorectum; UD2 as division of the root of the superior rectal artery (SRA) and lymph node dissection below this level; UD3 as division of the root of the inferior mesenteric artery (IMA) and lymph node dissection below this level; and UD4 as UD3 with para-aortic lymph node dissection. IVC = Inferior vena cava; LCA = left colic artery.

Statistical Analysis

Survival curves were traced using the Kaplan-Meier method. The differences between curves were tested using the log-rank test. Comparisons between groups were performed using χ^2 test. $p < 0.05$ was considered significant. All statistical calculations were made using SPSS computer software (SPSS 11.0, SPSS Inc., Chicago, Ill., USA).

Results

The characteristics of 285 patients according to the UD classification are shown in table 1. There were 78 (27.4%), 133 (46.7%) and 74 (26.0%) patients who underwent UD2, UD3 and UD4, respectively. All patients were followed up until death or for at least 3 years with a mean follow-up period of 66 months. The rate of sphincter-pre-

Table 1. Patient characteristics according to the UD classification

	Total (n = 285)	UD2 (n = 78)	UD3 (n = 133)	UD4 (n = 74)
Age, years (mean)	58.2	58.1	58.2	58.4
Sex ratio (male:female)	191:94	53:25	90:43	48:26
Follow-up period (mean)	66	59	57	88[a, c]
Surgical procedure				
Sphincter-preserving surgery	143 (50.2)	53 (67.9)	64 (48.1)	26 (35.1)[a, b]
Non-sphincter-preserving surgery	142 (49.8)	25 (23.1)	69 (51.9)	48 (64.9)
Lateral LNs dissection				
No	68 (23.9)	32 (41.0)	31 (23.3)	5 (6.8)[d]
Yes	217 (76.1)	46 (59.0)	102 (76.7)	69 (93.2)
Evaluated LN, n (mean)	42	31	39	57[d]
Metastatic LN, n (mean)	3	2	3	3
TNM classification				
Stage II	94 (33.0)	29 (37.2)	38 (28.6)	27 (36.5)
Stage III	191 (67.0)	49 (62.8)	95 (71.4)	47 (63.5)

Values in parentheses are percentages.
[a] $p < 0.05$ UD2 vs. UD3, [b] $p < 0.05$ UD2 vs. UD4, [c] $p < 0.05$ UD3 vs. UD4, [d] $p < 0.05$ between each UD classification.

serving surgery was higher in UD2 patients than in those who underwent UD3 or UD4. The rate of undergoing lateral lymph node dissection and the number of evaluated lymph nodes increased significantly with the extension of upward lymph node dissection. However, there were no significant differences in the number of metastatic lymph nodes and the ratio of stage II to III among UD classifications.

In each TNM stage, the overall survival curves in relation to the extent of upward lymph node dissection were evaluated and there were no significant differences according to the extent of upward lymph node dissection (fig. 2). Recurrence sites after curative resection are demonstrated in table 2. In both groups with or without lymph node dissection at the root of the inferior mesenteric artery, the lung was the most common site of recurrence followed by the liver. Recurrence sites did not significantly differ between the groups, including para-aortic or mediastinal lymph node metastases.

Table 3 summarizes the characteristics and outcomes of 4 patients with lymph node metastases at the root of the inferior mesenteric artery. They accounted for 1.9% of the 207 patients who underwent UD3 or UD4. Recurrences developed in all cases and their prognoses were significantly worse than those of the other stage III patients who underwent UD3 or UD4 ($p = 0.011$) (fig. 3). None of 4 patients survived for 5 years.

Table 2. Recurrent sites after curative resection

Recurrent site	UD2 (n = 78)	UD3/UD4 (n = 207)	p value
Lung	16 (20.5)	36 (17.4)	0.543
Liver	6 (7.7)	19 (9.2)	0.692
Pelvic cavity	7 (9.0)	15 (7.2)	0.626
Para-aortic or mediastinal LNs	3 (3.8)	4 (1.9)	0.352

Values in parentheses are percentages.

On the other hand, lymph node metastases along the superior rectal artery were discovered in 14 patients, excluding 3 patients with metastatic lymph nodes at the root of the inferior mesenteric artery, and table 4 shows their characteristics. They accounted for 4.9% of all patients. Ten patients developed recurrence and the lung was the most common site (6 patients), followed by the liver (2 patients). The 5-year overall survival rate was 61.2% in this group and there were no significant differences in overall survival among the patients with and without lymph node metastases along the superior rectal artery ($p = 0.338$) (fig. 4a). In addition, there were no significant differences in survival of the patients with lymph node metastases along the superior rectal artery according to the extension of upward lymph node dissection performed (UD2 or UD3/4) ($p = 0.642$) (fig. 4b).

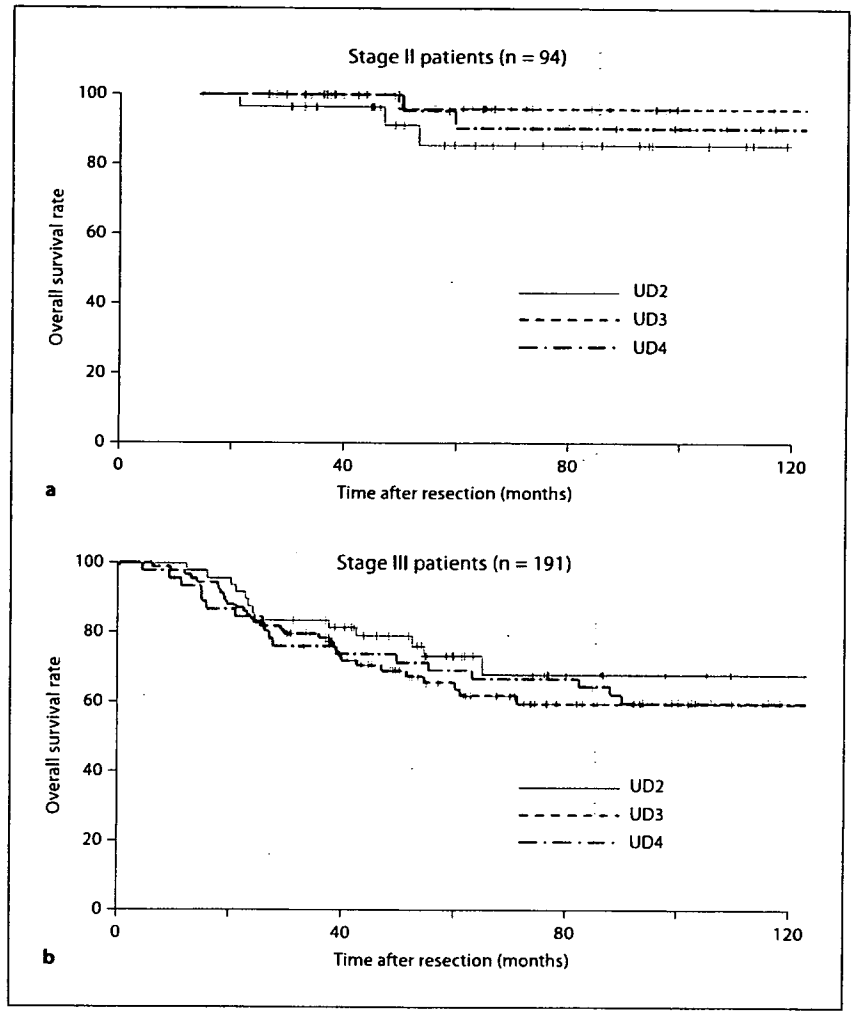

Fig. 2. Overall survival curves in relation to the extent of upward lymph node dissection at each stage: (**a**) stage II and (**b**) stage III. There were no significant differences in each stage.

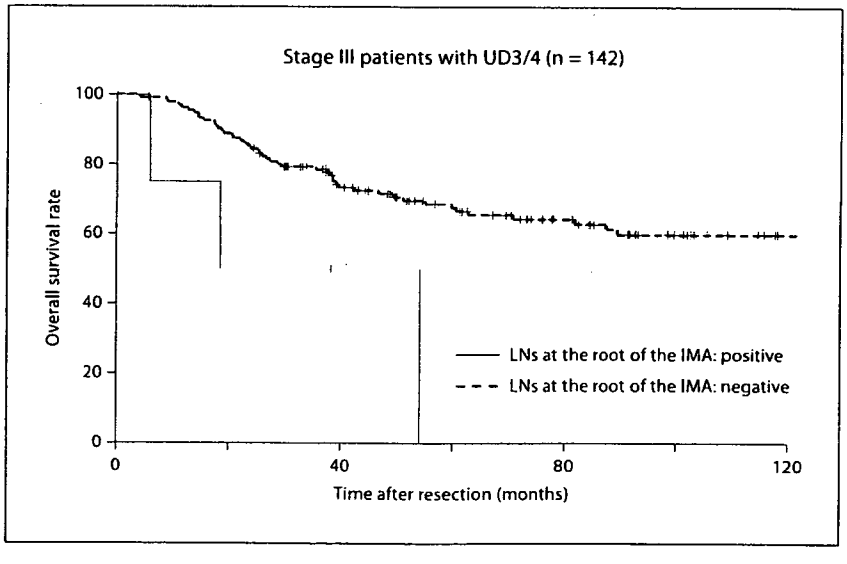

Fig. 3. Overall survival curves for the stage III patients with or without metastatic lymph nodes at the root of the inferior mesenteric artery (IMA). The former was significantly worse than the latter ($p = 0.011$).

Table 3. Characteristics of the patients with metastatic LNs at the root of the inferior mesenteric artery

Age	Sex	UD	Histology	pT	Metastatic LNs, n	Recurrent site	Disease-free time, months	Outcome months
33	F	3	well-differentiated adenocarcinoma	pT3	3	lung, bone	25	died (54)
64	F	3	moderately differentiated adenocarcinoma	pT3	4	lung	22	alive with recurrent tumor (39)
51	M	3	poorly differentiated adenocarcinoma	pT3	25	pelvic cavity	11	died (19)
57	M	3	poorly differentiated adenocarcinoma	pT3	16	pelvic cavity, peritonium	4	died (6)

Discussion

Surgical decisions regarding upward lymph node dissection for advanced lower rectal carcinoma remain controversial. In our study, patients with metastatic lymph nodes at the root of the inferior mesenteric artery comprised a small minority (4 patients, 1.9%) and their prognoses were very poor. Their prognoses seemed to be almost equal to those of patients who underwent UD4 dissection and were pathologically proven to have metastatic para-aortic lymph node, although such patients are classified as stage IV in TNM classification and were excluded from this study. Furthermore, we could not demonstrate an effect of prophylactic lymph node dissection at the root of the inferior mesenteric artery in patients with any stage of disease. Moreover, lymph node dissection without the root of the inferior mesenteric artery did not result in increased para-aortic or mediastinal lymph node metastases, which we had thought might be caused by failing to perform lymph node dissection. We conclude that lymph node dissection at the root of the inferior mesenteric artery does not provide any survival advantage for patients with advanced lower rectal carcinoma and metastatic lymph nodes at this level have systematic disease.

Likewise, there were also a small number of patients with metastatic lymph nodes along the superior rectal artery (14 patients, 4.9%) and the positive rate was far below the rate of lateral lymph nodes (55 of 217 patients who underwent lateral lymph node dissection, 25.3%) in this series. However, the 5-year overall survival rate in this group was 61.2% and there were no significant differences among stage III patients with and without lymph node metastases along the superior rectal artery. In addition, survival is no worse in patients with positive lymph node along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. We conclude that UD2 lymph node dissection is adequate even for stage III patients with lymph node metastases along the superior rectal artery.

Table 4. Characteristics of the patients with metastatic LNs along the SRA (exception for three with metastatic LNs at the root of the IMA)

Patients		14
Age, years (mean)		58.8
Sex ratio (male:female)		12:2
Upward LNs dissection	UD2	4
	UD3	6
	UD4	4
Lateral LNs dissection	no	5
	unilateral pelvic	2
	bilateral pelvic	7
pT category in TNM classification	pT1	2
	pT2	2
	pT3	7
	pT4	3
pN category in TNM classification	pN1	7
	pN2	7
Recurrence	yes	10
	no	4

SRA = Superior rectal artery; IMA = inferior mesenteric artery.

There are some problems with the existing classifications of rectal carcinoma. TNM classification considers lymph nodes at the root of the inferior mesenteric artery as regional lymph nodes for colorectal carcinoma without regard to the location of the tumors, as well as lymph nodes along the superior rectal artery [10]. Under this classification, patients with metastatic regional lymph nodes are regarded as stage III and are subcategorized into three groups by the depth of tumor invasion and number of metastatic lymph nodes, not by the location of metastatic lymph nodes. The problem with this classification is that we cannot distinguish whether stage III patients have lymph node metastases at the root of the inferior mesenteric artery.

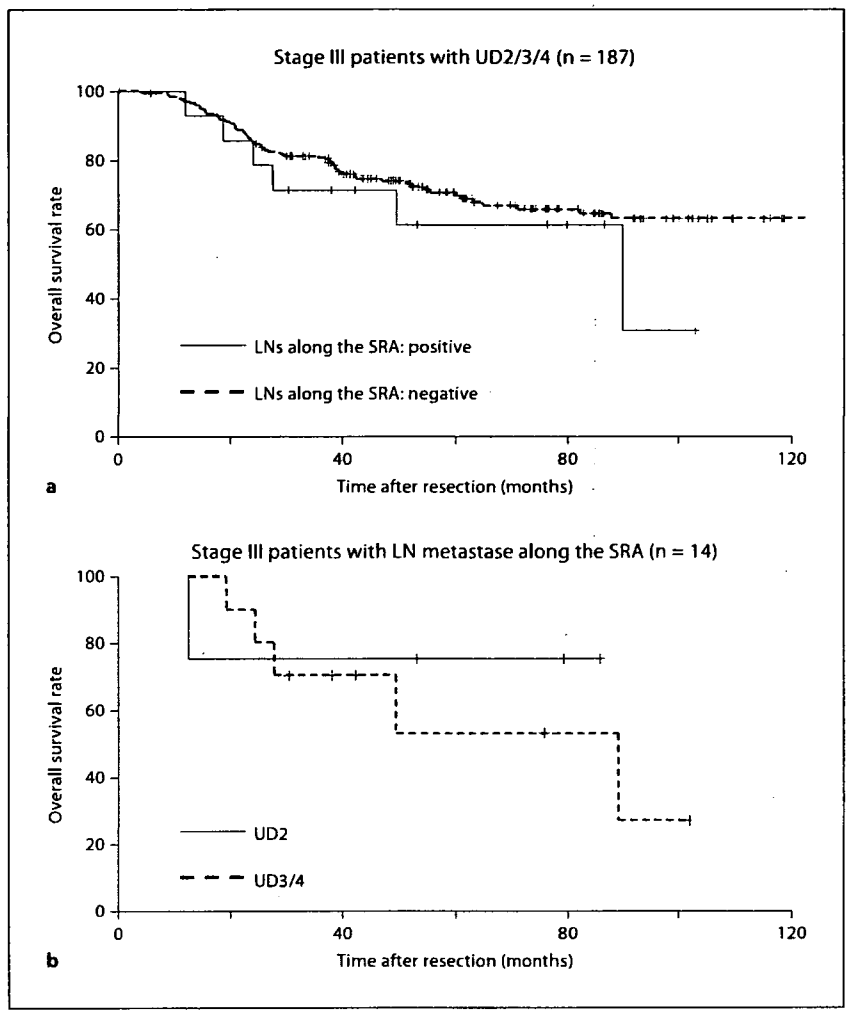

Fig. 4. a Overall survival curves for stage III patients with or without metastatic lymph nodes along the superior rectal artery, excluding 4 patients with lymph node metastases at the root of the inferior mesenteric artery. There were no significant differences in overall survival between both groups (p = 0.338). **b** Overall survival curves in relation to the extent of upward lymph node dissection for stage III patients with metastatic lymph nodes along the superior rectal artery, excluding 3 patients with lymph node metastases at the root of the inferior mesenteric artery. There were no significant differences in survival of the patients with lymph node metastases along the superior rectal artery according to the extension of upward lymph node dissection performed (UD2 or UD3/4) (p = 0.642).

In comparison, the Japanese classification of colorectal carcinoma [9] treats regional lymph nodes in rectal carcinoma as follows: pararectal lymph nodes are defined as group 1, lymph nodes along the superior rectal artery as intermediate lymph nodes (group 2) and lymph nodes at the root of the inferior mesenteric artery as the main lymph nodes (group 3). However, this classification defines patients with metastatic lymph nodes in group 2 and/or group 3 as same stage (stage IIIb). Based on the results of this study, these criteria should be reevaluated.

In recent years, sphincter-preserving surgery has been increasingly adopted in patients with lower rectal carcinoma [15, 16]. The most important postoperative complication in this procedure is anastomotic leakage. To avoid this complication, all colorectal surgeons pay attention to blood flow in the remnant colon, together with the tension of the anastomosis. Therefore, Western surgeons perform mobilization of the splenic flexure for most patients [17], but the position of the splenic flexure in Japanese is usually very deep in the left upper subphrenic area and it is sometimes rather difficult to mobilize the left side colon. However, Japanese patients usually have a long sigmoid colon, and if the surgeon preserves 1 or 2 arcades of marginal vessels of the sigmoid colon by dividing the sigmoid artery between the superior rectal artery and these marginal vessels, mobilization of the splenic flexure becomes unnecessary. In this situation, arterial blood flow is not being compensated. Preservation of the blood flow of the left colic artery is one solution to this problem,

because the appropriate extent of upward lymph node dissection for lower rectal carcinoma is considered to be UD2. When the length of the vascular pedicle for lower anastomosis is short, we can cut the periphery of the left colic artery. Some surgeons choose left colic artery-preserving lymph node dissection at the root of the inferior mesenteric artery, but this increases the risk of damaging the lumbar splanchnic nerve.

Another problem encountered with lymph node dissection for lower rectal surgery is lateral lymph node dissection. Some reports mainly from Japan have supported the effectiveness of lateral pelvic lymph node dissection, and it is well established as the standard procedure in leading hospitals in Japan. However, in Western countries, the survival benefits of lateral pelvic lymph node dissection are regarded as doubtful. Instead, preoperative chemoradiotherapy is widely performed [18, 19]. To resolve this disparity, a multicentric randomized clinical trial that compares lateral pelvic lymph node dissection with autonomic nerve preservation to total mesenteric excision (JCOG-0212) is underway in Japan and data regarding this issue will become available in the near future [20].

In conclusion, survival of a minority with metastatic lymph nodes at the root of the inferior mesenteric artery was very poor. In addition, survival is no worse in patients with positive lymph node along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. Surgeons should take these data into consideration and recognize that low ligation is adequate for advanced lower rectal carcinoma.

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Laparoscopic Resection for Malignant Lymphoma of the Ileum Causing Ileocecal Intussusception

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Abstract: A 22-year-old man was admitted with right lower abdominal pain. Colonoscopy revealed a ball-like tumor at the ileum. Abdominal sonography and computed tomography showed ileocecal intussusception. Microscopic examination of the biopsy specimen showed malignant lymphoma. Laparoscopic ileocecal resection was performed. Histologic diagnosis of the resected tumor was diffuse large B cell-type malignant lymphoma. Intussusception due to malignant lymphoma is relatively rare in adults. If contraindications of laparoscopy are not present, laparoscopic resection can be performed safely and should be considered for diagnosis and treatment for intussusception in ileocecal lesions in adults.

Key Words: malignant lymphoma, intussusception, laparoscopic resection

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Intussusception is primarily a childhood disease. It is uncommon in adults and about 90% of adult intussusception cases have a demonstrable cause.[1] Malignant lymphoma of the ileum is one cause of intussusception.[2] As adult patients are at high risk of malignancy, surgical intervention is recommended in cases of adult intussusception. In recent years, laparoscopy has been able to confirm diagnosis and to resect the tumor causing intussusception of the small intestine in adults.[3]

We report a case of malignant lymphoma causing intussusception in the ileocecal region and successfully resected by laparoscopy.

CASE REPORT

A 22-year-old man visited a local hospital because of right lower abdominal pain. Colonoscopy disclosed a mass with intussusception in the terminal ileum near the ileocecal valve. The mass was a ball-like form and the surface was irregular (Fig. 1). Intussusception was temporarily relieved by colonoscopy. The tumor was diagnosed as malignant lymphoma confirmed by biopsy specimen. He was referred to the National Cancer Center Hospital, Tokyo, Japan.

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On physical examination, no palpable mass was noted in the abdomen. There was no swelling of superficial lymph nodes. He had no specific past history or family history.

Laboratory studies on admission yielded normal blood hematology and chemistry results. The levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal limits.

An x-ray of the abdomen was normal. Abdominal ultrasonographic images showed the wall thickness of the terminal ileum and double concentric rings of sonolucency surrounding a central echogenic core demonstrating a short axis (Fig. 2). Lymph nodes enlargement around the terminal ileum was found.

Abdominal computed tomography (CT) scans showed mild bowel wall thickening and a large round mass in the ileocecal region (Fig. 3). Lymph node enlargement was detected round the terminal ileum and inferior vena cava.

The diagnosis was intussusception caused by malignant lymphoma in the ileocecal region. His symptoms were not remarkable and the risk of further intussusception and mesenteric vascular compression was low. So, elective laparoscopic ileocecal resection was scheduled.

At surgery, we used 4 trocars (Fig. 4). Pneumoperitoneum was established by the open laparotomy technique through a supraumbilical incision. Under laparoscopic guidance, two 5-mm ports were inserted in the right lower quadrant region and mid-lower abdominal region, and one 12-mm port was inserted in the epigastrium. Through inspection of the abdomen, the small intestine had invaginated through the ileocecal valve and enlarged mesenteric lymph nodes were observed. After mobilization of the ileocecal region, the bowel loop was delivered under protection through a small incision made in the middle upper abdomen and the involved parts of the bowel were resected (Fig. 5A).

Macroscopically, the tumor measured 3.5 × 3.0 cm, 8 cm from the ileocecal valve. The tumor was ball-like with an irregular surface and firm consistency. The cut surface was white. The appendix was swollen and wall thickening was found (Fig. 5B).

Histologically, atypical lymphoid cells characterized by marked polymorphism and multiple nuclei had infiltrated diffusely through all layers of the bowel wall. These atypical lymphoid cells were positive for CD20. The diagnosis was diffuse large B cell-type malignant lymphoma. Tumor cells were found in the 10 regional lymph nodes dissected from the mesentery.

Postoperative recovery was good and he was discharged on the eighth postoperative day. One month later, he began to receive CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) plus rituximab therapy. At present, 1 year after surgery, he is free of symptoms and continues an uneventful course.

FIGURE 1. Colonoscopic picture shows a ball-like tumor with an irregular surface.

DISCUSSION

Laparoscopic surgery is now widely used for the resection of benign and malignant gastrointestinal tumors; however, its application in patients with intussusception is still controversial. In recent years, acute peritonitis and previous abdominal surgery have not been an absolute contraindication to laparoscopic colectomy.[4,5] Kirshtein et al[6] reported that the laparoscopic approach is a safe and effective technique for most cases of small bowel obstruction and recommended its use as the first-line treatment. There are several reports of benign ileocolic intussusception successfully treated by laparoscopy.[7] Similarly, we successfully resected a malignant lymphoma causing intussusception by laparoscopy, and to date, only Chiu et al[8] have described an ileocolic intussusception caused by primary ileal lymphoma which was successfully resected laparoscopically.

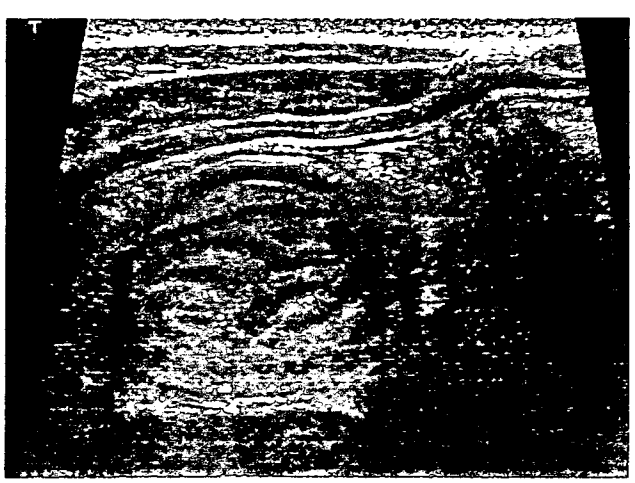

FIGURE 2. Ultrasound reveals double concentric rings of sonolucency surrounding a central echogenic core.

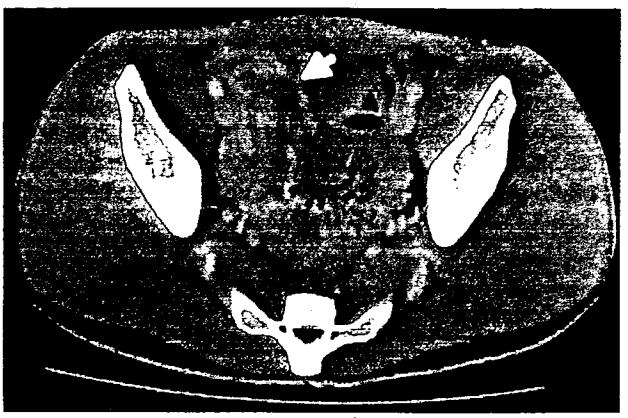

FIGURE 3. Abdominal CT showing mild bowel wall thickening and large round mass in the ileocecal region (white arrow).

Intussusception is a major cause of intestinal obstruction in children and is relatively rare in adults. Although idiopathic cases account for more than 90% of those seen in children, about 80% of adult cases are neoplastic.[9] Common clinical presentations are abdominal pain, nausea, vomiting, and abdominal distension.[10] Because of its nonspecific clinical presentation, the preoperative diagnosis of intussusception is sometimes difficult. Abdominal ultrasonography is useful for diagnosis. Classic signs are pseudokidney in the longitudinal view and target sign in the transversal view. Abdominal CT is also of great help in diagnosis and shows a targetlike sign.[11] If the patient does not have complete obstruction, colonoscopy is helpful for a pathologic diagnosis of the intussusception.

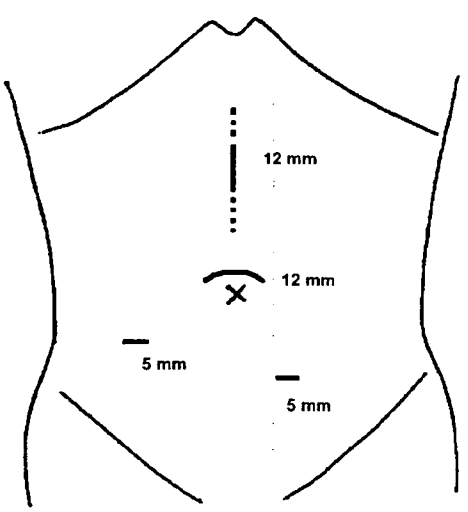

FIGURE 4. Two 5-mm ports are inserted in the right lower quadrant region and mid-lower abdominal region. Two 12-mm ports are inserted in the epigastrium and supraumbilicus. The small incision used for resection and specimen removal is in the middle upper abdomen (dotted line).

FIGURE 5. A, Intraoperative findings show that the small intestine has invaginated through the ileocecal valve. B, In the resected specimen, the ball-like tumor measures 3.5 × 3.0 cm, 8 cm from the ileocecal valve, the appendix is swollen and wall thickening is found.

Dennis et al reported that intussusception of the small intestine in adults is due to benign (63%), idiopathic (23%), and malignant causes (14%).[11] The occurrence of primary lymphomas in the small intestine accounts for less than 2% of all gastrointestinal malignancies and 10% to 20% of small intestinal malignancy.[10]

In most infants and young children, the reduction of intussusception may be tried using barium enema or surgery, but in adults, reduction is not suggested for the treatment of intussusception of unknown etiology considering the possibility of malignancy. Therefore, surgical intervention is indicated in all cases of adult intussusception.[8] In our case, surgical intervention was recommended to relieve persistent intussusception symptoms and to prevent further intussusception.

The disadvantage of laparoscopy is its inability to evaluate the entire small and large bowel. To inspect the small intestine carefully, the hand-to-hand retrograde running technique used by 2 atraumatic graspers is recommended.[12,13] In the case of intussusception caused by malignancy, the possibility of port site metastasis should be considered. So, protection of the small incision by a wound protector is needed.

In conclusion, we think that laparoscopic treatment can be performed safely for ileocecal intussusception caused by ileocecal malignant lymphoma in adults and should be considered if contraindications are not present.

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ORIGINAL ARTICLE

Randomized, Multicenter Trial of Antibiotic Prophylaxis in Elective Colorectal Surgery

Single Dose vs 3 Doses of a Second-Generation Cephalosporin Without Metronidazole and Oral Antibiotics

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Hypothesis: Use of prophylactic antibiotics in elective colorectal surgery is essential. Although single-dose prophylactic antibiotics are recommended, the efficacy of single-dose cephalosporin without metronidazole and oral antibiotics is not fully proven. We conducted a multicenter, randomized trial of a single dose vs 3 doses of the second-generation cephalosporin cefmetazole.

Design: A prospective, randomized, multicenter trial in patients undergoing elective colorectal surgery.

Setting: Seven major hospitals in Japan that offer cancer treatment.

Patients: Patients with colorectal cancer treated from May 6, 2004, to April 25, 2005.

Interventions: Patients were randomized to 1 of 2 groups: a single-dose group given a single dose of cefmetazole just before skin incision and a 3-dose group given 2 additional doses of cefmetazole every 8 hours after the first dose just before skin incision.

Main Outcome Measures: Incidences of incisional surgical site infection (SSI), organ or space SSI, and all other infectious complications within 30 days after surgery.

Results: A total of 384 patients were enrolled. Seven patients were excluded because of additional surgery or the inability to tolerate mechanical preparation. The incidence of incisional SSI was higher in the single-dose group (27/190 or 14.2%) than in the 3-dose group (8/187 or 4.3%) ($P=.009$). Incidences of organ or space SSI and other postoperative infectious diseases did not differ significantly between the 2 groups. In multivariate analysis, antibiotic dose was the only significant factor related to the incidence of incisional SSI.

Conclusion: Three-dose cefmetazole administration is significantly more effective for prevention of incisional SSI than single-dose antibiotic administration.

Trial Registration: clinicaltrials.gov Identifier: NCT00292708

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PROPHYLACTIC ANTIBIOTICS have become a standard treatment for patients undergoing colorectal surgery,[1,2] but controversy still persists concerning the administration route for antibiotics (oral, intravenous, or both) and the number of administrations.[3] A recent meta-analysis[1] and a literature review[4] have suggested that oral administration of antibiotics is of no added value

when appropriate parenteral antibiotics are administered. Moreover, preoperative oral antibiotics increase the incidence of *Clostridium difficile* colitis[5] and gastrointestinal symptoms, including nausea, vomiting, and abdominal pain.[6] A single dose of antibiotics has been shown to be as effective as multiple doses in many trials that have compared a single-dose regimen with a multiple-dose regimen.[1] Although the 1999 Hospital Infection Control Practices Advisory Committee guidelines for prevention of surgical site infection (SSI)[2] recommend cefoxitin or some other second-generation cephalosporin in the distal intestinal tract, the efficacy of a single-dose regimen of cephalosporin without metronidazole and oral antibiotics is not clear, because combination regimens, such as cephalosporin and metronidazole or cephalosporin and oral antibiotics, have been used in most studies of antibiotics dose.[1] In fact, in trials without metroni-

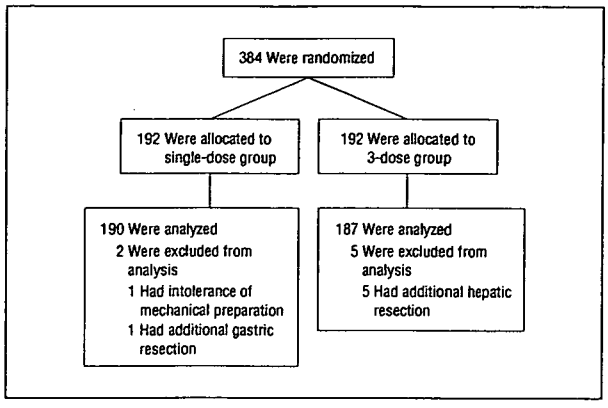

Figure. Flowchart of the trial.

dazole, the number of enrolled patients was small and the difference in the incidence of incisional SSI between a single-dose and a multiple-dose regimen was unclear.[7] Moreover, a single-dose regimen of cephalosporin without metronidazole was associated with a slightly higher incidence of incisional SSI than a regimen of metronidazole alone.[7-9] Therefore, we conducted a multicenter, randomized trial of single-dose vs 3 doses of the second-generation cephalosporin cefmetazole without metronidazole and oral antibiotics.

METHODS

This randomized multicenter trial was conducted at 7 major hospitals in Japan that offered cancer treatment from May 6, 2004, to April 25, 2005. The protocol was approved by the institutional review board at each hospital, and written informed consent was obtained from all of the patients who participated.

Patients aged 20 through 80 years scheduled to undergo elective colorectal surgery were eligible for enrollment in the study. Exclusion criteria included emergency operations, obstruction of the small bowel, stomal surgery or bypass surgery, preoperative infectious diseases, penicillin or cephalosporin allergy, antibiotic administration before hospitalization, inflammatory bowel diseases, angina or myocardial infarction, mild or severe renal dysfunction, mild or severe diabetes mellitus, and steroid administration before surgery.

Patients underwent mechanical bowel preparation with 2 L of polyethylene glycol–electrolyte solution (Niflec, Ajinomoto Pharma, Tokyo, Japan) 1 day before surgery. On the basis of a block-randomized, computer-generated list balancing tumor site, the patients were randomized by a study secretary into 1 of 2 groups: a single-dose group given a single intravenous dose of 1 g of cefmetazole just before skin incision and a 3-dose group given an intravenous dose of 1 g of cefmetazole just before skin incision and 2 postoperative 1-g doses at 8 and 16 hours after the first administration. Although additional doses during surgery and every 3 or 4 hours were recommended in the 1999 guidelines for prevention of SSI,[2] no additional dose was given, even for operations that lasted more than 3 hours. The surgeon was notified of the allocation after the randomization. To ensure that the trial results were applicable generally, specific instructions on surgical techniques and on postoperative management were not included in the protocol.

The primary end point was incidence of incisonal SSI. Secondary end points were incidences of organ or space SSI and other infectious diseases, including urinary tract infection, pneumonia, septicemia, infective diarrhea, and intravenous line sepsis. Other postoperative complications and postoperative hospital stay were also examined. Demographic data, including sex, age, operative procedure, operative time, and operative blood loss, were collected for all patients. Incisional SSI, organ or space SSI, and other infectious diseases were checked for daily by an attending surgeon until hospital discharge and checked for again at the first postoperative hospital visit.

This trial was designed as a noninferiority test to detect a 5% difference in the incidence of incisional SSI between the 2 groups, with a confidence interval of 95% and a power of 90%, assuming that the incidence of incisional SSI in the 3-dose group would be 5%. Therefore, a sample size of 238 was required in both arms. After 1 year of enrollment, interim analysis was performed. Because a significant difference in the incidence of incisional SSI was seen between the groups, enrollment was stopped. The χ^2 test or Fisher exact test, which was used when the variables were lower than 5, was used to analyze categorized variables. The *t* test was used to analyze continuous variables. In multivariate analysis, logistic regression analysis was used. Significance was defined as $P<.05$.

Table 1. Patient Characteristics[a]

Characteristic	Single-Dose Group (n = 190)	3-Dose Group (n = 187)	*P* Value
Age, mean ± SD, y	59.4 ± 11.1	62.1 ± 9.8	.01
Sex			.07
Male	126	107	
Female	64	80	
Tumor site			.91
Colon	122	119	
Rectum	68	68	
Type of surgery			.50
Conventional	129	133	
Colectomy	73	77	
Anterior resection	56	53	
Abdominoperineal resection	0	3	
Laparoscopic	61	54	
Colectomy	49	42	
Anterior resection	12	12	
Operative time, mean ± SD, min	178.8 ± 69.4	170.0 ± 77.5	.25
Blood loss, mean ± SD, mL	164.3 ± 272.6	162.7 ± 397.9	.96

[a]Data are presented as number of patients unless otherwise indicated.

RESULTS

PATIENT CHARACTERISTICS

A total of 384 patients were enrolled in this study (**Figure**). Seven patients were excluded because of additional surgery (gastric and hepatic resection) or the inability to tolerate mechanical preparation. Therefore, 377 patients were examined. All of the enrolled patients had colon or rectal cancer. The numbers of patients in the single-dose and 3-dose groups were 190 and 187, respectively. Patient characteristics are given in **Table 1**. Although patient age was significantly higher in the 3-dose