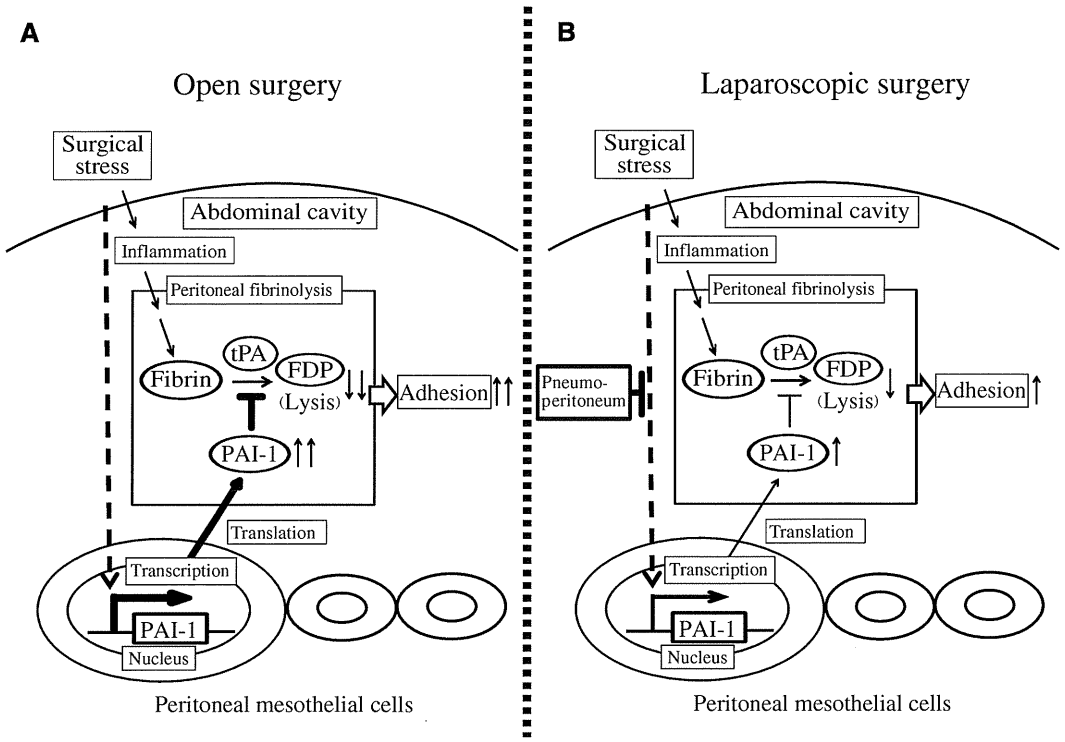

Fig 8. Schema of transcriptional regulation of PAI-1 in peritoneal mesothelial cells for postoperative adhesion formation. *A*, Postoperative adhesions were administered by peritoneal hypofibrinolysis, which induced transcriptional upregulation of PAI-1 in peritoneal mesothelial cells in response to surgical stress caused by OP. *B*, Decreased transcription of PAI-1 in peritoneal mesothelial cells suppresses postoperative adhesion formation in LAP. Although the mechanism of transcriptional decrease in PAI-1 in peritoneal mesothelial cells in LAP has not yet been clarified, pneumoperitoneum using CO_2 may affect peritoneal mesothelial cells. *FDP*, Fibrin degradation products.

levels of tPA and PAI-1 in peritoneal mesothelial cells, we first demonstrated that decreased expression of PAI-1 transcript in peritoneal mesothelial cells suppresses postoperative adhesion formation in LAP using animal and clinical samples. Our proposed schema based on our findings is indicated in Fig 8. Although the mechanism of decreased PAI-1 transcript expression in peritoneal mesothelial cells after LAP has not yet been clarified, pneumoperitoneum using CO_2 may affect the reduction of peritoneal mesothelial cells.

In the present study, we utilized a unique model of intestinal adhesion formation,[12] with cecal cauterization to establish intestinal adhesions in rats. This model could minimize the technical bias of cecal cauterization and provided better reproducibility than previously described models of intestinal adhesion formation, such as the cecal abrasion model (in which the cecum is abraded by scrubbing with surgical gauze).[29,30] Our data demonstrated that quantification of adhesion at day 7 reflects the status of small intestinal adhesion with good reproducibility. To compare solely the difference in peritoneal fibrinolytic activity between pneumoperitoneum and laparotomy, we aimed to minimize the effect of technical bias between LAP and OP for cecal cauterization. For this reason, we induced cecal cauterization in the same manner with a small skin incision across all experimental groups, and we defined rats treated with pneumoperitoneum after cecal cauterization as the LAP group. We defined adequately the control group (only cecal cauterization without any intervention); therefore, we were able to directly compare the difference between pneumoperitoneum and laparotomy after the same extent of peritoneal injury through the use of this control group. The adhesion score, PAI-1 activity in peritoneal lavage, and PAI-1 mRNA expression in peritoneal mesothelium were greater in the OP group than the control and LAP groups. By contrast, tPA was activated at the transcriptional level in peritoneal mesothelial cells; however, tPA activity in plasma and peritoneal lavage was suppressed by PAI-1, which demonstrated a more drastic effect on fibrinolysis than tPA as shown in Fig 2. Moreover, PAI-1 mRNA expression level and subsequent adhesion formation were induced by prolonged

operative time in the OP group but not the LAP group in this model. To the best of our knowledge, this is the first animal model to demonstrate that preservation of peritoneal fibrinolysis by a decrease in transcription of PAI-1 in peritoneal mesothelial cells after LAP may contribute to the decrease of postoperative adhesion formation (Fig 8). Consistent with this rat model, tPA mRNA expression levels were similar in both OP and LAP groups in human patients, although PAI-1 mRNA expression level was significantly greater in the OP group. Furthermore, PAI-1 mRNA levels and subsequent adhesion formation were significantly induced by prolonged operative time in the OP group but not in the LAP group. To further confirm our hypotheses in this clinical study, we extracted HPMCs from omentum during operation. Few molecular markers that indicate clearly the efficacy of LAP compared with OP have been reported previously. We identified PAI-1 mRNA in peritoneal mesothelium as such a molecular marker and believe this finding to be of clinical importance.

Based on our animal model without manual manipulation during laparotomy or pneumoperitoneum, physiologic and/or biologic responses under pneumoperitoneum may lead to the observed effects on peritoneal mesothelial cells directly or via indirect effects by changing arterial or venous blood flow or pH levels in vivo. Sawdey et al[31] reported that the treatment of mice with lipopolysaccharide, tumor necrosis factor-α, or transforming growth factor-β increased the steady-state levels of PAI-1 mRNA within 3 hours in all tissues examined. Other studies reported that statins (HMG-CoA reductase inhibitors) decreased postoperative adhesions by increasing peritoneal fibrinolytic activity.[32,33] In a rat model, lovastatin and atorvastatin significantly decreased adhesion formation without affecting anastomotic burst pressure by upregulating tPA expression and activity in the peritoneum. Statins increased tPA and decreased PAI-1 production in cultured human mesothelial cells, and these effects were reversed by their inhibitors, although this effect may be mediated by inactivation of RhoA, a small GTPase, leading to increased tPA expression and activity, not PAI-1 expression. The antioxidant NAC (*N*-acetyl-L-cysteine) is a clinically relevant antioxidant that donates its L-cysteine moiety to the synthesis of the intracellular antioxidant glutathione. In a rat model, intraperitoneal administration of NAC increased the tPA/PAI-1 protein ratio in peritoneal tissue and peritoneal fluid through a decrease in PAI-1 mRNA and protein expression, suggesting that decreased peritoneal oxidative stress downregulates PAI-1 gene expression to result in a fibrinolytic state.[34] In endothelial cells, oxidative stress upregulates PAI-1 expression through a NADPH oxidase-dependent nuclear factor-$\kappa\beta$ signaling pathway.

PAI-1 is well known as the main regulator of fibrinolysis, and thus, increased plasma PAI-1 levels are associated with the formation or progression of atherosclerosis.[35] In the present study, therefore, we confirmed that preoperative body mass index, HbA1c, total cholesterol, triglyceride, and prothrombin time values demonstrated no difference between LAP and OP patients. In addition, elevated PAI-1 was found to be related to poor prognosis of several malignancies.[36] In the present human study, the LAP group contained significantly more patients with early stage disease than the OP group, owing to their indication for operation. To minimize this effect, we excluded patients with metastatic diseases, serosal invasion, and positive peritoneal cytology. PAI-1 mRNA levels in patients with advanced stage disease were not greater than those with early stage disease in the present study (data not shown); therefore, this difference in disease stage was not a substantive confounder of our results.

In our institution, only patients who were expected to have invasion to the mucosa or submucosa without lymph node metastasis were selected for LAP (T1 N0 stage IA and T2 N0 stage IB). Therefore, in this study, we examined prospectively consecutive patients according to this selection criterion who were treated by the same surgical team without selection bias by the surgeons. In addition, in the present human study we examined samples obtained prospectively from relatively early-stage gastric cancer patients who underwent standard partial gastrectomy. Further exploration is required to determine whether patients undergoing gastric cancer resection differ from those undergoing operation (laparoscopic or open) for other types of abdominal operations.

In conclusion, the results of the present study suggest strongly that achieving a more prolonged hypofibrinolytic state by inhibition of PAI-1 upregulation during LAP may predispose patients to less intestinal adhesion than OP. Elucidation of the precise mechanisms underlying the downregulation of PAI-1 gene expression during LAP may reveal a potential therapeutic target without inhibiting the fibrin formation that is indispensable for wound healing in response to operative trauma.

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Single-port laparoscopic colectomy versus conventional laparoscopic colectomy for colon cancer: a comparison of surgical results

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Abstract

Background: Single-port laparoscopic surgery is a new technique that leaves no visible scar. This new technique has generated strong interest among surgeons worldwide. However, single-port laparoscopic colon surgery has not yet been standardized. Our aim in this study was to evaluate the feasibility of single-port laparoscopic colectomy compared with conventional laparoscopic colectomy for colon cancer.

Methods: We conducted a case-matched, controlled study comparing single-port laparoscopic colectomy to conventional laparoscopic colectomy for right-sided colon cancer.

Results: A total of ten patients were included for the single-port laparoscopic colectomy (S-LAC) group and ten patients for the conventional laparoscopic colectomy (C-LAC) group. The length of the skin incision in the S-LAC group was significantly shorter than that of the C-LAC group.

Conclusion: Our early experiences indicated that S-LAC for right-sided colon cancer is a feasible and safe procedure and that S-LAC results in a better cosmetic outcome.

Keywords: Single-port laparoscopic surgery, Single-incision laparoscopic surgery, Conventional laparoscopic surgery, Laparoscopic colectomy, Colon cancer, Gelport

Background

Laparoscopic surgery has been a standard strategy for a variety of gastrointestinal diseases. The first report about laparoscopic colectomy was published by Jacobs *et al.* [1] two decades ago. Since then the use of laparoscopic colectomy for colon cancer has gradually increased, and it is now acceptable treatment not only for early colon cancer but also for advanced cases because of its oncological safety and feasibility [2,3]. Recently, natural orifice transluminal endoscopic surgery (NOTES) has been studied as the next generation of minimally invasive surgery. This new technique was described for the first time by Kalloo *et al.*, who introduced their work performing transgastric peritoneoscopy in a porcine model [4]. Marescaux *et al.* also reported successful NOTES in a clinical case [5]. However, the feasibility and safety of NOTES have not been evaluated. Single-port laparoscopic surgery is also a new technique which leaves no visible scar. This new technique has generated interest among surgeons worldwide. Although the use of single-port laparoscopic cholecystectomy has spread rapidly, single-incision laparoscopic colon surgery has not yet been standardized. Our aim in this study was to evaluate the feasibility of single-port laparoscopic colectomy compared with conventional laparoscopic colectomy for colon cancer which requires D2 lymph node dissection.

Methods

This study was performed with permission of the Ethics Committee of the Hiroshima University.

We conducted a case-matched, controlled study comparing single-port laparoscopic colectomy to conventional laparoscopic colectomy for right-sided colon

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cancer. The inclusion criteria were right-sided colon cancer which required colon resection with D2 lymph node dissection. The single-port laparoscopic colectomy group included selected patients who completed their treatment between February 2010 and March 2011 (n = 10). Patients who underwent conventional laparoscopic surgery for right-sided colon cancer between April 2006 and March 2010 were selected as the control group for this study (n = 10). These patients were matched with regard to the patient's age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, history of abdominal surgery, disease type and tumor location. No consideration or analysis of surgical parameters and outcomes was made until these groups were definitively selected as the best comparison cohort based only on preoperative variables.

Surgical technique

After obtaining informed consent, we placed patients with right-sided colon cancer in the supine position. The surgical methods for both single-port laparoscopic colectomy (S-LAC) and conventional laparoscopic colectomy (C-LAC) were performed using a mediolateral approach, and the hand-sewn anastomoses were performed extracorporeally. In the S-LAC group, a 3-cm skin incision was made in the umbilicus and laparotomy was performed. The Gelport (Applied Medical, Rancho Santa Margarita, CA, USA) was inserted through this incision and used as the access port. We usually used three trocars of different sizes (Ethicon, Inc, Cincinnati, OH, USA) to prevent clashes between these trocars. The camera was a flexible videolaparoscope (Olympus Medical Systems Corp, Tokyo, Japan), and the energy source was the Harmonic Ace (Ethicon, Inc). The other laparoscopic instruments were the same as those used in conventional laparoscopic colonic surgery (Figure 1). For the C-LAC group, the first trocar was inserted through the infraumbilical incision, and another four trocars were inserted sequentially. After intracorporeal completion of the procedure, a small skin incision was made in the lower abdomen or umbilicus. All instruments used, including the camera and energy device, were the same in both the C-LAC and S-LAC groups.

The perioperative outcomes, including the surgical method, length of skin incision, length of operation, estimated blood loss and conversion rate to conventional laparoscopic surgery or open surgery, as well as the complications, were analyzed (Table 1). The pathological findings included the degree of differentiation, depth, presence of lymph node metastasis, lymphatic vessel invasion, vascular invasion and the number of lymph nodes resected, and these results were analyzed as well (Table 2).

Statistical analysis

All continuous variables are expressed as the median (range) and were compared using the Mann-Whitney U test. The χ^2 test and Fisher's exact test were used to compare discrete variables. Statistical calculations were performed with the help of the SPSS version 18.0 software program (SPSS, Chicago, IL, USA), and a P value < 0.05 was considered to indicate statistical significance.

Results

Twenty patients (8 males and 12 females) were enrolled in this study, and they were distributed into two groups: S-LAC and C-LAC. All patients were matched as closely as possible in terms of their selection criteria. The data for both groups are shown in Table 3. There was no surgical mortality or reintervention within 30 days in either group. There were no significant differences in the lengths of the operations between the S-LAC group (median 192 minutes, range 156 to 231 min) and the C-LAC group (median 222 minutes, range 44 to 244 minutes). There also were no significant differences in the estimated blood loss between the S-LAC group (median

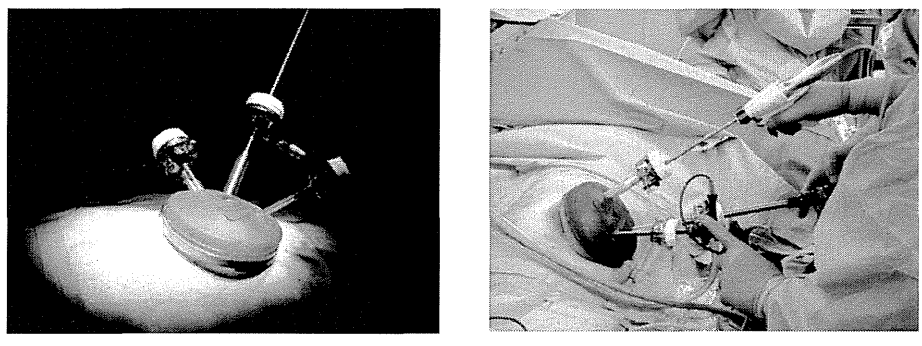

Figure 1 The Gelport was used as the access port. The flexible videolaparoscope, the Harmonic Ace energy source and other laparoscopic instruments used were the same as those used in the conventional laparoscopic colectomy group.

Table 1 Perioperative outcomes[a]

	Laparoscopic colectomy for colon cancer		
Parameters	**S-LAC (*N* = 10)**	**C-LAC (*N* = 10)**	***P* value**
Method			0.141
Ileocecal resection	8	5	
Right hemicolectomy	1	5	
Transverse colectomy	1	0	
Operative time (minutes)	192.0 (156 to 231)	222.0 (44 to 244)	0.063
Estimated blood loss (ml)	48.0 (0 to 110)	51.5 (21 to 244)	0.190
Length of skin incision (cm)	3 (2 to 3)	5 (3 to 6)	< 0.001
Conversion rate (%)	0 (0%)	1 (10.0%)	0.474
Hospital stay after operation (days)	8.0 (6 to 13)	10.5 (7 to 21)	0.023

[a]C-LAC = conventional laparoscopic colectomy; S-LAC = single-port laparoscopic colectomy. Data are expressed as median (range) or as raw numbers.

48.0 ml, range 0 to 110 ml) and the C-LAC group (median 51.5 ml, range 21 to 244 ml). Although there was one conversion to open surgery in the C-LAC group due to anatomical difficulties, there were no conversions in the S-LAC group. Regarding the length of the skin incision, that in the S-LAC group (median 3.0 cm, range 2.0 to 3.0 cm) was significantly shorter than that of the C-LAC group (median 5.0 cm, range 3.0 to 6.0 cm; $P < 0.001$). In terms of the hospital stay, the median stay of 8.0 days in the S-LAC group (range 6 to 13 days) was significantly shorter than the median of 10.5 days in the C-LAC group (range, 7 to 21 days; $P = 0.023$), as shown in Table 1. There were no surgical complications, including anastomotic leakage, surgical site infection, ileus, pneumonia, liver and renal dysfunction, or cardiovascular disease in either group (data not shown). With regard to the pathological findings, including the tumor differentiation, depth of the tumor, node metastasis, lymphatic invasion and vascular invasion, there were no significant differences between the groups. Moreover,

Table 2 Pathological outcomes[a]

	Laparoscopic colectomy for colon cancer		
Parameters	**S-LAC (*N* = 10)**	**C-LAC (*N* = 10)**	***P* value**
Differentiation			0.661
Well	7	6	
Moderate	1	2	
Pap	1	0	
Well-differentiated endocrine carcinoma	0	1	
Adenoma	1	1	
Depth			0.459
m (membrane)	4	3	
sm (lymphatic invasion)	6	4	
mp (vascular invasion)	0	1	
a	0	2	
n			1.000
Negative	10	9	
Positive	0	1	
ly			0.211
Negative	10	7	
Positive	0	3	
V			1.000
Negative	9	9	
Positive	1	1	
Lymph node harvest, median (range)	15.0 (3 to 30)	16.5 (3 to 23)	0.853

[a]C-LAC = conventional laparoscopic colectomy; S-LAC = single-port laparoscopic colectomy. Data are expressed as median (range) or as raw numbers.

Table 3 Preoperative parameters of patients[a]

	Laparoscopic colectomy for colon cancer		
Demographics	**S-LAC**	**C-LAC**	***P* value**
Number of Patients	10	10	
Age (years)	68.5 (61 to 81)	68.0 (33 to 84)	0.853
Sex			1.000
Male	4	4	
Female	6	6	
BMI (kg/m^2)	22.5 (19.6 to 24.6)	21.9 (17.1 to 26.2)	0.353
ASA score			1.000
1	8	7	
2	2	3	
Prior abdominal surgery rate (%)	2 (20%)	3 (0%)	1.000
Type (Japanese Society for Cancer of the Colon and Rectum, 7th edition)			0.087
0	10	6	
1	0	3	
2	0	1	
Location			0.057
C (Cecum)	5	1	
A (Ascending colon)	4	9	
T (Transverse colon)	1	0	

[a]ASA = American Society of Anesthesiologists; BMI = body mass index; C-LAC = conventional laparoscopic colectomy; S-LAC = single-port laparoscopic colectomy. Data are expressed as median (range) or as raw numbers.

the median number of lymph nodes extracted was also not significantly different between the S-LAC group (median 15.0, range 3 to 30) and the C-LAC group (median 16.5, range 3 to 23), as shown in Table 2.

Discussion

The use of single-port laparoscopic cholecystectomy has spread rapidly, and many procedures have already been performed throughout the world. On the other hand, single-port laparoscopic colon surgery for colon cancer has not yet been standardized. There are only a few reports of small sample size studies in the literature [6-14]. It has been suggested that single-port laparoscopic colectomy for colon cancer provides a better cosmetic outcome for patients than conventional laparoscopic surgery, with equivalent invasiveness between the procedures. However, there has been no adequate evidence regarding not only these issues but also the feasibility and safety of this operation. In this study, we compared various parameters between S-LAC and C-LAC to evaluate the feasibility and safety, as well as the outcomes, of single-port laparoscopic colectomy for colon cancer which required D2 lymph node dissection.

The apparent advantage of single-port laparoscopic colectomy is a better cosmetic outcome. Our data also reveal that the median length of the skin incision in the S-LAC group of 3.0 cm (range 2.0 to 3.0 cm) was significantly shorter than that of 5.0 cm in the C-LAC group (range 3.0 to 6.0 cm) ($P < 0.001$). To evaluate the invasiveness of the procedure, we compared the length of the operation, estimated blood loss and hospital stay. In our series, there were no significant differences between the S-LAC and C-LAC groups regarding the length of the operation or estimated blood loss. In terms of the hospital stay, the median of 8.0 days in the S-LAC group (range 6 to 13 days) was significantly shorter than the median of 10.5 days in the C-LAC group (range 7 to 21 days) ($P = 0.023$). Generally, the duration of the hospital stay has been used as one of the most important parameters of invasiveness. However, the hospital stay is defined not only by the patient's situation but also based on the characteristics of many Japanese patients who hope to stay for a long period in the hospital. Hence, the hospital stay is not necessarily a reliable parameter on which to objectively assess the invasiveness of such patients. However, these findings demonstrate that S-LAC is not more invasive than C-LAC or open colectomy.

The main disadvantage of this procedure is the difficulty in performing it, owing to the lack of instrument triangulation, clashing of the instruments outside the abdomen, a requirement for articulated instruments and the potential for pneumoperitoneum leaks. To resolve these problems, we primarily use the Gelport as the access port. In other words, the most important point for ensuring successful single-port laparoscopic colectomy is the selection of the access port to use. Initially, the multiple fascial puncture

technique under a skin flap [15] was used for single-incision laparoscopic surgery, especially for cholecystectomy. However, the disadvantages of this technique are the weakness of the fascia due to the creation of multiple defects, as well as seroma formation. Therefore, several new access ports have already been developed. We usually use the Gelport, which has been used for hand-assisted laparoscopic surgery, as the access port for single-port laparoscopic colectomy. The benefit of using the Gelport is that several trocars can be inserted multiple times if necessary, and the trocars can be kept apart for as long as possible to maintain instrument triangulation and to prevent instrument clashing outside the abdomen. The most important issue affecting single-port laparoscopic colectomy is the much smaller space outside the abdomen than is present during conventional laparoscopic surgery. This difficult situation requires the use of articulated instruments. However, we did not need to use any articulated instruments when we used the Gelport as the access port. Moreover, the Gelport was able to maintain an airtight seal during the operation. Therefore, we concluded that our method using the Gelport has the potential to successfully address these limitations [16].

Our series of single-port laparoscopic colectomies for colon cancers (n = 10) had no conversions (Table 1) and no surgical complications, including anastomotic leakage, surgical site infection, ileus, pneumonia, cardiovascular disease and so on. These results revealed the feasibility and safety of single-port laparoscopic colectomy for colon cancer during the perioperative period.

In terms of the median number of extracted lymph nodes, there were no significant differences between the S-LAC group (median 15.0, range 3 to 30) and the C-LAC group (median 16.5, range 3 to 23) (P = 0.912), as shown in Table 2. These results demonstrate the feasibility regarding the short-term oncologic outcomeof single-port laparoscopic colectomy for colon cancer which requires D2 lymph node dissection.

This study is limited by its small sample size. However, it provides an initial comparison between S-LAC and C-LAC and can provide the foundation for large, randomized controlled studies.

Conclusion

Our early experiences indicates that S-LAC for right-sided colon cancer is a feasible and safe procedure. Although there were no significant benefits regarding the perioperative and oncological results, S-LAC does provide a better cosmetic outcome. Before extending the indications of this procedure to advanced cases and those with rectal cancer, however, it will be necessary to evaluate this technique's perioperative and long-term oncological safety in a large, randomized controlled trial.

Abbreviations

ASA: American Society of Anesthesiologists; BMI: Body mass index; C-LAC: Conventional laparoscopic colectomy; NOTES: Natural orifice transluminal endoscopic surgery; S-LAC: Single-port laparoscopic colectomy.

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Authors' contributions

HE participated in the treatment of these patients and the literature search and drafted the manuscript. MH helped to draft the manuscript. TH, YT, YK, MS, MT, TA, TU and TI participated in the treatment of these patients. HO participated in treatment planning for these patients and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Identification of patients likely to benefit from metastasectomy in stage IV colorectal cancer

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Abstract
Purpose The aim of the present study was to determine selection criteria for patients with stage IV colorectal cancer (CRC) who were likely to show survival benefits of metastasectomy.
Methods Clinicopathological data of 119 patients with stage IV CRC who underwent primary CRC resection were retrospectively reviewed. The prognostic factors were analyzed according to the disease resectability status, and patients likely to show survival benefits of metastasectomy were identified.
Results Metastasectomy was performed in 63 patients. Among these patients, R0 resection was reported in 55 patients, who comprised the curable group. The other 64 patients comprised the noncurable group. For the noncurable group, postoperative chemotherapy was identified as the only significant prognostic factor. In the curable group, T stage, histological type, elevated serum carcinoembryonic antigen (CEA) level and the presence of extra hepatic disease were identified as independent prognostic factors. Patients within the curable group were further classified into a low-risk group (zero to two prognostic factors) and a high-risk group (three or more prognostic factors). The overall survival (OS) of the high risk patients in the curable group was as poor as that of the patients in the noncurable group.
Conclusions Stage IV CRC patients consisted of heterogeneous populations who had different prognostic factors, stratified by the disease resectability status. No prognostic benefit of metastasectomy was observed in high-risk patients undergoing curative metastasectomy. These results suggested that patients showing survival benefits of metastasectomy can be identified by considering the prognostic factors in patients undergoing curative metastasectomy.

Keywords Colorectal cancer · Stage IV · Metastasectomy · Selection criteria · Resectability status

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Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and the fourth leading cause of cancer death worldwide [1]. Although the early stage disease of some patients is potentially curable, the detection of distant metastases at the time of presentation is common [2]. Although recent advances in chemotherapeutic regimens, including molecular targeted agents, have led to improved survival in patients with metastatic CRC, patients with stage IV disease have a very poor prognosis, with a 5-year survival of only 10–20 % [3].

Complete surgical resection of both primary CRC and its metastases remains the only potential curative therapy for stage IV CRC patients [2]. An increasing body of data suggests that patients who undergo curative resection of isolated metastases show survival benefits regardless of the metastatic site such as liver [4–6], lung [7–9], peritoneal [10, 11], ovarian metastases [12, 13] and extra regional lymph nodes [14, 15]. Although complete surgical resection of these metastases contributes to long-term survival in selected patients, some patients have early recurrence and very poor prognosis.

To identify the patients with poor prognosis after hepatic or pulmonary resection of metastatic CRC, investigators have proposed several different prognostic scoring systems

[5, 8, 16, 17]. However, the factors contributing to the identification of patients likely to benefit from resection of metastatic disease have not been defined [18]. The actual indication of metastasectomy depends on the decision of surgeons or oncologists in each institution. The establishment of selection criteria for metastasectomy in patients with stage IV CRC is necessary.

Stage IV CRC encompasses a heterogeneous patient population in which both palliative and curative treatment strategies may be used [19]. The different treatment strategies are determined by the disease resectability status, and wide variation in the outcome has been shown [20]. In the present study, prognostic factors were compared between patients who underwent curative resection and those who did not to determine which patients are likely to benefit from metastasectomy among patients with stage IV CRC. The aim of this study is to establish selection criteria for metastasectomy in patients with stage IV CRC, based on the disease resectability status.

Patients and methods

We identified 131 patients with stage IV CRC disease from a prospective database from January 1992 to December 2008 at the Department of Surgery of Hiroshima University. Among these 131 patients, 119 patients underwent primary CRC resection (90.8 %), regardless of the resection of metastatic disease. These 119 patients were retrospectively analyzed based on the availability of detailed information about tumor-related factors.

Surgical treatment considered resection of the primary CRC when possible, with the exception of patients in poor condition. Determination of treatment strategy did not depend on the presence of tumor-related complications such as small bowel obstruction, bleeding or pain. In all cases with resectable synchronous metastases, simultaneous resection of both the primary and metastatic tumor was performed, regardless of the location of primary tumors and the extent of metastasis. Exceptionally, staged metastasectomy after resection of the primary tumor was performed in patients with lung metastasis or showing complications such as small bowel obstruction. For primary tumor resection, all patients underwent standard resection of colon and rectum with regional lymphadenectomy according to the Japanese general rules for clinical and pathological studies on cancer of the colon, rectum and anus, 7th edition (JGR) [21]. The indications for metastasectomy were the ability of the patient to tolerate the required surgical procedure and surgically controllable disease including primary lesion. For resection of liver metastases, radical operation was possible along with the preservation of at least 30 % of normal parenchyma. These criteria were independent of the number and size of liver tumors. The indications for pulmonary resection were the preservation of adequate postresection respiratory function. Potentially resectable bilateral or multiple lesions were not excluded from the selection criteria [7]. The resection of ovarian, peritoneal and extra regional lymph nodes was performed, if these metastases were isolated and could be completely removed. Curative resection (R0) was defined as microscopically free tumor margins.

Individual demographic and clinicopathological data were collected including age, sex, tumor location, tumor stage (T stage), nodal stage (N stage), tumor histology, presence of lymphovascular invasion, preoperative serum carcinoembryonic antigen (CEA) level, the presence of extra hepatic disease, the extent of hepatic lesions, the presence of lung metastasis, the presence of peritoneal dissemination, the presence of postoperative complications, application of postoperative therapy and survival rate. T stage, N stage and tumor histology were pathologically determined from resected specimens. All patients were staged according to the American Joint Commission for Cancer Staging (AJCC/TNM the sixth edition) system [22]. Survival data were updated until March 2011. Survival was computed from the date of the primary tumor resection. All postoperative complications were reviewed for at least 30 days following surgery. The complications were graded according to the method described by Dindo et al. [23]. Complications with a grade above III were categorized as morbid. Postoperative mortality was defined as any death that occurred within 30 days of surgery.

Statistical analysis

Survival curves were plotted by the Kaplan–Meier method, and univariate analyses of factors thought to influence overall survival (OS) were estimated using the logrank test. The Cox proportional hazard model was used for multivariate analyses. To achieve an optimal cutoff value of serum CEA levels, receiver operating characteristic (ROC) curve analysis for survival was performed to obtain the area under the ROC curve (AUC), and optimal cutoff values were defined as the point on a ROC curve nearest to the point where both sensitivity and specificity were one. In all analyses, statistical significance was set at a p value of less than 0.05. All statistical analyses were performed using JMP 8 software (version 8.02, SAS Institute Inc., Cary, NC, USA).

Results

Clinicopathological features

The clinicopathological features of the 119 patients are summarized in Table 1. Seventy-five male and 44 female

Table 1 Patients' characteristics

	n=119
Male/female	75/44
Age (mean)	61.8 (range, 23–85)
Median follow up time (month)	23.8 (range, 1.0–141.4)
Tumor location	
Colon/rectum	70/49
Number of metastatic organs	
One organ/more than 2 organs	94/25
Metastatic organs	
Liver	88
Lung	9
Extra regional lymph node	22
Peritoneal dissemination	26
Ovary	2
Metastasectomy	63 (52.9 %)
Curative/noncurative	55/8

patients were included in this study, with a median age of 61.8 years (range, 23–85 years). The median follow-up period was 23.8 months (range, 1.0–141.4 months). The distribution of tumor location included 70 colon and 49 rectal cancers. Ninety-four patients had metastatic disease in only one organ, and the other 25 patients had metastasis to more than two organs. The distribution of metastases was 88 in the liver, nine in the lung, 22 in extra regional lymph nodes, 26 with peritoneal dissemination and two in the ovary (including overlapped cases).

Metastasectomy was performed in 63 patients (52.9 %). Synchronous resection of primary and metastatic tumors was performed in 59 patients, and staged resection was performed in four patients. Among these 63 cases, histological tumor-free margin was seen in 55 patients (R0), and histological positive tumor margin was seen in the other eight patients (R1, 2). In the 55 patients with curative resection, the metastatic organ distribution was liver in 47 cases, peritoneal dissemination in four cases, lungs in two cases, extra regional lymph nodes in two cases and ovaries in two cases (including overlapped cases). In cases with liver surgery (n=47), ten cases had more than three subsegments of the liver resected. Postoperative complications were reported in six cases (10.2 %) for patients with only primary CRC resection (n=59) and ten cases (16.7 %) for patients with both primary and metastatic CRC resection (n=60), respectively. There were no reports of mortality in either of the groups.

Overall survival (OS) and classification based on the disease resectability status

The 5-year OS was 24.9 % for all patients combined. The 5-year OS for patients who underwent curative resection (R0), those who underwent noncurative resection (R1, 2) and those who did not undergo metastasectomy were 45.9 %, 12.5 % and 6.7 %, respectively (Fig. 1). The OS of patients who underwent curative resection for both primary and metastatic diseases was significantly better than that of the other two groups (p<0.001, Fig. 1). On the other hand, the OS of patients who could not undergo curative resection of primary or metastatic disease was as poor as that of the patients who did not undergo resection of metastases (p= 0.257, Fig. 1). Therefore, we stratified patients with stage IV CRC into two subgroups according to the disease resectability status: the patients who underwent curative resection for both primary and metastatic diseases (R0) were classified as the 'curable group' (n=55), and the patients who did not undergo curative resection for primary or metastatic diseases (R1, 2) and those who did not undergo resection of the metastatic disease were classified as the 'noncurable group' (n=64). The prognostic factors for both curable and noncurable patient groups were analyzed separately.

Postoperative chemotherapy

Among the patients in the noncurable group (n=64), 52 patients (82.8 %) received postoperative chemotherapy after primary tumor resection. The first-line postoperative therapy regimens were as follows: peroral drug regimen, such as S-1 (n=11) and tegafur-uracil (n=7), 5-FU/leucovorin (n=14), irinotecan-based regimen (n=7), transarterial chemotherapy (n=8) and oxaliplatin-based regimen (n=5).

For patients in the curable group (n=55), postoperative chemotherapy after metastasectomy was administered to 52 patients (94.5 %). The first-line postoperative therapy regimens were as follows: peroral drug regimen, such as S-1 (n=9), tegafur-uracil (n=8), tegafur-uracil/oral leucovorin (n=6) and capecitabine (n=1), transarterial chemotherapy (n=20), 5-FU/leucovorin (n=5) and oxaliplatin-based

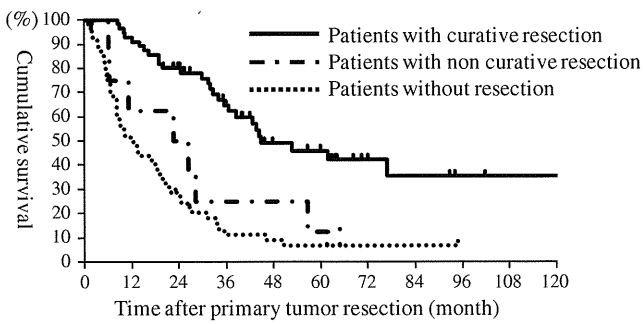

Fig. 1 Overall survival (OS) in patients with stage IV CRC classified by resectability status of the diseases. The OS of patients with curative resection was significantly better than that of the other two groups (p< 0.001). On the other hand, the OS of patients with noncurative resection was as poor as that of the patients without resection of metastases (p=0.257)

regimen (n=3). Before 2001, transarterial chemotherapy with fluorouracil was the main postoperative treatment for colorectal liver metastases. After 2002, peroral drug regimens were included in the treatment. More recently, oxaliplatin-based regimens have been considered as standard therapy in patients with high risk of cancer recurrence.

No patients were treated by molecular-targeted agents as a first line of treatment in either of the two groups, and these agents were applied as a second line of treatment or after the study period. In the noncurable group, one patient was treated with bevacizumab, and another patient was treated with cetuximab. In the curable group, three patients were treated with bevacizumab, and another three patients were treated with cetuximab. In both groups, cetuximab was administrated to the patients without KRAS mutation.

Prognostic factors for patients with noncurable stage IV CRC

To estimate prognostic factors, univariate analysis was performed for the following variables: age (<70 vs. ≥70 years old), sex (male vs. female), primary tumor location (colon vs. rectum), tumor stage (T1–T3 vs. T4), N stage (negative vs. positive), histological type (well-differentiated adenocarcinoma vs. other types), lymphatic invasion (negative vs. positive), venous invasion (negative vs. positive), serum CEA level (<30.0 ng/ml vs. ≥30.0 ng/ml), number of liver metastasis (0–3 vs. ≥4), maximum liver tumor diameter (<5 cm vs. ≥5 cm), lung metastases (absent vs. present), peritoneal dissemination (absent vs. present), extra hepatic disease (absent vs. present), postoperative complications (absent vs. present) and postoperative chemotherapy (no vs. yes). Tumor-related factors were not identified as significant prognostic factors, and only postoperative chemotherapy was identified as a significant prognostic factor (p<0.001, Table 2).

Table 2 Prognostic factors in patients with noncurable stage IV CRC (n=64)

Variables		Number	5-year OS	p value
Age	<70	46	8.0 %	0.281
	≥70	18	5.9 %	
Sex	Male	41	6.1 %	0.681
	Female	23	9.6 %	
Location	Colon	38	3.0 %	0.162
	Rectum	26	14.1 %	
T factor	T1–3	25	8.7 %	0.738
	T4	39	6.4 %	
N factor	Negative	9	0.0 %	0.878
	Positive	55	9.0 %	
Histology	Well	52	0.0 %	0.830
	Other types	12	8.1 %	
Lymphatic invasion	Negative	3	33.3 %	0.153
	Positive	61	6.0 %	
Venous invasion	Negative	19	0.0 %	0.897
	Positive	45	10.2 %	
CEA (ng/ml)	<30	39	9.0 %	0.611
	≥30	25	5.0 %	
Number of liver metastasis	0–3	34	11.5	0.147
	≥4	30	3.5	
Maximum liver tumor diameter (cm)	<5	36	10.2	0.091
	≥5	28	4.3	
Lung metastasis	Absent	55	8.5 %	0.331
	Present	9	0.0 %	
Peritoneal dissemination	Absent	40	8.7 %	0.170
	Present	24	5.9 %	
Extra hepatic disease	Absent	22	5.0 %	0.875
	Present	42	9.7 %	
Postoperative complication	No	57	8.2 %	0.076
	Yes	9	0.0 %	
Postoperative therapy	No	12	0.0 %	<0.001
	Yes	52	9.4 %	

CRC colorectal cancer, *OS* overall survival, *CEA* carcinoembryonic antigen

Prognostic factors for patients with curable stage IV CRC

To estimate prognostic factors, univariate analysis was performed for the same variables as those considered for noncurable disease and extent of liver resection (resection of two or fewer liver subsegments vs. three or more liver subsegments). T stage (T4, p=0.004), N stage (positive, p=0.026), histological type (other types, p=0.026), serum CEA level (≥30.0 ng/ml, p=0.002), peritoneal dissemination (present, p<0.001), extra hepatic disease (present, P<0.001) and postoperative chemotherapy (yes, p=0.036) were identified as significant prognostic factors (Table 3).

In multivariate analysis of selected variables found to be significant in the univariate analysis, T stage (T4, p=0.032), histological type (other types, p=0.043), serum CEA level (≥30.0 ng/ml, p=0.007) and the presence of extra hepatic disease (present, p=0.015) were identified as independent prognostic factors (Table 4).

Risk classification based on the independent prognostic factors for patients with curable stage IV CRC

To identify patients who might show a survival benefit from metastasectomy, we established a risk classification based on the following independent prognostic factors: T stage (T4), histological type (other than well-differentiated adenocarcinoma), serum CEA level (≥30.0 ng/ml) and the presence of extra hepatic disease. We, then, classified patients into two groups, a low-risk group (zero to two risk factors) and a high-risk group (three or more risk factors). Forty-six patients were classified into the low-risk group,

Table 3 Prognostic factors in patients with curable stage IV CRC (n=55)

Variables		Number	5-year OS	p value
Age	<70	45	48.5 %	0.371
	≥70	10	37.5 %	
Sex	Male	34	50.0 %	0.813
	Female	21	39.3 %	
Location	Colon	32	45.7 %	0.898
	Rectum	23	46.7 %	
T factor	T1–3	38	56.5 %	0.004
	T4	17	19.2 %	
N factor	Negative	16	70.2 %	0.026
	Positive	39	35.7 %	
Histology	Well	17	65.7 %	0.026
	Other types	39	37.6 %	
Lymphatic invasion	Negative	11	72.7 %	0.262
	Positive	44	42.5 %	
Venous invasion	Negative	16	45.8 %	0.213
	Positive	39	47.8 %	
CEA (ng/ml)	<30	34	67.5 %	0.002
	≥30	21	16.7 %	
Number of liver metastasis	0–3	46	44.1	0.431
	≥4	9	53.3	
Maximum liver tumor diameter (cm)	<5	48	45.5	0.647
	≥5	7	51.4	
Extent of liver resection	2 or fewer subsegments	44	46.2	0.859
	3 or more subsegments	11	43.8	
Lung metastasis	Absent	53	48.0 %	0.070
	Present	2	0.0 %	
Peritoneal dissemination	Absent	52	48.8 %	<0.001
	Present	3	0.0 %	
Extra hepatic disease	Absent	48	52.0 %	<0.001
	Present	7	0.0 %	
Postoperative complication	No	46	45.1 %	0.843
	Yes	9	48.6 %	
Postoperative therapy	No	3	0.0 %	0.036
	Yes	52	47.4 %	

and nine patients were classified as a high risk group. For patients with curable stage IV CRC, the OS of the high-risk group was significantly poorer than that of the low-risk group (p<0.001, Fig. 2). Furthermore, the OS of this group was as poor as that of patients with noncurable stage IV CRC (p=0.474, Fig. 2).

Discussion

Complete surgical resection of metastases contributes to the long-term survival of patients with stage IV CRC. The present study confirmed that the OS of patients with curative metastasectomy was significantly better than that of patients with noncurative or without metastasectomy. However, there is no consensus regarding the upper limits of operative indications for metastatic tumors. The current guidelines state that the aim of liver resection in patients with colorectal liver metastases is to remove all macroscopic disease, to achieve clear resection margins and to leave a sufficiently functioning liver [4, 18, 24]. These criteria apply to patients with solitary, multiple and bilobar disease as well as extra

Table 4 Prognostic factors in patients with curable stage IV CRC: multivariate analysis

Selected variables	p value	Odds ratio	95 % confidential interval
T factor (T4)	0.032	2.681	1.087–6.623
N factor (positive)	0.272	3.678	0.562–7.752
Histology (other types)	0.043	3.259	1.037–10.242
CEA (≥30 ng/ml)	0.007	3.717	1.443–9.615
Peritoneal dissemination (present)	0.899	1.147	0.137–9.615
Extra hepatic disease (present)	0.015	7.143	1.468–34.483
Postoperative chemotherapy (no)	0.069	5.826	0.875–38.811

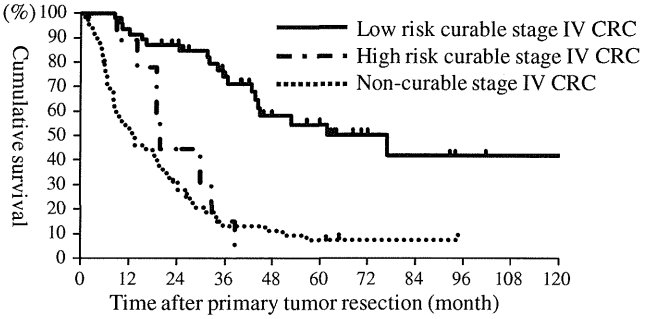

Fig. 2 The OS in patients with noncurable and curable stage IV CRC classified by the independent prognostic factors. For patients with curable stage IV CRC, the OS of the high risk group was significantly poorer than that of the low risk group ($p<0.001$). Furthermore, the OS of this group was as poor as that of patients with noncurable stage IV CRC ($p=0.474$)

hepatic disease that is confirmed in the lungs, ovary, peritoneal dissemination and extra regional lymph nodes [2, 3, 18, 24]. Therefore, the operative indications for metastasectomy are dependent on the decisions of surgeons or oncologists in each institution. Before resecting the metastatic tumor, it is important to recognize who is likely to benefit from the procedure. We, therefore, aimed to identify the patient population who likely benefit from metastasectomy.

Previous studies showed a wide variation in outcomes according to the baseline resectability status of metastases for stage IV CRC [20]. For the majority of patients, treatment remains of palliative benefit, with the possibility of cure, were restricted only to those patients who are suitable for surgical resection. Thus, stage IV CRC encompasses a heterogeneous patient population in which both palliative and curative treatment strategies may be used. In the present study, we also showed differences in the prognostic outcome according to the disease resectability status (curable group vs. noncurable group). Furthermore, among patients with noncurable stage IV CRC, tumor-related factors did not reflect the prognosis. Conversely, for patients with curable stage IV CRC, tumor-related factors, such as T stage, histological type, preoperative CEA level and the presence of extra hepatic disease, were indicative of the prognosis. These results implied that stage IV CRC patients consist of heterogeneous populations in which the prognoses and prognostic factors are different and can be stratified by the resectability status of the disease.

To address the controversial topic of patient selection for metastasectomy, various groups have proposed using a prognostic scoring system to stratify patients into different risk categories. Nordlinger et al. [16] and Fong et al. [5] each proposed a prognostic scoring system after hepatic resection using several clinical parameters. Recently, Kattan et al. [17] and Kanemitsu et al. [6] proposed a prognostic nomogram to identify high-risk patient groups. In these systems, age, gender, primary site, primary T and N stage, short disease free interval, the size and number of liver tumors, surgical margin, preoperative CEA level and the presence of extra hepatic disease were found to be prognostic markers. However, there is no ideal prognostic system for the clinical management of patients with colorectal liver metastases [18]. As in liver metastases, a number of prognostic factors have been suggested to predict outcome after pulmonary metastasectomy [7–9]. In general, the number of pulmonary metastases, short disease free survival, preoperative CEA levels and nodal status of perihilar and mediastinal lymph nodes were reported as prognostic factors. However, disagreement exists over which prognostic factors determine who will benefit most from aggressive surgical treatment [25]. In the present study, T4, histological type (other than well-differentiated adenocarcinoma), elevated serum CEA level (≥30 ng/ml) and the presence of extra hepatic disease were identified as independent prognostic factors, considering only the patients with curative metastasectomy. In addition, a patient population likely to show a survival benefit of metastasectomy was identified, stratified by these prognostic factors. To best of our knowledge, the present study is the first to identify a patient population likely to show survival benefits from curative metastasectomy. These present results suggest that the identification of patients who would benefit from metastasectomy is possible, considering the prognostic factors extracted from patients with curative metastasectomy.

Although the presence of extra hepatic disease has long been considered a contraindication for resection, recent reports of long-term survival of patients who undergo resection of both sites suggest that some patients may show long-term benefits [25, 26]. Similar to the management of liver metastases, pulmonary resection for metastatic CRC is increasingly being considered as appropriate and beneficial in selected patients [7, 8]. Resection of metastases in more unusual sites, such as ovary, peritoneal dissemination and extra regional lymph nodes, is more controversial. However, several retrospective studies have suggested that selected patients may be cured with resection of these tumors [2, 10–15]. In the present study, the presence of extra hepatic disease was also selected as an independent prognostic factor in patients with curative metastasectomy. However, our data also showed that the prognostic benefit of resection of extra hepatic disease is limited to patients with two or less other prognostic factors (T4, other than well-differentiated adenocarcinoma and elevated serum CEA level). Our data supported the notion that surgical metastasectomy can be beneficial in well-selected patients with stage IV CRC, despite the number or site of metastatic organs.

Recent advances in chemotherapeutic regimens have produced good results with preoperative chemotherapy; thus, neoadjuvant chemotherapy followed by hepatectomy has

gradually gained acceptance for both initially nonresectable metastases and resectable metastases [2]. The high tumor response rates achieved with modern chemotherapeutics now enable a greater proportion of patients with initially inoperable disease to achieve an operable status and undergo liver resection with curative intent. This type of chemotherapy is termed 'conversion therapy' to differentiate it from 'neoadjuvant therapy' in upfront resectable metastases [27, 28]. The current study did not include so-called 'conversion therapy,' which is aimed at the complete resection after preoperative chemotherapy for patients with unresectable CRC. The present study did not show the prognostic benefit of metastasectomy for the initial treatment of patients with three or more risk factors, even if curative resection of metastases was performed. Although further investigation is required, preoperative chemotherapy may be recommended for such patients.

For the resection of isolated metastases with a curative intent, it is critical that the primary colorectal tumor has been or can be completely resected [2]. In cases with unresectable metastases, the role of primary tumor resection has been controversial, in particular with the improvement in newer chemotherapeutic agents [29]. Although a recent meta-analysis suggested the efficacy of primary CRC resection from a prognostic point of view [30], another study recommended the introduction of chemotherapy without removal of primary tumors in patients without any tumor-related complications [29]. In the present study, our criteria for primary tumor resection did not include the presence of tumor-related complications. However, we recently introduced chemotherapy in patients with asymptomatic and minimally symptomatic tumorus, to avoid the delay of chemotherapy because of the resection of the primary tumors.

The timing of the synchronous resection of metastases and primary tumor has been a subject of debate [2, 4]. Recent studies have demonstrated equivalent outcomes without increased morbidity and mortality in patients who undergo simultaneous resection [31, 32]. In the present study, simultaneous resection of both the primary and metastatic tumors was performed in all cases of resectable synchronous metastases, regardless of the location of primary tumors and the extent of metastasis. The mortality and morbidity rate was low in this study as compared to previous reports [31, 32], which suggested that for well-selected patients, simultaneous resection of primary CRC and abdominal metastases is a safe approach.

This study had several limitations. First, the possible influence of the variable regimen of postoperative therapy cannot be ignored. Second, the current patient cohort included few patients treated with newer chemotherapy agents such as bevacizumab and cetuximab. There were no significant differences in the use of molecular-targeted therapies among the three groups (low-risk curable group, $n=1$; high-risk curable group, $n=1$; and noncurable group, $n=2$; $p=0.221$). Therefore, we can safely assume that the application of these agents would not confound our results.

In conclusion, we demonstrated that stage IV CRC patients consist of a heterogeneous patient population with different prognostic factors, stratified by the disease resectability status. Consideration of the prognostic factors in patients treated with curative metastasectomy (T4, other than well-differentiated adenocarcinoma, elevated serum CEA level and the presence of extra hepatic disease) allowed the identification of patients who would most benefit from this procedure. This study is a retrospective trial with relatively low number of patients, therefore, our data is needed to validate with large series in order to establish universal selection criteria of metastasectomy for stage IV CRC. Regardless of this limitation, however, our data demonstrated the possibility of establishing ideal prognostic models based on the disease resectability status for stage IV CRC.

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Primary lung cancer presenting with metastasis to the colon: a case report

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Primary lung cancer presenting with metastasis to the colon: a case report

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Abstract

Although about 50% of lung cancers have distant metastasis at the time of initial diagnosis, colonic metastases are extremely rare. This report presents a rare clinical case of colonic metastasis from primary squamous cell carcinoma of the lung.

A 60-year-old female with anorexia and fatigue was referred to the department of pulmonary surgery in our hospital. The patient was diagnosed with primary squamous cell carcinoma of the lung, T2b N3 M1b Stage IV, and chemoradiotherapy was initiated. This treatment led to a good partial response in the primary lung lesion without any new metastatic lesions.