agents to the liver with a minimal systemic toxicity[13] and thus provides high response rates of up to 83%.[13] However, HAI alone cannot cure such patients.[14–17] Indeed, there were at best only one or two 5-year survivors in each HAI trial.[15–17]

To overcome this problem, we had conducted a pilot study of multimodality therapy with hepatic resection after HAI and portal vein embolization for unresectable hepatic metastases and reported the feasibility and potential benefit for selected patients.[18] The purpose of the present study was to evaluate the long-term efficacy of HAI and hepatic resection after HAI for patients with initially unresectable liver metastases from colorectal carcinoma.

Patients and Methods

Between 1988 and 1999, 72 patients with synchronous or metachronous unresectable hepatic colorectal metastases received HAI. Of them, nine patients received HAI after resection of two liver segments or more and ten after resection of one liver segment or less. Informed consent was obtained from each patient. All patients had multiple liver metastases involving three or four hepatic segments (Table 1), which were detected by computed tomography (CT) and ultrasonography (US) and/or confirmed by intraoperative US and biopsy. These metastases were considered unresectable because the remaining functional parenchymal volume of the liver after resection was estimated to be too small to maintain normal liver function or the tumors were contiguous to essential intrahepatic vascular structures. If hepatic metastases became resectable after HAI, resection was performed. All patients were followed up for at least 5 years or until death. Retrospective analysis of clinicopathologic data from the prospective database and medical records of these patients was conducted.

All patients underwent hepatic arterial catheterization and placement of an implantable reservoir[19] or an Infusaid model 400 pump (Infusaid, Norwood, MA, USA)[18] with or without a laparotomy. In the laparotomy group, the gall bladder was removed and the right gastric and gastroduodenal arteries and small branches supplying the stomach and duodenum were ligated. An arterial catheter was placed into the gastroduodenal artery, with the tip placed at the junction of the proper hepatic artery and gastroduodenal artery. In the non-laparotomy group, the gastroduodenal and right gastric arteries were occluded with steel coils. A catheter was placed into the proper hepatic artery via the subclavian or femoral artery. After the catheter was connected to the reservoir or the pump, fluorescein dye or indigo carmine was injected through the catheter to confirm complete perfusion of the liver.[18,19]

Table 1 Patient Characteristics

	No. of patients
Patient	
Sex	
Male	50
Female	22
Age (years)	59 (range 32–78)[a]
Primary tumor	
Site	
Colon	39
Rectum	32
Unknown	1
Histological grade[b]	
Well-differentiated	28
Moderately differentiated	41
Poorly differentiated	3
Transmural invasion depth (pT)[b]	
T2	3
T3	63
T4	4
Unknown	2
Regional lymph node metastasis (pN)[b]	
N0	10
N1	19
N2	30
Unknown	3
Pathologic stage[b]	
I	1
II	3
III	14
IV	52
Unknown	2
Liver metastasis	
Appearance	
Synchronous	52
Metachronous	20
No. of tumors[c]	
2	2 (2)
3	3 (2)
4	4 (1)
5–9	25 (4)
≥10	38
Sum of tumor diameters (cm)[c]	
5–9	27 (8)
10–14	30 (1)
15–19	8
≥20	7
Number of involved segments	
3	10
4	62
CEA levels (ng/ml)	61.3 (range 1.6–6,000)[a]

CEA carcinoembryonic antigen

[a] Numbers are median and range

[b] UICC TNM classification (6th edition)

[c] Numbers in parenthesis represent the number of patients who underwent resection of two liver segments or more before hepatic arterial infusion

HAI was initiated 2–3 weeks after recovery from simultaneous colorectal resection or the next day after catheter placement alone. The protocols for HAI were as follows:

Protocol 1 The initial dose of 360 mg/m^2 per day of 5-fluorouracil (FU) was infused for 7 days by using an extracorporeal continuous infusion pump (CADD-1, Pharmacia, St. Paul, MN, USA), followed by 180 mg/m^2 per day of 5-FU for 21 days. After a 7-day interval without infusion, 180 mg/m^2 per day of 5-FU was infused for 7 days. This 7-day infusion/7-day no infusion cycle was repeated.[19]

Protocol 2 The initial dose of 360 mg/m^2 per day of 5-FU was infused for 14 days by the same pump. After a 7-day interval without infusion, 180 mg/m^2 per day of 5-FU was infused for 7 days. This 7-day infusion/7-day no infusion cycle was repeated.

Protocol 3 The initial dose of 1,000 mg/m^2 of 5-FU was administered over 5 h once a week by the same pump, and this therapy was repeated as long as possible.

Protocol 4 The starting doses of 120 mg/m^2 per day of 5-FU was administered by continuous infusion through the Infusaid pump for 21 days, alternating with normal saline for 7 days, and 4 mg/m^2 per day of mitomycin C was given by injection through the side port of the pump once a month. This treatment cycle was repeated as many times as possible.[18]

We used 5-FU instead of the floxuridine (FUDR) because FUDR was not permitted in Japan. The patients underwent a physical examination, complete blood count, and blood biochemistry profile every 2 weeks. When abdominal symptoms or abnormal values in the blood test attributable to HAI were noted, HAI was discontinued until the complications were resolved. After resolution of the complications, subsequent doses were administered at half of the starting dose. Upper gastrointestinal endoscopy and angiography via the implanted reservoir were performed when symptoms of epigastric pain and/or vomiting were observed. When severe complications such as bleeding from a duodenal ulcer, sclerosing cholangitis, occlusion of the hepatic artery or extravasation, appearance of extrahepatic metastases, and regrowth of hepatic tumors occurred, HAI was terminated. Treatment was continued for as long as the liver tumors were evaluated to have either decreased in size or remained unchanged.[18]

All of the patients were examined before the initiation of HAI and every 2 months thereafter with CT and US of the abdomen and chest X-ray. The tumor response was evaluated with CT and US and was defined according to the World Health Organization criteria.[20] A complete response (CR) denoted the disappearance of all liver tumors for more than 4 weeks by CT and/or US. A partial response (PR) indicated a reduction of more than 50% in the sum of the largest diameters of all tumors for more than 4 weeks by CT. Progressive disease (PD) was defined as an increase in tumor size of greater than 25% or an appearance of new liver tumors. The patients with other response were considered to have stable disease (NC). The duration of the response was measured from the onset of a tumor reduction of more than 50% to disease progression.

Survival curves were estimated with the Kaplan–Meier method and differences in survival were evaluated with the log-rank test. All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Tokyo, Japan). All P values were two-sided and a P value of less than 0.05 was considered to be statistically significant.

Results

The characteristics of the patients are shown in Table 1 and treatment results in Table 2. The overall response rate was 38% (eight patients with CR, 19 with PR; Table 2). NC was found in 20 patients and PD in 25. The response rates for the protocols 1, 2, 3, and 4 were 50% (one patient with CR, five with PR), 67% (two CR, four PR), 20% (two CR, six PR), and 64% (three CR, four PR), respectively. Minor complications including epigastric pain, nausea, vomiting, and back pain were observed in 44 patients (61%). Of eight patients (11%) with severe complications, six patients had duodenal ulcers, one sclerosing cholangitis, and one both duodenal ulcer and sclerosing cholangitis. Among the seven patients with duodenal ulcers, six suffered bleeding and four underwent emergency surgery. The two patients with sclerosing cholangitis developed liver abscesses and received US-guided drainage, but died at 40 and 82 months after the initiation of HAI, respectively.

All patients were followed for at least 5 years or until death. At the last follow-up, three patients (4%) undergoing hepatectomy after HAI were alive. Two patients (3%) died of liver abscess due to sclerosing cholangitis without recurrence and 67 patients (93%) died of the disease. Extrahepatic recurrences appeared in 45 patients (62%), including lung metastases in 41 patients, bone metastases in nine, local recurrence in five, lymph node metastases in three, and brain metastases in two.

The median survival of the 72 patients after the initiation of HAI was 18 (range, 3–167) months. Seven patients (10%) survived more than 58 months. The 1-, 2-, 3-, 4-, and 5-year survival rates were 72%, 32%, 18%, 10%, and 7%, respectively (Fig. 1). The survival of the responders (CR

Table 2 Treatment Results

Protocol no.	No. of patients	Response rate (%)	CR rate (%)	Complication rate (%)	Rate of severe complication[a] (%)	Resection rate (%)
1	12	50	8	75	8	0
2	9	67	22	77	11	33
3	40	20	5	65	5	5
4	11	64	27	90	36	18
Total	72	38	11	72	11	10

CR complete response

[a] Sever complications were sclerosing cholangitis and duodenal ulcer

plus PR) was better than that of the non-responders (NC plus PD; $P<0.001$). The median survival time was 26 months for the responders versus 12 months for the non-responders.

Table 3 shows details of the eight patients with CR. Of them, seven patients developed liver and/or lung metastases afterward, and only one patient maintained CR who died of liver abscess due to sclerosing cholangitis at 40 months. Of the seven patients with relapses, one patient undergoing resection of metastases confined to the liver was alive at 118 months. Another patient received HAI again, but died at 27 months. The remaining five patients received systemic chemotherapy because of extrahepatic disease or occlusion of the hepatic artery.

Owing to shrinkage of liver metastases after HAI, seven patients (10%) could undergo hepatectomy. Details of these patients are shown in Table 4. Of the three patients with PR whose remaining metastases were confined to the right lobe, one patient could undergo right lobectomy and two extended right lobectomy after portal vein embolization. Another patient could undergo left lobectomy and wedge resection after portal vein embolization. The other three patients underwent wedge resection. Postoperative complications included bile leakage in two patients and liver
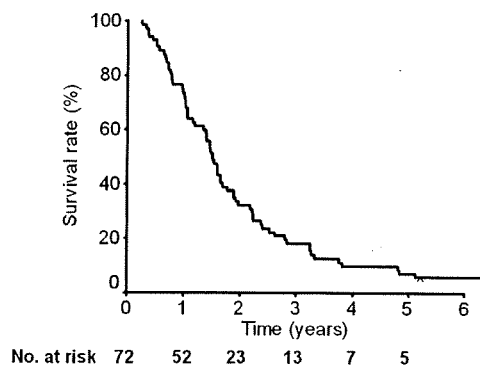

Figure 1 Survival curve of the overall patients who received hepatic arterial infusion chemotherapy for unresectable hepatic colorectal metastases ($n=72$). Time is from the initiation of hepatic arterial infusion.

abscesses in two. One patient died of liver abscesses due to sclerosing cholangitis at 82 months, and three patients died of liver and/or lung metastases. The median survival of these patients was 63 months, whereas it was 17 months for those who could not undergo hepatectomy ($P<0.001$; Fig. 2). The 1-, 3-, and 5-year survival rates of the patients with hepatectomy after HAI were 100%, 86%, and 71%, respectively, and five patients (7%) survived more than 5 years.

Discussion

Complete surgical resection is currently the only treatment that can provide long-term survival and cure for patients with hepatic colorectal metastases.[4–10] Although only 10–25% of the patients can undergo complete resection,[2,3,12,21] the resection rate may be improved if chemotherapy sufficiently reduces the size and number of the tumors.[3,12,18,21]

The current systemic regimens consisting of 5-FU, leucovorin, oxaliplatin, irinotecan, bevacizumab, and cetuximab bring about response rates of 70% or more so that they are regarded as standard therapy for unresectable metastatic colorectal cancer.[11,12] However, the median survival after such chemotherapy alone is up to 20 months.[22] Although the systemic chemotherapy also enables resection in 15–30% of patients with disease limited to the liver,[12] the 5-year survival rates following such resection are still around 33%.[12,21] In addition, the current regimens cannot be used for patients who suffer toxicity or refractory disease after the current systemic therapy.

On the other hand, the response rates of HAI with FUDR are reported to be 42–62% and the median survival after HAI have ranged from 13 to 17 months.[13,15,16,23,24] In our previous study, the median survival of eight patients with unresectable liver metastases, who had undergone resection of the primary tumor and received HAI with 5-FU, was 30 months with a response rate of 75%.[18] Therefore,

Table 3 Details of the Patients with Complete Response

Case no.	Age (years)/sex	No. of tumors	Sum of tumor diameters (cm)	Protocol no.	Duration of CR (months)	Site of relapse	Treatment after relapse	Survival (months)[a]	Outcome
1	78/M	10	7.3	P-4	28	None	None	40	Dead[b]
2	62/M	7	5.6	P-4	15	Liver	SCT	46	DOD
3	44/M	5	11.4	P-2	10	Liver	Resection	118	ANED
4	65/M	11	10	P-4	9	Liver, Lung	SCT	58	DOD
5	57/M	7	7.2	P-3	7	Liver, Lung	SCT	45	DOD
6[c]	66/F	2	2	P-1	4	Liver	SCT	26	DOD
7	61/F	12	9.7	P-2	4	Liver	SCT	21	DOD
8	59/F	11	9	P-3	3	Liver	HAI	27	DOD

CR complete response, SCT systemic chemotherapy, HAI hepatic arterial infusion, DOD dead of disease, ANED alive with no evidence of disease

[a] Survival from initiation of hepatic arterial infusion

[b] The patient died of liver abscess due to sclerosing cholangitis

[c] The patient underwent resection of eight liver metastases before HAI

although HAI is not effective for extrahepatic diseases and has some technical difficulties, HAI seems to have a certain role for selected patients with disease limited to the liver.

In this study, the response rate was 38% overall, but ranged from 20% to 67% according to the protocols. Reflecting these response rates, the median survival time was 18 months. These results are comparable to those following HAI with FUDR and are approaching those with the current systemic regimens. Although this was not a randomized controlled study and the number of patients was limited, protocol 2 showed the highest response rate of 67%, the highest resection rate, the moderate rate of severe complications, and seemed to be the best among our protocols. However, 62% of our patients developed extrahepatic relapses, mostly lung metastases, for which HAI has limitations.

The median survival of our patients with CR was 42 months and the survival of the responders was significantly better than the non-responders in line with previous reports.[19] However, most patients showing CR had relapses eventually as reported before.[12] Actually, of the eight patients with CR, seven had relapses and only one patient who underwent hepatectomy for relapsed liver metastases has been free of disease. Therefore, as is recommended in the Expert Consensus Statement,[12] hepatic metastases should be resected when they become resectable.

Although there have been many studies on hepatectomy following systemic chemotherapy,[12,21,25] the number of studies on hepatectomy after HAI is limited,[18,26,27,28,29] particularly with a few long-term follow-up studies.[18,26,27,28,29] Elias et al.[26] reported that liver tumors in 6% of 239 patients who received HAI with 5-FU and other

Table 4 Details of Seven Patients Who Underwent Hepatectomy After Hepatic Arterial Infusion Chemotherapy

Case no.	Age (years)/sex	No. of tumors	Sum of tumor diameters (cm)	Protocol no./response	PVE	Type of surgery	Complication after surgery	Site of relapse	Survival (months)[a]	Outcome
1	40/M	5	12.8	P-4/PR	Yes	RL	Bile leakage	None	167	ANED
2	44/M	5	11.4	P-2/CR	No	W	None	None	118	ANED
3	46/M	14	13	P-4/PR	Yes	ERL	None	None	82	Dead[b]
4	56/F	7	11.4	P-3/PR	Yes	LL+W	None	Lung	63	ANED[c]
5	35/F	8	20	P-2/PR	Yes	ERL	Bile leakage	Liver	62	DOD[d]
6	67/M	8	8.1	P-3/PR	No	W	Liver abscess	Lung	58	DOD[d]
7	62/M	5	10.4	P-2/PR	No	W	Liver abscess	Liver	22	DOD[d]

PVE portal vein embolization, PR partial response, CR complete response, RL right lobectomy, W wedge resection, ERL extended right lobectomy, LL left lobectomy, ANED alive with no evidence of disease, DOD dead of disease

[a] Survival from initiation of hepatic arterial infusion

[b] The patient died of liver abscess due to sclerosing cholangitis

[c] The patient is still alive after hepatectomy and after partial resection of the lung for lung metastasis

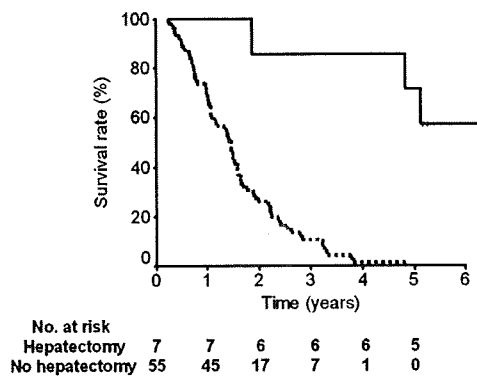[d] The patient died of lung and/or liver metastases

Figure 2 Survival curves according to the additional hepatectomy after hepatic arterial infusion chemotherapy for unresectable hepatic colorectal metastases. Survival of the patients with additional hepatectomy ($n=7$, solid line) was significantly better than that of those without hepatectomy ($n=65$, broken line; $P<0.001$). Time is from the initiation of hepatic arterial infusion.

agents for unresectable hepatic tumors subsequently became resectable, and five of the nine patients with hepatic colorectal metastases had been free of disease, with a mean follow-up time of 36 months. Link et al.[27] evaluated 168 patients with unresectable hepatic colorectal metastases treated with HAI with FUDR and others. The overall resection rate was 5%, and seven patients were alive 2–58 months after resection. Meric et al.[28] reported that 18 of 383 patients (5%) treated with HAI with FUDR or 5-FU and others for unresectable hepatic colorectal metastases could undergo resection. Of them, 15 patients developed recurrence at a median follow-up of 17 months and three died of other causes within 7 months. Clavien et al.[29] used HAI with FUDR and induced resectability in six of 23 previously treated patients (26%) with unresectable hepatic colorectal metastases (including 20 previously treated with irinotecan). The actuarial survival rate at 3 years was 50%.

In the present study, although the resection rate was 10%, the median survival of the seven patients with hepatectomy was 63 months and six patients survived more than 58 months. In terms of resection rate and survival, our results seem to be preferable to those of the previous HAI series[26,27,28] and almost similar to the recent results with FUDR.[29] In addition, our survival results appear to approach those with the current systemic regimens.[12,21,25] In resection rate, however, ours are worse than those with the systemic regimens. Moreover, in spite of long-term survival, 43% of our patients eventually died of the disease. Therefore, the current HAI are not sufficiently effective for unresectable colorectal liver metastases in terms of long-term survival.

Integration of targeted agents such as cetuximab and bevacizumab into the current systemic regimens has been shown to raise response rates up to 70% or more[12] and may improve the resection rate and survival. Another possible

option is a combination of HAI and systemic therapy, which simultaneously utilizes a high drug concentration in the liver brought about by HAI and the suppression of extrahepatic disease by systemic therapy. A third possibility is postoperative adjuvant chemotherapy. Portier et al.[30] conducted a randomized controlled trial and showed that postoperative 5-FU plus leucovorin improved disease-free survival of the patients who underwent liver resection for colorectal metastases. All these options and their combinations seem to be promising and warrant further investigation.

Timing of hepatectomy is another important issue for improving the outcomes. If we had performed hepatectomy for the seven patients with CR, the resection rate would have been 19% (14/72) and they might have avoided relapses. Therefore, as is recommended in the Expert Consensus Statement,[12] resection should be performed as soon as hepatic metastases become technically resectable. Also, resection should encompass the segments involved based on pre-chemotherapy imaging.[12]

In this study, four patients (57%) suffered postoperative complications consisting of bile leakage and liver abscess. This morbidity is higher than expected in hepatectomy without neoadjuvant chemotherapy. Indeed, we have seldom experienced liver abscess in surgery alone. Elias et al.[26] reported that postoperative complications were significantly more frequent after hepatectomy following HAI than after hepatectomy alone (57% versus 18%). The rates of complications directly associated with hepatectomy, including hemorrhage, biliary fistula, abscess, and atelectasis, were 29% in the HAI group versus 11% in the non-HAI group. HAI with 5-FU or FUDR is known to cause nodular regenerative hyperplasia, steatohepatitis, chemical hepatitis, and biliary sclerosis.[11,13] Although their pathogenesis has not been well established,[11,13] these high complication rates are attributable to such hepatobiliary toxicity. In this aspect, early resection has an advantage of shortening the duration of HAI and thus reducing damage to the liver.

During HAI in our series, two patients developed liver abscesses due to sclerosing cholangitis and four had bleeding duodenal ulcers, both of which were life-threatening and necessitated emergency intervention. The etiology of sclerosing cholangitis is not well understood, but is mainly attributable to a combination of ischemia and inflammation.[13] The incidence of sclerosing cholangitis with FUDR HAI was reported to rise with an increase in the infusion dose[16] and the duration of infusion.[15] Therefore, we should reduce dosage and shorten duration as less as possible. The addition of dexamethasone to HAI regimens, circadian modification, and drug alternation also have been attempted[13] and may be beneficial. Gastrointestinal toxicity, mainly gastroduodenal inflammation and ulceration, is directly related to extrahepatic perfusion.[13] This can be

avoided by careful hepatic artery dissection, including ligation of the right gastric artery and all the small branches in the hepatoduodenal and hepatogastric ligaments, during catheter placement.[13] Oral histamine receptor blockers may decrease the severity of gastric toxicity.[13] Early detection of toxicity and discontinuation of HAI are also important to prevent the occurrence of severe complications. We should pay careful attention to elevations of aspartate aminotransferase, alkaline phosphatase, and bilirubin in addition to gastrointestinal symptoms.[13]

In conclusion, the present study showed that almost all patients showing CR or PR after HAI for unresectable hepatic colorectal metastases had relapses, but overall long-term survival of patients undergoing hepatectomy after HAI was favorable. Therefore, when HAI makes liver metastases resectable, they should be resected. This approach appears helpful for patients with unresectable colorectal metastases limited to the liver who suffered toxicity or refractory disease after the current systemic therapy. Although the standard drug for HAI is FUDR, efficacy of the current HAI regimen with 5-FU appears almost similar. To improve survival further, measures to increase candidates for resection, reduce liver and lung relapses, and reduce complications are necessary.

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● 原　著 ●

高度な肝機能障害を伴い切除不能多発肝転移を有する
大腸癌症例に対する肝動注併用 FOLFOX 療法の検討

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Combination of Hepatic Arterial Infusion Therapy and FOLFOX for Colorectal Cancer with Multiple Unresectable Liver Metastases Causing Severe Liver Dysfunction: Takeshi Suto[*1], Toshihiko Sato[*1], Naoki Mori[*1], Naruhisa Takano[*1], Koshiro Ishiyama[*1], Naoki Sakurai[*1], Kiyohiro Saito[*2], Hajime Iizawa[*1] and Eiichi Ikeda[*1] (Dept. of[*1]Gastroenterological Surgery, [*2]Radiology, Yamagata Prefectural Central Hospital)
Summary

Purpose: The purpose of this study was to evaluate the efficacy of the combination of hepatic arterial infusion therapy and FOLFOX for colorectal cancer with multiple unresectable liver metastases causing severe liver dysfunction.

Subjects and Methods: The subjects were 13 colorectal cancer patients who had undergone resection of the primary tumor, and showed multiple, unresectable liver metastases and severe liver dysfunction. They consisted of 8 men and 5 women, with a median age of 63 (29-77) years. Of these patients, 7 and 6 had colon and rectum cancers, respectively. They had an average of 8 (3-22) liver metastases of 4.6 (1.5-14.5) cm in diameter. During surgery, extrahepatic lesions were found in 3 patients (P in 2, and CY in 1). The preoperative serum LDH and ALP levels were high, at 1,099 (322-1,418) and 1,011 (644-2,384), respectively. The follow-up period was approximately 500 (248-928) days. Only 5-FU in FOLFOX4 or 6 m therapy was infused into the hepatic artery, and LV and L-OHP were injected into the central venous port about every two weeks. Response rates and adverse events were evaluated according to the RECIST criteria and CTCAE ver 3.0, respectively.

Results: The therapy was performed 14 (6-22) times, with a response rate of 84.6% for liver metastases, facilitating hepatectomy in 1 patient. The overall response rate was 61.5%, with 1 patient dying of the primary cancer on the 265th day. Grade 3 adverse events were neutropenia and anorexia in only 1 patient each, and no adverse events were specific to hepatic arterial infusion.

Conclusion: Since the follow-up period after this therapy was still short, only 13 patients have received the therapy. However, it appears that it can be performed relatively safely, and is effective for the control of extrahepatic lesions as well. Therefore, this therapy provides good control, and can be a treatment option. Key words: Colorectal cancer, Multiple liver metastases, Hepatic arterial infusion, FOLFOX (Received Apr. 2, 2008/Accepted Jul. 3, 2008)

要旨　目的: 高度な肝機能障害を伴う切除不能多発肝転移を有する大腸癌症例に対する肝動注併用 FOLFOX 療法の有効性について検討する。対象と方法: 高度な肝機能障害を伴う切除不能多発肝転移を有し, 原発巣を切除した大腸癌症例 13 例を対象とした。男性 8 例, 女性 5 例, 年齢は中央値 63 (29~77) 歳であった。結腸 7 例, 直腸 6 例, 肝転移個数は 8 (3~22) 個, 大きさ 4.6 (1.5~14.5) cm であり, 術中肝外病変は 3 例 (P 2 例, CY 1 例) に認めた。術前血中 LDH 1,099 (322~1,418), ALP 1,011 (644~2,384) と高値であった。観察期間は約 500 (248~928) 日であった。FOLFOX4 または 6 m 療法の 5-FU のみ肝動注より動注し, LV と L-OHP は中心静脈ポートより静注し, 約 2 週間ごとに施行した。奏効率は RECIST に, 有害事象は CTCAE ver 3.0 に従い評価した。結果: 施行回数は 14 (6~22) 回であった。肝に対する奏効率は 84.6% で, 1 例に切除可能であった。全体では 61.5% の奏効率であり, 死亡例は 1 例 (265 日目原癌死) であった。grade 3 の有害事象は neutropenia 1 例, anorexia 1 例のみで肝動注特有の有害事象は認めなかった。まとめ: 肝動注併用 FOLFOX 療法は観察期間がまだ短く, 症例数が 13 例と少ないものの比較的安全に施行でき, 肝外病変のコントロールも含めて比較的有効と思われるため, 局所制御の良好な肝動注療法を併用した FOLFOX 療法は治療法の選択肢になり得ると思われた。

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は じ め に

大腸癌のうち肝転移は同時性に 10%, 異時性に 15% と最も高頻度に認める転移形式である[1]。大腸癌の両葉多発肝転移例の予後は不良といわれ, 無治療例の 50% 生存期間は 4.5〜12.5 か月と報告されている[2-6]。かつて本邦においては Arai らにより 5-fluorouracil (5-FU) 単剤による肝動注療法が施行され, 良好な局所制御効果を認めていたが[7], 欧米での全身化学療法とのランダム化比較試験においては生存期間延長効果を認めないと報告されていた[8]。近年では FOLFOX などの奏効率の高い全身化学療法を施行し, down-staging 後に肝切除を行い, 生存率など良好な成績が報告されている[9]。そのため今回われわれは, 高度の肝機能障害を有する切除不能な大腸癌肝転移症例に対し, 局所制御効果の高い 5-FU の肝動注療法に levofolinate calcium (LV) と oxaliplatin (L-OHP) の全身投与との併用療法を施行し, その有効性と安全性について検討した。化学療法の腫瘍縮小効果は RECIST (Response Evaluation in Solid Tumors) ガイドライン, 有害事象は CTCAE ver. 3.0 (Common Terminology Criteria for Adverse Events v3.0) に従った。組織学的腫瘍効果判定基準は大腸癌取扱い規約第 7 版に従った。

Ⅰ. 対象および方法

1. 対 象
2005 年 6 月〜2007 年 8 月までに切除不能肝転移を有する大腸癌症例に対し, 当科にて原発巣切除後 first-line

Table 1 Subjects

Gender	
Male/female	8/5
Age	63 (29〜77)
Performance status	
0/1/2/3/4	11/2/0/0
Tumor location	
Colon/rectum	7/6
Number of liver metastases	8 (3〜22)
Diameter of liver metastases (cm)	4.6 (1.5〜14.5)
Extra hepatic metastases	
yes/no	3/10
P/CY	2/1
GOT (IU/L)	104 (31〜228)
GPT (IU/L)	110 (32〜208)
γ-GTP (IU/L)	252 (85〜631)
T-Bill (mg/mL)	0.8 (0.3〜1.3)
LDH (IU/L)	1,099 (322〜1,418)
ALP (IU/L)	1,011 (644〜2,384)
CEA (ng/mL)	362.1 (65.6〜3,832)
CA19-9 (U/mL)	451.3 (46.9〜73,816)

にて FOLFOX 療法を施行した進行大腸癌症例 65 例中, 高度の肝機能障害を有する多発肝転移にて術後, 全身状態の悪化が考えられた 13 例を対象とした。13 例の臨床病理学的特徴を Table 1 に示す。肝外病変を有する症例は 3 例 (術中所見にて腹膜播種 2 例, 肝門部リンパ節腫脹 1 例) に認めた。術前 ALP 値の中央値は 1,011 (644〜2,384) と高値であった。

2. 方 法
術前に放射線科医師により IVR にて胃十二指腸動脈と右胃動脈の血流改変術を施行し, 同時期に右大腿動脈から肝動脈内にカテーテルを留置し, ポートを皮下に埋め込んだ。術中に外科医師により鎖骨下静脈より中心静脈ポートの留置を施行した。投与方法は FOLFOX4 または 6 m のレジメンと同様に施行したが, 5-FU のみ肝動注ポートより注入し, LV と L-OHP を中心静脈ポートより注入した。約 2 週間ごとに PD または全身状態悪化, 有害事象にて中止となるまで施行した。

Ⅱ. 結 果 (Table 2, 3)

1. 投 与 状 況
肝動注併用 FOLFOX 療法の施行回数は中央値で 14 (6〜22) 回あった。4 例が治療継続中であり, 中止の理由は 1 例が肝臓切除により, 3 例が PD により, 1 例が肝動脈閉塞により, 4 例が有害事象などであった。

Table 2 Response rate and prognosis

Response	Liver	Overall
Complete response, No	0	0
Partial responses, No	11	9
Stable disease, No	1	1
Progressive diseases, No	1	4
Response		
No.	11	8
%	84.6	61.5
Death		
No (days after chemotherapy)		1 (265 days)
Courses of chemotherapy		14 (6〜22)

Table 3 Adverse events

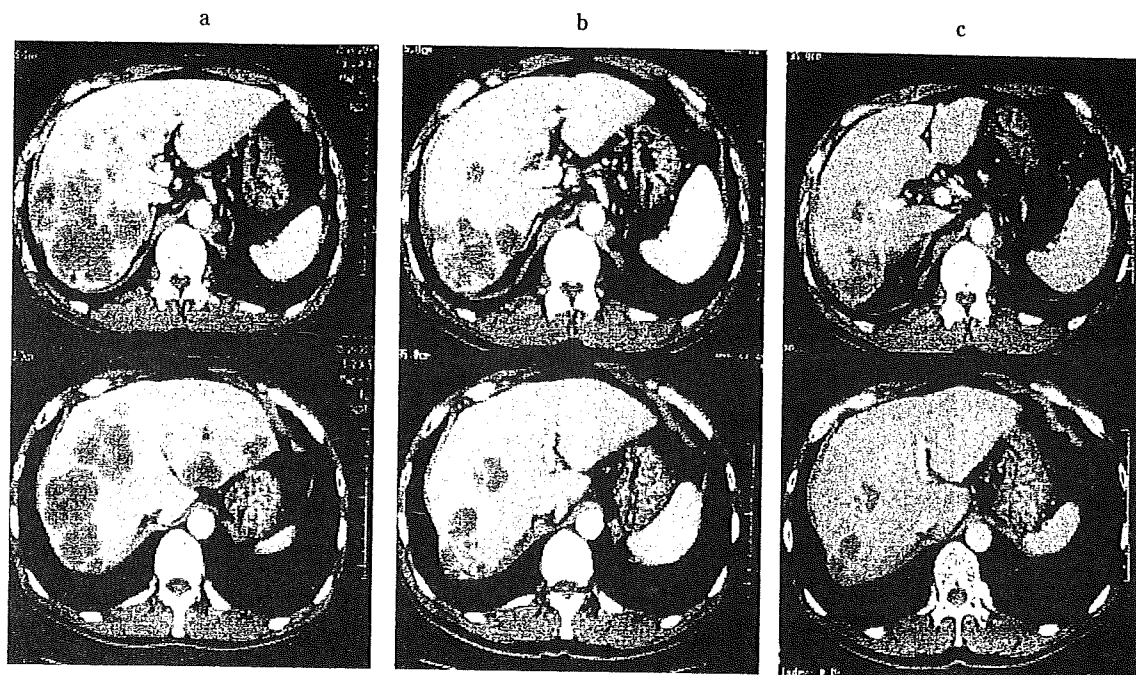| Adverse events	grade			2〜3 No. (%)
	1	2	3	
Neutropenia	1	1	1	2 (15.3)
Hb	1	0	0	0 (0)
Platelet	1	0	0	0 (0)
Anorexia	1	0	1	1 (7.7)
Nausea	1	1	0	1 (7.7)
Diarrhea	1	0	0	0 (0)
Paresthesias	7	2	0	2 (15.3)
Allergy	0	0	0	0 (0)

Fig. 1　Case 1
a: Before surgery and chemotherapy.
b: After 6 courses of combined hepatic arterial infusion therapy and FOLFOX6m.
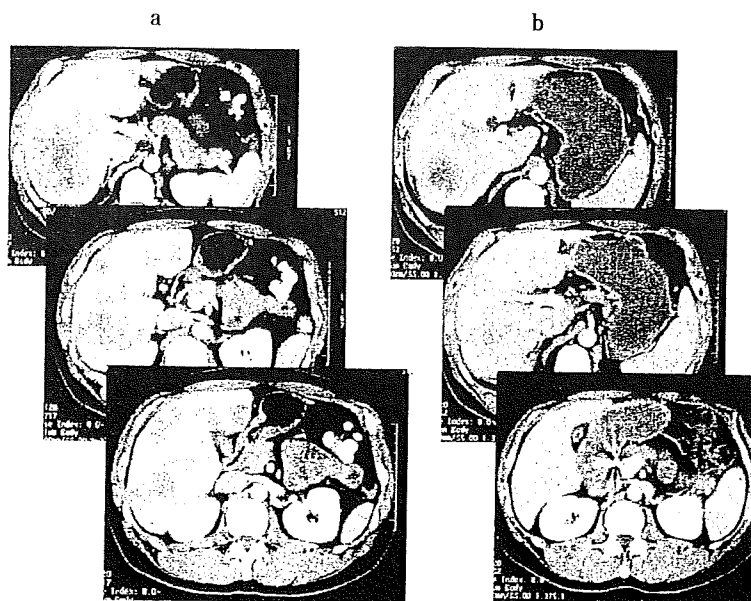c: After 16 courses of therapy. Reduction rate: 61%.

Fig. 2　Case 2
a: Before surgery and chemotherapy.
b: After 17 courses of combined hepatic arterial infusion therapy and
　FOLFOX6m. Reduction rate: 72%.

2．抗腫瘍効果

　肝臓病変における抗腫瘍効果は CR を認めないものの約 85％と高率であり，Fig. 1〜4 に著効例を示すが，Fig. 4 は著効後に切除可能例となり，Fig. 2 は今後切除予定である。臨床的奏効率は 61.5％であり，肝病巣の悪化と他病巣の出現により 4 例に PD を認めたが比較的肝外病変のコントロールも良好であった。

3．予後と後治療について

　死亡例は 1 例のみで投与後 265 日であった。投与後観察期間が中央値で 495（248〜928）日と短いこともあるが，2 年以上生存例は 2 例，1 年以上生存例は 5 例と予後は比較的良好であった。2 次治療として 8 例に FOLFIRI 療法を，切除可能例は切除後 S-1 内服を施行している。
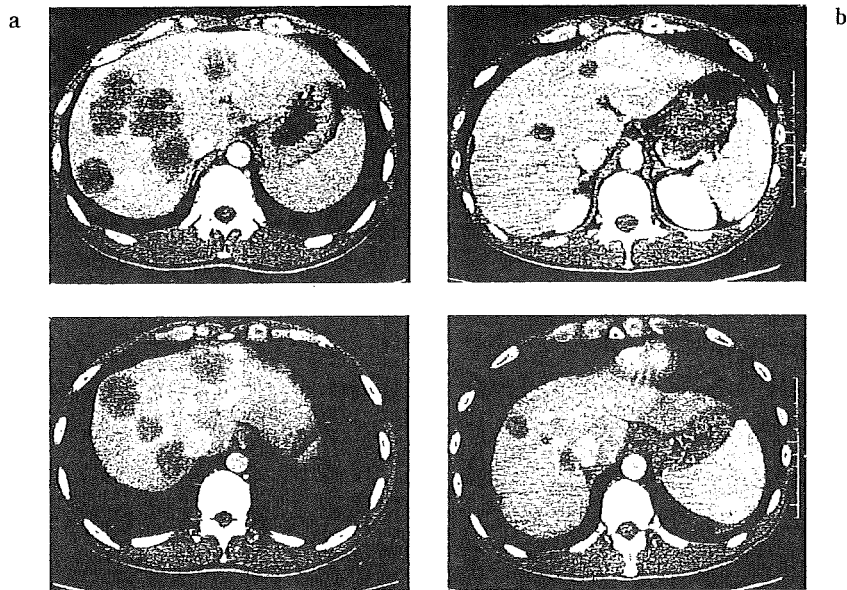
Fig. 3　Case 3
a: Before surgery and chemotherapy.
b: After 9 courses of combined hepatic arterial infusion therapy and
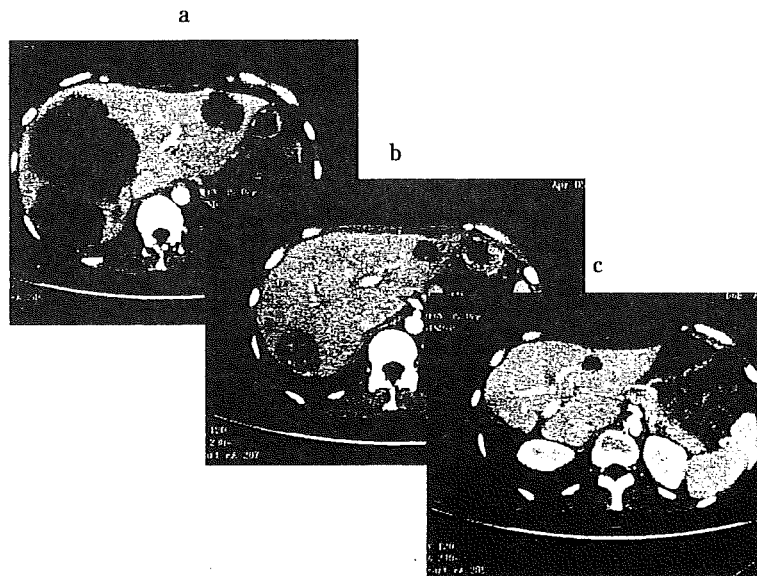　 FOLFOX6m. Reduction rate: 68%.

Fig. 4　Case 4
a: Before chemotherapy. Multiple metastatic lesions were observed in
　 both liver lobes.
b: After 9 courses of combined hepatic arterial infusion therapy and
　 FOLFOX4. A marked tumor reduction (56%) was observed and
　 tumor was resected.
c: After 3 courses of FOLFIRI therapy. A 20% tumor reduction was
　 noted and rest tumor was resected.

4. 有害事象

　grade 3 以上の有害事象例は好中球減少例 1 例と ano-
rexia 1 例であり，grade 2 は重複を含むものの nausea
など 2 例と L-OHP に特有の末梢神経障害 2 例であっ
た。重篤なアレルギーなどは認めなかった。

Ⅲ. 考　察

　肝転移例に対する治療法は切除療法が良好であると報
告されているが[10]，Ballantyne らは単発あるいは少数個
（3 個）転移までが積極的切除の適応と述べている。これ
らの適応に含まれる症例は大腸癌全体の 5% であり，肝
切除による生存率の向上は 1～2% と述べられている[11]。

そのため，生存率を改善させるためには適応外の症例の生存率を改善することが全体の生存率を向上させると思われる。

　海外では切除不能，あるいは肝外病変を伴う大腸癌遠隔転移例に対し，積極的に奏効率の高い FOLFOX を neoadjuvant chemotherapy として用い，切除率を向上させている[9,12]。大腸癌肝転移切除不能例に対する術前化学療法の意義は転移病巣の縮小により手術が可能になることであり，術前化学療法の奏効率と切除率は相関すると述べられている[13]。また Adams らは，術前化学療法後に切除可能となった症例の 5 年生存率は，診断時に切除可能であった症例の切除成績と同等であると述べている[14]。

　本邦では 1990 年代前半には確立されていた肝動注療法は全身化学療法との比較試験において，腫瘍縮小効果において勝るものの生存期間の延長において優位性が示されず，肝外病変の増悪の抑制が弱く，カテーテル留置の手技的困難性より first-line として活用されなくなっていた。しかし，これらの検討では本邦において施行されていた肝動注療法と異なりカテーテル留置が開腹下で施行されており，肝動注群の 37％で治療開始できず，治療開始例の 29％でカテーテルトラブルにて治療継続不可能であり，最終的には 6 コース予定に対し，平均 2 コースの治療しか行われていなかった[8]。

　本邦においては 5-FU を週 1 回 5 時間かけて注入する治療法で奏効率は約 50〜80％，生存期間中央値は 18〜26 か月と良好な成績であった[7,15,16]。ランダム化比較試験は行われていないものの，近年の FOLFOX や FOLFIRI といった全身化学療法と差を認めていなかった。さらに最近の肝動注療法の報告では，山下らは weekly 5-FU＋LV 肝動注療法は肝病変に対する奏効率は 75％で生存期間中央値は 22 か月と報告し[3]，Kemeny らは FUDR の肝動注療法と 5-FU＋LV 全身療法の比較試験において奏効率が 47％と 24％，生存期間中央値が 24.4 か月と 20.0 か月で有意に肝動注療法が勝っていると報告している[17]。

　これらより ALP の高値など高度な肝機能障害を伴う切除不能肝転移を有する大腸癌に対する化学療法として，本邦の放射線科医師による高い技術のもとカテーテル留置を施行し，肝転移に対する腫瘍縮小効果の高い肝動注療法と，肝外病変の制御のため全身療法を併用することで予後の改善が得られると考えられるため，今回われわれは切除不能な大腸癌高度肝転移症例に対し 5-FU のみ肝動注ポートより注入し，LV と L-OHP を中心静脈ポートより注入する治療法を 13 例に施行した。L-OHP が本邦において承認されてから期間がまだ短いた

め，観察期間の中央値が約 500 日と短いものの，肝病変に対する奏効率は約 85％と高率であり，1 例に切除可能で，さらに 1 例に切除予定であった。肝外病変も含めても約 62％の奏効率と良好であり，比較的肝外病変のコントロールもされていると考えられた。また，13 例全例に留置可能で 1 例のみにカテーテル閉塞を認めたのみであった。肝動注併用 FOLFOX 療法の施行回数は中央値で 14（6〜22）回であったが，grade 3 以上の有害事象は好中球減少症と anorexia の 2 例のみで，grade 2 は重複を含むものの 4 例であり，肝動注療法に特異的な胆嚢炎や胃十二指腸潰瘍などは認めず，比較的安全に施行されていた。L-OHP に特異的な重度の末梢神経障害や，アレルギーも認めていなかった。予後においては，観察期間が短いものの後治療として FOLFIRI や S-1 の内服が施行されているが，死亡例は 265 日目の 1 例を認めたのみであった。

　欧米において，Ducreux らは薬剤分布が適当であっても腹痛を引き起こしたものの，L-OHP を肝動注に用い，5-FU＋LV を全身化学療法とし，奏効率 64％，MST 約 27 か月と報告し[18]，Kemeny らは FUDR の肝動注と，irinotecan，L-OHP の全身療法により奏効率 90％，MST 約 36 か月と報告している[19]。成績の向上は後治療の分子標的治療薬なども考慮しなければならないものの，肝動注化学療法と全身化学療法とを併用することで，現在最も施行されている標準的全身化学療法の FOLFOX，FOLFIRI 療法の MST 約 20 か月よりも優れた成績を示す可能性が考えられるため，今後はこれらを対照としたランダム化試験も必要と思われる。

　今回われわれは，肝機能障害を有する切除不能多発肝転移症例に対し，肝転移に関する局所治療としての肝動注療法と，肝外病変のコントロールとして全身化学療法を併用とした FOLFOX 療法を 13 例に施行した。観察期間が短く今後の長期的観察が必要であるが，奏効率や肝外病変に対するコントロールは比較的良好であり，安全に施行されていた。以前までは切除不能肝転移症例に対し延命を目的とした化学療法が主であったが，最近ではわれわれが経験した症例のように高度な肝機能障害を有する症例に対しても奏効率の高い肝動注療法と全身化学療法を併用することで根治切除が可能となり，治療法の一つの選択肢となる可能性が示唆された。今後は肝切除し得た症例の術後の補助化学療法も含め，集学的治療を施行することで切除不能肝転移症例の生存率の向上を図ることが重要と思われる。

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Risk Factors of Surgical Site Infection After Hepatectomy for Liver Cancers

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Abstract

Background Risk factors of surgical site infection (SSI) after hepatectomy under the guideline of Centers for Disease Control and Prevention (CDC) are not well examined.
Methods Hospital records of consecutive patients who underwent hepatectomy without biliary reconstruction for liver cancers were reviewed retrospectively. Prophylactic antibiotics were given to patients just before skin incision and every 3 hours during the operations. Clinicopathological factors were compared between patients who developed SSI and those without it.
Results There were 405 patients identified, and the incidence of SSI was 23 cases (5.8%). In multivariate analysis, intraoperative bowel injury, blood loss >2000 ml, and age older than 65 years were significant risk factors of SSI after hepatectomy.
Conclusions Prophylactic antibiotics were necessary only during the operation for most patients who underwent hepatectomy without biliary reconstruction. However, patients with intraoperative bowel injury, blood loss >2000 ml, and age older than 65 years are at risk to develop SSI and might need additional administration of prophylactic antibiotics after surgery.

Introduction

Use of antibiotics is one of the main techniques to prevent surgical site infection (SSI) after surgery. There has been tremendous accumulation of evidence during the last three decades with regard to the optimal methods of its administration [1]. The Centers for Disease Control and Prevention (CDC) recommended in its 1999 guideline to maintain therapeutic levels of prophylactic antibiotic during the operation and, at most, a few hours after closure of incisions [2]. However, it is well known that incidence of SSI is greatly influenced by patients' underlying general status and perioperative factors [3]. Disease and procedure-specific risks and use of prophylactic antibiotics are not well examined, except for colorectal surgery [4, 5], open heart surgery [6], cholecystectomy [7, 8], etc.

It is suggested that hepatectomy suppresses Kupffer cell and T-cell function significantly, which renders patients immunosuppressive [9]. Postoperative infection, including SSI, deteriorates hepatic failure in cases with limited hepatic functional reserve. There is a wide variety in operation time, blood loss, transfusion requirement, etc., depending on the extent of parenchymal resection. Underlying cirrhosis and hypoalbuminemia inhibits normal wound healing [10]. However, perioperative factors that should be considered a significant risk to develop SSI after hepatectomy have not been clear. The purpose of this study was to analyze the risk factors of SSI after hepatectomy with prophylactic antibiotics under CDC guideline and to clarify who might benefit from additional administration of prophylactic antibiotics after operation.

Materials and methods

Patients who underwent hepatectomy for liver cancers from November 2002 to December 2006 at National Cancer Center East Hospital, Kashiwa, Japan, were identified and reviewed retrospectively. Patients who

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underwent hepatectomy without biliary reconstruction regardless of diagnosis were included in the study. Patients who underwent cholecystectomy along with hepatectomy were included in the study, but those who underwent simultaneous procedures, such as colorectal resection or stoma closure, were excluded from the study.

The extent of hepatectomy was evaluated according to the disease progression, liver function, and general condition of patients [11]. Tumor progression and resectability was assessed by imaging studies, such as contrast enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), hepatic arterial angiography, ultrasound, and chest x-ray. Liver function was assessed by liver biochemistry test, Child-Pugh grade [12], and the indocyanine green retention rate at 15 minutes [13]. All patients were reviewed before surgery at weekly conferences by hepatic surgeons, medical oncologists, and interventional radiologists to discuss whether the planned procedures were appropriate. Hepatic resection was performed under intraoperative ultrasonographic guidance by the pean fracture method with or without inflow occlusion (Pringle's maneuver). Anatomic hepatectomy was performed whenever possible, whereas partial resection was performed in consideration of limited liver functional reserve or anatomic location of the tumor. During parenchymal resection, all blood vessels and bile ducts were ligated whenever possible with 2-0 or 3-0 braided silk or vessel clip. One or two closed drains were inserted at the end of operation in the right subphrenic space or wherever close to the resected liver parenchyma. Drains were removed when no rebleeding or bile leakage was observed on postoperative day (POD) 3 or 4.

SSI was defined as a condition in which purulent discharge was observed from any incision or space that was manipulated during an operation within 30 days after the operation with or without microbiological evidence as in the guideline issued by CDC [2], and it was identified retrospectively by reviewing clinical records of patients who underwent hepatectomy. Remote site infection was defined as a condition in which fever and leukocytosis were present with bacteria in sputum, urine, catheter-tip, blood, or other body fluid/space, or according to the physician's judgment regardless of microbiological evidence.

Patients were usually given two doses of cefazolin as prophylactic antibiotics. One gram of cefazolin was administered to patients within 30 minutes before skin incision and another dose 3 hours later. When the operation lasted more than 3 hours, additional doses were given every 3 hours thereafter during the operation. No antibiotics were given after incisions were closed if patients had already received two doses of cefazolin.

All data were compiled in a database for analysis (Microsoft Excel and SPSS 11.0 J for Windows).

Differences between numerical variables were tested with Mann-Whitney U test and those between categorical variables were tested with χ^2 statistics. Multivariate analysis was performed with logistic regression test. $p < 0.05$ was deemed significant.

Results

During the period of study, 405 patients underwent hepatectomy without biliary reconstruction for primary or secondary liver cancers at National Cancer Center East Hospital, Kashiwa, Japan. Of these 405 patients, 23 patients (5.8%) developed SSI (incisional, 20; organ/space, 3). Incisional SSIs were treated by opening incisions and organ/space SSIs were treated by drainage under ultrasound guidance. The patient characteristics and demographic variables are listed in Table 1. No differences in these basic characteristics, except age, were observed between patients with SSI and those without it. Mean age of patients with SSI was 68.2 years and was statistically older than those without SSI. A cutoff value of aged 65 years had the highest statistical power ($p = 0.016$). Patients' ASA score, comorbidities, and underlying liver pathology were statistically similar between the two groups.

Culture results of infecting organisms included *Bacteroides faragilis* (n = 3), *Staphylococcus aureus* (n = 2), *Klebsiera oxytoca* (n = 1), *Serratia marcescens* (n = 1), *Escherichia coli* (n = 1), *Streptoccoccus anginosus* (n = 1), *Streptococcus constellatus* (n = 1), *Enterobacter cloacae* (n = 1), *Citrobacter braakii* (n = 1), *Citrobacter freundii* (n = 1), Corynebacterium species (n = 1), and Candida species (n = 1).

The perioperative variables are listed in Table 2. Operation time, red blood cell (RBC) transfusion requirement, RBC transfusion volume, and intraoperative bowel injury were statistically different between the two groups. Blood loss did not reach statistical significance, but cutoff value of 2000 ml had the significant power to predict SSI ($p = 0.003$). Multivariate analysis of those variables found that intraoperative bowel injury, blood loss >2000 ml, and age older than 65 years were the significant risk factors to develop SSI after hepatectomy without biliary reconstruction (Table 3). Rates of SSI increased dramatically with the number of risk factors present (Fig. 1). Patients with two or more risk factors were statistically more likely to develop SSI than those with none or only one risk factor.

During the same period, three patients died within 30 days from the operations. One patient died from pulmonary embolism on POD 3, another died from brain stroke on POD 3, and the other died from esophageal varix rupture on POD 9. Incidence of remote site infection was

Table 1 Patient characteristics and demographic variables for patients with SSI compared with those without it

	SSI (−) (N = 382)	SSI (+) (N = 23)	P value
Age (yr)[a]	63.7 ± 0.5	68.2 ± 2	0.034
≥65[b]	194 (50.9)	18 (78.3)	0.016
<65	188 (49.1)	5 (21.7)	
Gender[b]			0.809
Male	285 (74.6)	18 (78.3)	
Female	97 (25.4)	5 (21.7)	
Body mass index (kg/m^2)[a]	23.8 ± 0.6	23.6 ± 0.7	0.583
Diabetes mellitus[b]	75 (19.6)	1 (4.5)	0.095
ASA score[b]			0.488
1	111 (29.5)	7 (30.4)	
2	243 (64.6)	16 (69.6)	
3	22 (5.9)		
Diagnosis[b]			0.566
HCC	239 (62.6)	13 (56.5)	
Metastases	126 (33)	8 (34.8)	
Others	16 (4.5)	2 (8.7)	
Viral hepatitis serology[b]			0.858
HBV	51 (14)	3 (13)	
HCV	141 (38.7)	8 (34.8)	
HBV and HCV	7 (1.9)		
Liver parenchyma[b]			0.758
Chronic hepatitis	105 (29.6)	9 (39.1)	
Liver cirrhosis	93 (26.2)	5 (21.7)	
Child class[b]			0.634
A	355 (94.4)	21 (91.3)	
B	21 (5.6)	2 (8.7)	
ICG15R[a]	14.6 ± 0.4	15.5 ± 1.6	0.571

[a] Mann-Whitney U test

[b] χ^2 test

Data are numbers with percentages in parentheses or means ± standard error of the mean

ASA American society of anesthesiology, *HCC* hepatocellular carcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG15R* indocyanin green 15 min retention rate

11 (2.5%) (pneumonia (n = 6), urinary tract infection (n = 1), catheter infection (n = 1), epididymitis (n = 1), unknown origin (n = 2)). Other morbidities included bile leak (n = 9), retractable ascites (n = 6), ileus (n = 4), transient renal insufficiency (n = 4), rebleeding (n = 3), pleural effusion (n = 3), skin rash (n = 2), poor oral intake (n = 2), delirium (n = 1), transient heart failure (n = 1), pulmonary embolism (n = 1), upper gastrointestinal bleeding (n = 1), wound dehiscence (n = 1). There were four reoperations for three rebleedings and one wound dehiscence.

Discussion

Our study clearly demonstrated the risk factors of SSI after hepatectomy with prophylactic antibiotics under the CDC guideline. Intraoperative bowel injury, blood loss >2000 ml, and age older than 65 years were the significant risk factors. Although both alimentary tract surgery and hepatobiliary surgery are classified as clean-contaminated

[14], biliary tract without calculus is normally sterile contrary to the alimentary tract, which has high bacterial densities [15, 16]. Intraoperative bowel injury is suspected to contaminate surgical field of hepatectomy without biliary reconstruction and to increase the risk of SSI. Blood loss reduces the concentration of antibiotics and is found to be a risk factor of SSI [17, 18]; 1500 ml to 2000 ml of blood loss is the suggested threshold to administer additional doses of cefazolin to maintain a concentration higher than the minimum inhibitory concentration for the common infecting organisms [19, 20]. Our threshold of 2000 ml of blood loss is compatible with previous findings. Elderly patients also are reported to be susceptible to SSI [18, 21]. Because aging involves complex physiologic changes, it is difficult to clarify a definitive mechanism of the vulnerability of elderly patients. Reduction in immune function is one suggested mechanism [10].

Rates of SSI increased dramatically with the number of the three risk factors present (Fig. 1). According to the National Nosocomical Infections Surveillance (NNIS) report, rates of SSI after hepatopancreaticobiliary complex

Table 2 Perioperative variables for patients with SSI compared with those without it

	SSI (−) (N = 382)	SSI (+) (N = 23)	P value
Operation time (min)[a]	210 ± 19	269 ± 23	*0.021*
≥300[b]	68 (17.8)	9 (39.1)	*0.017*
<300	313 (82.2)	14 (60.9)	
Pringle time (min)[a]	63.3 ± 2.1	75.9 ± 9.7	0.259
None[b]	26 (7.3)	0 (0)	0.23
>0	331 (92.7)	20 (100)	
Repeat resection[b]	110 (28.8)	4 (17.4)	0.338
Blood loss (ml)[a]	1070 ± 69	1928 ± 470	0.068
≥2000[b]	50 (13.2)	9 (39.1)	*0.003*
<2000	332 (86.8)	14 (60.9)	
RBC transfusion (ml)[a]	177 ± 29	537 ± 192	*0.003*
None[b]	297 (78.2)	12 (52.2)	*0.009*
>0	83 (21.8)	11 (47.8)	
Intraoperative bowel injury[b]	3 (0.8)	4 (17.4)	*<0.001*
Bile leak[b]	7 (1.8)	2 (22.2)	0.087
Resected segments (Couinaud)[b]			0.96
<2	285 (74.8)	16 (69.6)	
2–3	42 (11)	3 (13)	
≥4	54 (14.2)	4 (17.4)	
Resected weight (g)[a]	221 ± 19	269 ± 77	0.281
Largest tumor size (cm)[a]	3.8 ± 0.2	3.7 ± 0.4	0.253
NNIS index[b]			0.184
0	293 (76.9)	14 (60.9)	
1	86 (22.6)	9 (39.1)	
2	2 (0.5)		
Postoperative length of stay[a]	10.2 ± 0.2	23.7 ± 5.7	*<0.001*

[a] Mann-Whitney *U* test

[b] χ^2 test

Data are numbers with percentages in parentheses or means ± standard error of the mean

RBC red blood cell, *NNIS* national nosocomical infection surveillance

Table 3 Multivariate analysis of SSI risk factors

	P value	Odds ratio (95% confidence intervals)
Age ≥65 yr	*0.027*	3.4 (1.15–10.05)
Blood loss ≥2000 ml	*0.004*	4.4 (1.63–11.91)
Intraoperative bowel injury	*<0.001*	20.08 (4–100.8)
RBC transfusion	0.62	1.51 (0.31–7.42)
Operation time >300 min	0.67	1.35 (0.34–5.32)

SSI risk factors identified by univariate analysis were compared by multivariate analysis (logistic regression test)

The number of risk factors present
(incidence of SSI)

Fig. 1 Rates of SSI increased with the number of risk factors present. Rates of SSI were not statistically different between patients with one risk factor and those without any factors. However, patients with two or more risk factors developed SSI at a significantly higher rate than those with none or only one risk factor

surgery range from 3.24–7.04% [22]. Other reported rates of SSI after hepatectomy range from 4.6–25.2% [23, 24]. Compared with those previously reported rates, the rates of SSI for patients with none or only one risk factor, 1.9% and 4.3% respectively, are considered allowable. Prophylactic antibiotics for hepatectomy without biliary reconstruction are necessary only during operations for patients with none or only one risk factor. However, patients with two or more risk factors developed SSI at statistically higher rates. Fujita et al. [4] reported that two additional doses of
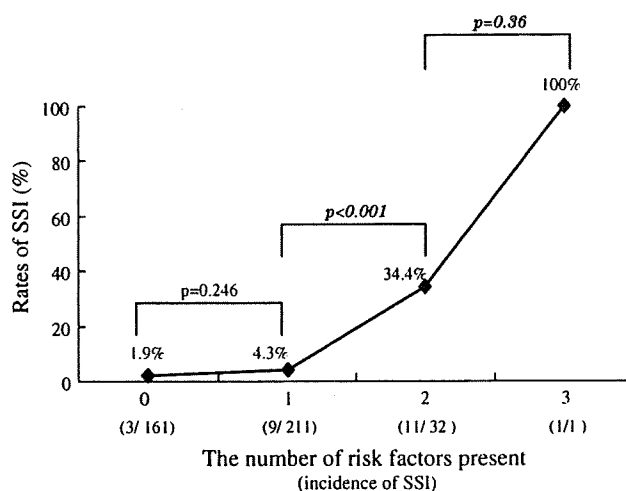
postoperative antibiotics reduced the incidence of incisional SSI from 14.2% to 4.3% compared with single-dose preoperative administration in elective colorectal surgery

[4]. Additional administration of postoperative antibiotics maintains therapeutic levels for longer hours and reduces the incidence of SSI more effectively for patients at higher risk. Although there have been no published data concerning the effectiveness of postoperative administration of antibiotics in hepatectomy, Fig. 1 illustrates that patients with two or more risk factors may receive some additional doses of postoperative antibiotics as in colorectal surgery. Appropriate doses of additional antibiotics are matters to be discussed.

There were five infecting organisms that were resistant to cefazolin: Bacteroides fragilis, Enterobacter, cloacae, Serratia marcescens, Corynebacterium species, and Citrobacter species. Because some patients lack microbiologic data, a definitive conclusion about the optimum choice of prophylactic antibiotics was not possible. However, it is evident that cefazolin alone was effective for most patients who underwent hepatectomy without biliary reconstruction. Two of the seven patients with intraoperative bowel injury developed SSI with Bacteroides fragilis. Because likely pathogens in alimentary tract surgery are gram-negative bacilli and anaerobes [2], postoperative antibiotics with anaerobic coverage might be more effective for patients with intraoperative bowel injury.

Postoperative infections, especially organ/space SSI, sometimes deteriorate hepatic function and may cause mortalities. We experienced 23 SSIs and 11 remote site infections, but none of the patients died from those infections. We speculate that our strict evaluation of extent of hepatectomy using CT volumetry and liver function test precluded some excessive hepatic resection and saved postoperative hepatic function. Postoperative infection is more likely to occur in patients with hepatic dysfunction [25]. Our relatively low rate of major hepatectomy in consideration of hepatic functional reserve might be related to the fewer incidence of SSI.

RBC transfusion requirement and operation time were significant risk factors of SSI in univariate analysis, but not in multivariate analysis. Transfusion has immunosuppressive effects on postoperative patients via reductions in natural killer cell number and cytotoxic T-cell function [26, 27] and is reported to be a risk factor of SSI in colorectal surgery [28, 29]. However, controversy exists concerning the causal relationship between transfusion and SSI [30], and a recent meta-analysis denies the association between transfusion and postoperative infection [31]. Our result is consistent with the meta-analysis. Operation time is another reported risk factor of SSI [18]. Cefazolin exhibits time-dependent decrease in serum and tissue concentration, and additional administrations are recommended every 3 or 4 hours during operation to maintain therapeutic levels of cefazolin [2]. Because all of our patients received a second dose of cefazolin at 3 hours

from incision, serum and tissue concentration of cefazolin was expected to exceed therapeutic levels during the whole time of operations for most patients. Influence of operation time on the incidence of SSI was suspected to be minimized with additional dose of cefazolin at 3 hours from incision.

Abdominal drainage after elective hepatectomy is controversial. Some randomized, controlled trials (RCTs) reported increased incidence of SSI and other morbidities associated with abdominal drainage and denied the routine placement of drainage catheters [32, 33]. However, the routine drainage group in those RCTs had drainage catheters placed for at least 5 to 9 days, which was unnecessarily long. We almost routinely placed drainage catheters but removed them on POD 3/4 or earlier if postoperative bleeding and bile leakage were denied. Early removal of prophylactic drains prevents intra-abdominal infections [34]. We do not consider that abdominal drainage causes more infections if drains are removed on POD 3/4 or earlier.

Our study has several limitations. First, SSI was detected indirectly by retrospectively reviewing patient records and laboratory data. It has been suggested to be a less accurate method than prospective direct observation of surgical sites [2]. Some SSI might be possibly undetected because of inappropriate patient records. However, indirect case-finding by reviewing daily records and laboratory data is the most widespread method of surveillance in the medical literature. Its reported sensitivity is as high as 83.8–92.3% compared with prospective direct finding of SSI [35]. Since then, we do not consider that our surveillance method precludes the importance of our findings. Second, it is a single-center study. Our department is one of the highest volume centers in Japan and performs 250 hepatopancreaticobiliary cancer surgeries in a year. Also, we do not perform operations on patients with end-stage renal disease on dialysis due to inadequacies of dialysis facilities. Our relatively low rate of SSI incidence may be attributable to the high volume of cases and to the patient selection.

Conclusions

Our study demonstrated that prophylactic antibiotics were necessary only during operations and, at most, a few hours after closure of incisions in most of the patients who underwent hepatectomy without biliary reconstruction. However, patients with intraoperative bowel injury, blood loss >2000 ml, and age older than 65 years were at risk for developing SSI. Patients with two or more risk factors may receive additional doses of postoperative antibiotics to prevent SSI more effectively.

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Safe and feasible inflow occlusion in laparoscopic liver resection

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Abstract

Background A major challenge in laparoscopic liver resection to avoid massive hemorrhage from the transection plane.

Methods This study investigated 32 consecutive patients who underwent laparoscopic or laparoscopically assisted hepatic resection and had the hepatoduodenal ligament encircled by vessel tape using an Endo Retract Maxi as a tourniquet for complete interruption of blood inflow to the liver.

Results Laparoscopic encircling of the hepatoduodenal ligament was performed in a few minutes without any complications for any of the 32 patients.

Conclusions Laparoscopic Pringle's maneuver using an Endo Retract Maxi can be performed easily for all patients undergoing laparoscopic liver resection.

Keywords Hepatectomy · Laparoscopy ·
Pringle's maneuver

Minimally invasive surgery has become widely accepted as a superior alternative to conventional open surgery in many gastrointestinal fields. Moreover, recent rapid developments in technological innovations, improved surgical techniques, and accumulation of extensive experience by surgeons have improved the feasibility and safety of laparoscopic liver surgery [1–4]. However, laparoscopy for liver resection remains a highly specialized field because laparoscopic liver surgery presents severe technical difficulties, such as control of hemorrhage from the transection plane.

Laparoscopy for major liver resection remains uncommon, partly because of the potential for massive hemorrhage. In particular, hepatocellular carcinoma usually occurs from a cirrhotic liver, which often causes bleeding problems. In addition, massive intraoperative blood loss is a good predictor of postoperative morbidity and mortality for patients who undergo liver resection for hepatic malignancies [5, 6]. Intraoperative inflow occlusion of the liver has thus been recommended to reduce blood loss during liver resection [7, 8].

Although various techniques of hepatic vascular control have been presented, Pringle's maneuver, the oldest and simplest, still is favored by many surgeons. However, laparoscopic encircling of the hepatoduodenal ligament can prove difficult because the field of view is narrow and the surgeon's blind spot may lead to unexpected bleeding or injury under laparoscopy.

In this report we describe a new technique whereby any surgeon with minimal or no laparoscopic experience can easily and safely perform Pringle's maneuver during laparoscopic liver resection.

Surgical procedure

The patient is placed in supine position with legs apart. The surgeon stands between the legs. A 12-mm trocar is placed 1 cm below the umbilicus, through which carbon dioxide gas is delivered. Pneumoperitoneum is controlled electronically to a pressure of 10 mmHg. Additional working ports are placed to optimize manipulation and mobilization

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