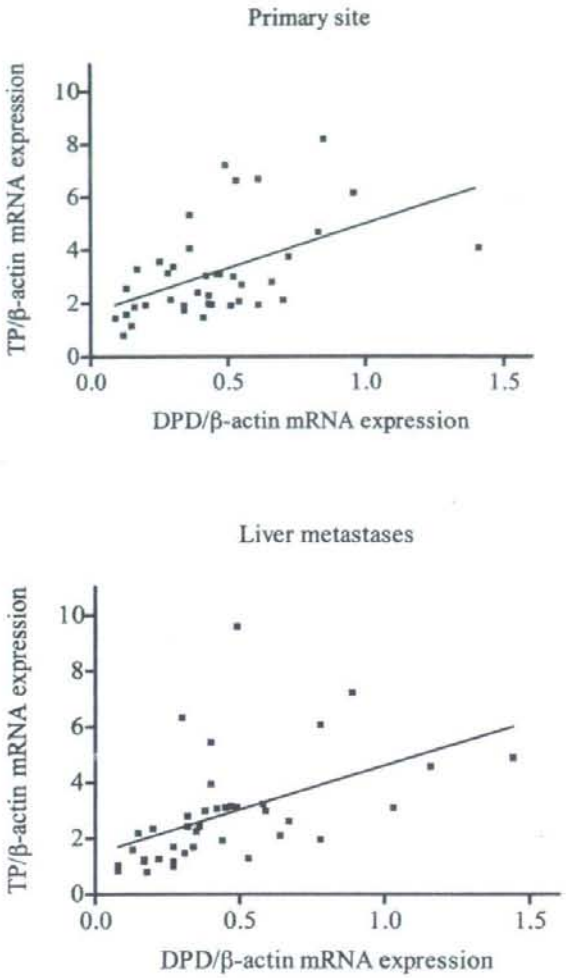

Figure 2. *Relationship between DPD and TP expression ratios to β-actin in primary sites (r=0.54, p=0.0004) and liver metastases (r=0.68, p<0.0001) of colorectal carcinomas.*

results were controversial. Inokuchi *et al.* reported that the DPD, OPRT and TP mRNA levels were significantly higher in liver metastases than in primary tumors and that TS mRNA levels did not differ significantly (18), however, they did not use the LCM method to purify tissue. DPD, TP and OPRT were reported to show higher expression levels in normal liver tissue than in the liver metastases (19). The contamination of normal liver tissue with metastatic liver tissue may have affected their results. Kuramochi *et al.* reported no significant differences between median mRNA expression levels of TS, DPD, TP and OPRT in primary carcinoma and those in corresponding liver metastases (19). Their TP expression levels were lower in the metastatic liver site than in the primary sites, but not significantly.

We also demonstrated that the mRNA expression levels of TS, DPD, TP and OPRT in liver metastases were significantly correlated to those in primary sites of CRCs. Kuramochi *et al.*, using the LCM method, reported a significant correlation for TS mRNA expression between primary carcinomas and corresponding liver metastases and no correlation for DPD, TP or OPRT (19). Their method was similar to ours. These different results may be due to the sample condition or sample size.

Among the four genes that were studied, a significant correlation was observed between DPD and TP both in the primary sites and the liver metastases. Inokuchi *et al.* and Kuramochi *et al.* reported similar results (18, 19). Mori *et al.* reported a positive correlation between DPD and TP protein levels in colorectal, pancreatic, esophageal, bladder, cervical, hepatic and gastric carcinomas (20). It was reported that DPD and TP gene expression in CRCs were associated with tumor progression (21, 22). A high level of TP gene expression is reported to be associated with non-responsiveness to 5FU (11). TP is supposed to play as an important role in tumor progression and 5FU sensitivity as TS or DPD.

The expression of 5FU-related enzymes has been used to predict the therapeutic efficacy and survival of 5FU-treated patients. It has been reported that the clinical response and survival rates in response to 5FU-based chemotherapy for patients with CRC are related to the expression of TS, DPD and TP (9, 23). We also reported that the expression levels of DPD and TP mRNAs in primary CRCs was significantly predictive of the therapeutic response to hepatic arterial infusion of 5FU (24). The expression of these enzymes is important for guiding the rational selection of chemotherapeutic regimens. Physicians should consider using a regimen that includes irinotecan (CPT-11) for patients who show a high expression of TS, DPD and TP in their carcinomas. In this study, we showed the positive correlation of gene expression of TS, DPD, TP and OPRT between primary carcinomas and liver metastases. Analysis of primary carcinomas can be used to predict the gene expression level in the liver metastases. Our results confirm the idea that the levels of gene expression in primary carcinomas can be used for directing the strategies of the chemotherapy against metastases. We have not examined the gene expressions in extrahepatic metastases such as lung metastases. Further studies are required for metastases from other organs.

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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)

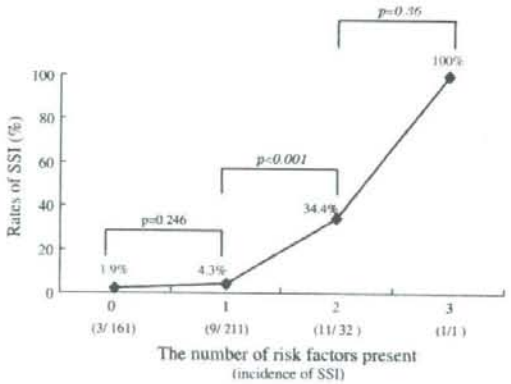

Fig. 1 Rates of SSI increased with the number of risk factors present. Rates of SSI were not statistically different between patients with one risk factor and those without any factors. However, patients with two or more risk factors developed SSI at a significantly higher rate than those with none or 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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特集　国外大規模臨床試験の意義と国内がん診療へのインパクト

切除可能大腸がん肝転移例に対する外科切除＋周術期FOLFOX4療法 vs. 外科切除単独の第 III 相試験*

高橋進一郎**

Key Words : hepatic metastasis, liver metastasis, colorectal cancer, adjuvant chemotherapy, neoadjuvant chemotherapy

はじめに

大腸がん治療は化学療法の進歩により大きく変化し予後の改善も著しい．Stage III 症例は切除＋術後補助化学療法が標準治療となり，stage IV 切除不能例の化学療法はオキサリプラチン，イリノテカン，分子標的薬の導入により予後が大幅に改善した．しかし，同じ大腸がんでありながら切除可能肝転移に対する治療は20年前から化学療法の隆盛をみる今日に至るまで切除単独を凌駕する新しい標準治療をみるに至っていない．EORTC40983「切除可能大腸がん肝転移例に対する外科切除＋周術期FOLFOX4療法 vs. 外科切除単独の第 III 相試験」は，切除可能肝転移補助療法で最初の全身化学療法 vs. 切除単独の大規模ランダム化比較試験(RCT)であり，stage II, III 大腸がんに対する補助療法で5FU/LVを上回る成績を示したFOLFOX4[1]を治療群で用いており，注目を集めた．結果は2007年ASCOの年次総会で発表された．ここではEORTC40983の結果，その位置づけ，および国内臨床試験への影響について述べる．

過去に行われたRCT(表 1)

大腸がん肝転移に対する肝切除は 5 年生存率が30～60％に及び長期生存，根治が期待でき

表 1　過去に行われた切除可能大腸がん肝転移に対するRCT

報告者	治療法	症例数	5 年無再発生存率(%)	無再発生存期間中央値(月)	*P* value	5 年生存率(%)	生存期間中央値(月)	*P* value
Lorenz, et al 1998	肝動注(5FU＋FA)	108	−	14.2	ns	−	40.8	0.15
	切除単独	111	−	13.7		−	34.5	
Kemeny, et al 1999	肝動注(FUDR)＋Systemic 5FU/LV	74	40(5y-PFS)	37.4	0.06	61	72.2	0.21
	Systemic 5FU/LV	82	34(5y-PFS)	17.2		49	59.3	
Kemeny, et al 2002 ECOG study	肝動注(FUDR)＋Systemic 5FU	30	46(4y-DFS)	−	0.04	62(4y-OS)	63.7	0.6
	切除単独	45	25(4y-DFS)	−		53(4y-OS)	49.4	
Portier, et al 2006 FFCD ACHBTH AURC 9002 trial	Systemic 5FU/LV	86	34	24.4	0.03	51	62.1	0.13
	切除単独	85	27	17.6		41	46.4	

* Treatment for resectable hepatic metastasis from colorectal cancer ; before and after EORTC Intergroup trial 40983.

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る[2][3]．化学療法が進歩した現在にあっても肝切除を行わなかった場合根治を得る可能性はほとんどない．しかし，切除症例の約3/4に認められる術後再発は大きな問題であり再発減少を目指した補助療法の臨床試験が試みられてきた．

過去に行われた大腸がん肝転移補助療法のRCTを振り返り特徴的なことは，当初，肝動脈注入療法(肝動注，HAI)が中心となって研究が進められていたことである．血行性転移病変の術後に肝動注という局所療法を行う根拠は，大腸がん肝転移術後再発の50%以上が肝再発であるということ[4][5]，切除不能大腸がん肝転移における肝動脈注入療法の抗腫瘍効果が高く[6]当時の標準的な全身化学療法(5FU/LV)と比較し予後も良好ではないかと期待されていたこと，があげられる．肝転移巣は動脈優位の血流支配を受けており[7]，肝動脈からの投与により腫瘍内に高濃度の薬剤を送ることができる．

Lorenzらは6個以下の大腸がん肝転移切除症例において5FU肝動注術後補助療法と切除単独を比較するRCTを行った[8]．肝動注は5FU 1,000mg/m^2×5日間を4週ごとに6コース繰り返すレジメンであったが，肝動注に伴う毒性のため8例の治療関連死を認めたことから登録226例で試験中止となった．226例の解析では，切除単独群の生存期間中央値が補助療法群を上回っているnegative studyであった．

Kemeny MMらは画像上3個以下の大腸がん肝転移例に対しFUDR肝動注＋5FU全身化学療法の術後補助療法と切除単独を比較するRCTを行った[9]．症例登録が伸びず109例の予定登録症例数に達するまでに10年間を要している．4年無再発生存，肝無再発生存では術後補助療法群が有意に良好であったが，全生存率では有意な差は認められなかった．術後補助療法による再発減少の可能性は示したが，症例集積に10年間を要している，術前登録であったためランダム化後に3分の1の症例が不適格，intention-to-treat解析でない，feasibilityが低い(治療完遂率43%)等の理由から切除単独に代わる標準治療を証明するには至らなかった．

Kemeny Nらは，大腸肝転移肉眼的完全切除例に対し全身化学療法(5FU/LV) vs. FUDRによる肝動注＋全身化学療法(5FU/LV)のRCTを行った[10]．当時stage IIIでは切除＋術後5FU/LVが標準治療であり，切除単独群をおいた試験の症例集積が難しいことから，この試験では5FU/LVをcontrol armとしている．HAI＋5FU/LV群で2年生存率，2年無増悪生存率が20%改善すると仮定し，156名を予定登録数としている．結果は，HAI＋5FU/LV群で肝無増悪生存率が有意に向上したが，無増悪生存率(log-rank検定)，全生存でcontrol armと比較し有意な差を認めなかった．

肝動注を用いた試験で明らかになったことは，上述の肝毒性やカテーテルトラブルによりfeasibilityが低く，肝内再発抑制効果と比べ肝外再発抑制効果に乏しいことであった．

一方，全身化学療法を用いた大腸がん肝転移術後補助療法のRCTはEORTC40983以前にはあまり行われていない．Portierらが報告した切除単独vs. 術後5FU/LV(5FU 400mg/m^2/日×5日間，28日毎投与，6サイクル)の多施設によるRCT(FFCD ACHBTH AURC 9002)は登録数173例と比較的規模の大きい試験であった[11]．この試験では全生存では有意差を認めなかったが，プライマリーエンドポイントである無再発生存率が術後補助療法群で有意に良好であった．しかし，症例集積に1991年より10年間かかっているため，試験開始当時最良の治療法であった5FU/LVはその座を発表時(2006年)より遥か昔に明け渡していた．MOSAIC trialでFOLFOXがInfusional 5FU/LVに比べstage III大腸がんの再発リスクを23%減らし3年無再発生存率が有意に良好であったインパクトを考えると[1]，術後5FU/LVを肝転移切除後の標準治療とすることは困難である．また，症例集積に要した10年間に診断手術を含めた医療環境の大きな変化があり，試験の結果にバイアスがかかった可能性も否定できない．FFCD ACHBTH AURC 9002は全身化学療法による大腸がん肝転移術後補助療法の可能性を示したといえるが，術後5FU/LVを標準治療と見なすことは難しい．

EORTC40983の特徴

肝動注を用いた補助療法の限界が明らかとなり，肝内だけでなく肝外再発に対する抑制効果

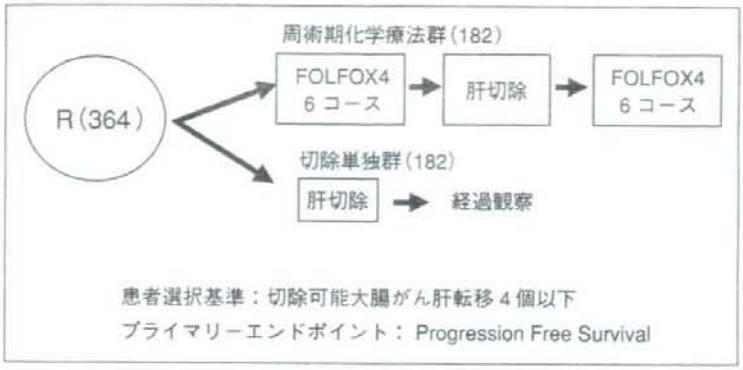


図1 EORTC40983のシェーマ

も期待できる全身化学療法を用いた補助療法に研究開発の方向性が変わってきた．また，切除不能stage IV大腸がんにおいてイリノテカン，オキサリプラチンを用いた全身化学療法の治療成績が従来の5FU/LVより良好であることが明らかとなった[12][13]．

以上のような治療変遷の中，EORTC40983は，切除可能大腸がん肝転移例に対する外科切除＋周術期FOLFOX4療法vs. 外科切除単独の第III相試験として計画された[14]（図1）．

EORTC40983の特徴として，①treatment armが全身化学療法，②切除可能肝転移にオキサリプラチン併用化学療法をはじめて使用，③control armが切除単独，④術前＋術後化学療法，⑤術前登録・ランダム化，があげられる．

切除単独をcontrol armに置いた試験が軒並み症例集積に苦労をしており，あえて切除単独を置く第III相試験を行わず有望な補助療法の第II相試験を行う傾向がみられた．そのような状況下，EORTC40983は節目的RCTとしてその後の研究計画に大きな影響を与える位置づけにあった．また，EORTC40983は術前＋術後補助療法をはじめて採用している．術前＋術後補助療法とした根拠は，切除不能大腸がん肝転移に対するオキサリプラチン併用化学療法奏効後切除の成績が良好で長期生存例が認められること，術前化学療法を行うことで完全切除率と予後の向上が期待できるためとしている．また，欧米では同時性肝転移の場合，原発巣と肝転移巣を同時に切除することは稀で，原発巣切除後インターバルをおいて肝切除を行うのが通例である．よって，インターバルの間に術前化学療法を行う臨床側の要求があったと考えられ，術前＋術後補助療法は欧米の臨床に即している．治療群が術前＋術後補助療法であるため登録，割付は術前となる．腫瘍因子の適格性，つまり切除可能か否かは画像診断をベースとしている．

EORTC40983の概要は図2に呈示している．

EORTC40983の結果

注目されていたEORTC40983の結果は2007 ASCO年次総会の本会議で発表された[15][16]．予定よりもイベント数が少なかったが，臨床サイドより早期公表の要望が強く中間解析を経て公表に至った．

本試験の結果を理解するにはtrial profileを十分理解する必要がある（図3）．全体で364例が登録され化学療法群，切除単独群にそれぞれ182例が割り付けられた．登録時の基本特性は両群ほぼ均等である．

切除単独群182例のうち，手術施行170例，腫瘍切除例は152例であり手術がなされなかった，腫瘍切除できなかった原因のほとんどは進行した腫瘍状況にあった．

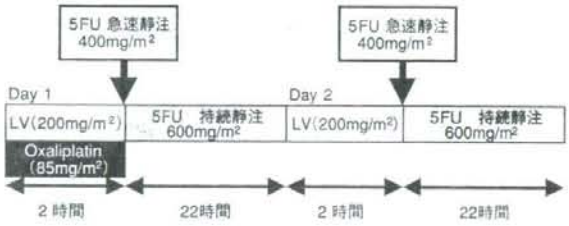
化学療法群182例では，11例（そのうち不適格例が7例）を除く171例に術前化学療法が施行された．約80%の症例で全6サイクルが行われ，オキサリプラチン，5FUともにdose intensityは90%とコンプライアンスは良好で，有害事象はgrade 3以上の下痢8%，嘔吐4%，発熱を伴う好中球減少2%，神経症状6%を認めたが中毒死を認めず術前FOLFOX4の耐性も良好であっ

エンドポイント：Primary endpoint　—無増悪生存
Secondary endpoint　—全生存，腫瘍切除率，抗腫瘍効果

主な患者選択基準：
・肝外転移を認めないpotentially resectableな大腸がん肝転移
(1) 原発巣完全切除(R0)異時性肝転移例
(2) 原発巣切除後1か月以上経過した同時性肝転移例
(3) 原発巣の切除を3〜4か月待機可能な切除可能同時性肝転移例
・化学療法歴なし
Oxaliplatinを含まない原発巣に対する補助療法は許容される

画像診断によるresectabilityのガイドライン：
・切除後残肝が30%以上保持可能
・切除断端は腫瘍より1cm以上離すことが望まれる
(完全切除であればよい)
・腫瘍個数4個以下
・左右両側肝動脈浸潤もしくは門脈浸潤がない
・肝静脈3枝浸潤がない
・RFAを併用していない
・術前診断より腫瘍が進展した場合可能なかぎり切除を行う

治療：　化学療法群　FOLFOX4



・15日毎
・術前，術後各6コース
・術後化療は肝切除後2〜5週に開始

統計(Sample Size)：化学療法群で無再発生存期間中央値が40%増加する(HR=0.714相当)と想定し330例(片群165例)．α=5％　検出力80%　両側検定

図2　EORTC40983の概要

た．抗腫瘍効果はCR 4％，PR 40%，SD 38%，PD 7％とPR以上の症例を半数弱認め平均最大径は5 cmから3.3cmに縮小したが，PD 12例のうち8例は切除不能となっている．化学療法群の手術施行例は159例，腫瘍切除例は151例であり，手術がなされなかった，切除できなかった原因のほとんどは切除単独群と同じく進行した腫瘍状況であった．

肝切除の内訳は両群ともほぼ5割の症例で2区域切除以上の手術が，2割に複数切除が施行されており術式に有意差はない．術後合併症は表2に示すように化学療法群で有意に多く認められるが術死は切除単独群2例，化学療法群1例でともに許容範囲内であった．

術後FOLFOX4施行例は115例(化学療法群の63%)，6コース完遂例は80例(43%)であった．治療拒否，術後合併症，術前の有害事象，腫瘍増悪等の理由により術後補助療法を開始できない症例が多く術後補助療法の施行率は低かった．

プライマリーエンドポイントである無増悪生存期間の解析は，第一義的であるintention-to-treatの解析(182 vs. 182)，および，適格例(171 vs. 171)，切除例(152 vs. 151)の2つのサブセット解析が行われた．Intention-to-treatの解析では，化学療法群で良好な傾向がみられるがHR=0.79，P=0.058と有意な差を認めなかった(図4-A)．一

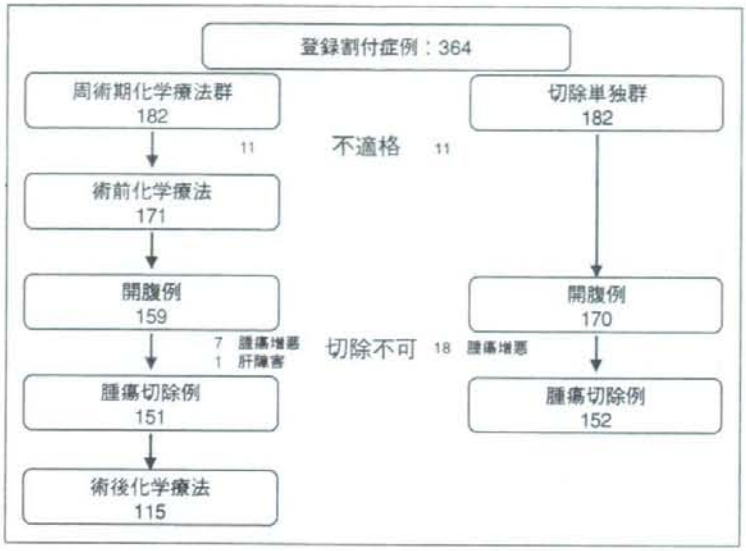


図3 EORTC40983のtrial profile

表2 EORTC40983 術後合併症

	周術期補助療法群	切除単独群
すべての術後合併症*	40/159(25.2%)	27/170(15.9%)
循環・呼吸器系合併症	3	2
術後出血	3	3
胆汁漏	12	5
（排出量 > 100ml/d, >10d）	(9)	(2)
肝不全	11	8
（血清bilirubin>10mg/dl, >3d）	(10)	(5)
創感染	4	4
腹腔内出血	8	2
再手術例	5	3
その他	25	16
術後治療関連死	1	2

*P=0.04

方，適格例と切除症例の2つのサブセット解析では，それぞれ，HR=0.77，P=0.041(図4-B)とHR=0.73，P=0.025と切除単独群と比較し化学療法群で無増悪生存期間が有意に延長していた．

術前・術後FOLFOX4は新しい標準治療か？

研究者は，適格例と切除症例の2つのサブセット解析での結果を強調し，術前・術後FOLFOX4の有効性を主張する．Intention-to-treat解析で両群間に有意な差が認められなかった原因は不適格例，非切除例がイベントとして計算されたため，術前・術後FOLFOX4による無増悪生存期間延長が薄まってしまったとしている．

しかし，プロトコールは一次解析であるintention-to-treat解析を前提としてデザインされている．適格例と切除症例の2つのサブセット解析は参考に値するが，あくまでintention-to-treat解析を優先するべきであり，術前・術後FOLFOX4の有効性は明確ではなかったと言わざるを得ない．したがって，術前・術後FOLFOX4を切除可能大腸がん肝転移の新しい標準治療と見なすことは難しい．

術前・術後FOLFOX4の有効性が明確にならなかった原因はいくつか想定される．

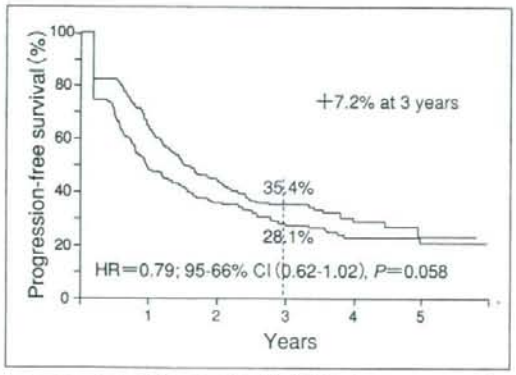


図 4-A　全登録例の無増悪生存期間(EORTC40983)
(文献[16]より引用改変)

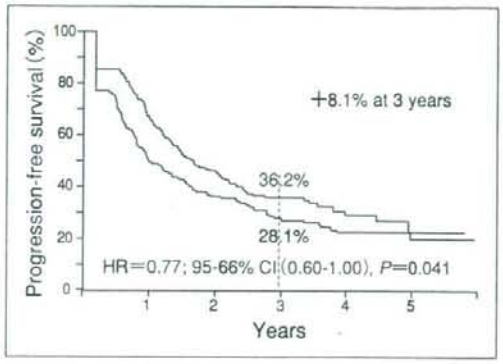


図 4-B　適格例の無増悪生存期間(EORTC40983)
(文献[16]より引用改変)

1．不適格例の多さ

不適格例を22例(6％)に認めている．Stage II, III術後補助療法のRCTであるMOSAIC試験では登録2,246例の大規模試験であったが不適格例はわずか44例(1.8％)であった[1]．EORTC40983は切除可能な同時性・異時性の肝転移を組み入れ基準としているが，切除可能か否かは詳細な「Resectabilityのガイドライン」を参照しなければならず，外科医でなければ判断のつきかねる部分も多い．不適格例が多くなることはいたしかたのない面もあるが6％の不適格例は比較的多いと言わざるを得ず，不適格例も解析の対象となるintention-to-treat解析にバイアスが加わった可能性がある．

2．画像診断によるstage migration

EORTC40983は術前登録のため，腫瘍因子にかかわる適格性は画像診断の精度に左右される．切除単独群182例中腫瘍切除が可能であったのは152例であり非切除30例の切除不可能であった理由の多くは術前診断以上に進行した腫瘍状況であった．より進行した不適格の症例が画像診断精度の問題によるstage migrationのため適格例になっていたと考えられる．化学療法群も同程度の症例にstage migrationがあったと考えられ，これらの症例が切除頻度を押し下げ，想定された対象と実際の対象が異なることにより異なった結果が導き出された可能性がある．しかし，大腸がん肝転移手術予定患者の16％が非切除という頻度は決して多すぎることはない．術前登録の場合，画像診断によるstage migrationは避けがたく，統計解析にバイアスを与える．

3．肝切除のquality control

完全切除は，切除単独群の89％，化学療法群の96.5％で可能であったとされている．病理学的断端陰性がそれぞれどれくらいの症例で得られたかは定かではない．肝切除における根治性の評価が十分検討されたとはいえない．両群間における完全切除率の差は，化学療法群で腫瘍が縮小したため完全切除が得られやすかったとも理解できるが，切除単独群で肝切除の精度が低かった可能性も否定できない．無増悪生存期間は再発がイベントとなるため肝切除のquality controlが解析に影響を与えた可能性がある．

4．リードタイム・バイアスを考慮した統計解析

プロトコール上，化学療法群は切除単独群と比較し肝切除のタイミングが遅くなる．実際に切除単独群の肝切除日は登録後14日，化学療法群114日と両群間で100日の差があった．手術のタイミングが異なると，開腹時に非切除と判明しイベントとして認識される時期が両群間で異なり無増悪生存期間の解析にバイアスが生じる可能性がある．本試験では，開腹時に切除不可能と判明した症例，切除されたが登録後1～20週に再発が判明した症例，登録後1～20週に死亡した症例はすべて10週をイベント日とすることにより上記のリードタイム・バイアスを解消しようと努めている．しかし，化学療法群で開腹時切除不能であった症例が切除単独群と同様に当初から切除不能であったか否かは不明であり，

化学療法群と切除単独群の開腹時切除不能症例等のイベント日をそろえることがどれだけバイアスを解消しているのか不明である．詳細は統計学者の検討に譲る．

以上のような問題が統計解析に影響を与えた可能性があるため，術前・術後FOLFOX4が切除可能大腸がん肝転移の治療として不十分だと結論づけることも難しい．適格例の解析で有意差が出ているだけに，より精度の高いRCTを行えばintention-to-treat解析でも差が出たのではないかという可能性はある．

Intention-to-treat，適格例，切除例のKaplan-Meireはほぼ似たような曲線を描く．最初の10週目に生じた両群間の差が4年後まで続くがそこから減少して5年後には差がわずかになる．術後FOLFOXの有効性を示したMOSAIC試験では，FOLFOX群と5FU/LV群の無再発生存は2年間で明確な差が認められ，その差は5年後までほぼ同等であった．腫瘍切除が可能であった症例は化学療法群と切除単独群でほぼ同等であることからEORTC40983における最初の10週目の差は術前化学療法による切除後極早期の再発抑制を示しているのかもしれない．しかし，4年後から化学療法群での増悪例が多くなり，その結果5年DFSは両群でその差が小さい．MOSAIC試験ではFOLFOXによるstage II, III の再発抑制が治癒につながったが，EORTC40983ではFOLFOXによる肝転移術後の早期再発抑制が必ずしも治癒に結びついておらず再発時時期の遅延にとどまっている可能性がある．この結果をもってFOLFOXが力量不足であるとは決して言いきれないが，術後の再発率が非常に高く微小転移巣の量が多いと推定される切除可能肝転移例にはstage II, III における臨床試験の結果を外挿することは難しいのかもしれない．

本邦での臨床試験

本邦では切除単独と術後mFOLFOX6を比較するJCOG0603「大腸癌肝転移切除後患者を対象としたフルオロウラシル/l-ロイコボリンとオキサリプラチン併用補助化学療法(mFOLFOX6) vs. 手術単独によるランダム化 II/III 相試験」が進行中である(図5)．EORTC40983と同様に切除単独をコントロールとしてFOLFOXの有効性を検証するRCTであるが，研究デザイン，適格基準が異なる．組織学的に完全切除された大腸がん肝転移を術後登録・割付し術後補助療法としてのmFOLFOX6の有効性をみるデザインになっている．したがって，EORTC40983の問題点であった，画像診断によるstage migration, 肝切除のquality control, リードタイム・バイアスの諸問題が生じない．切除可能大腸がん肝転移に対するFOLFOXの再発抑制効果をより高い精度で検証することが可能と思われる．

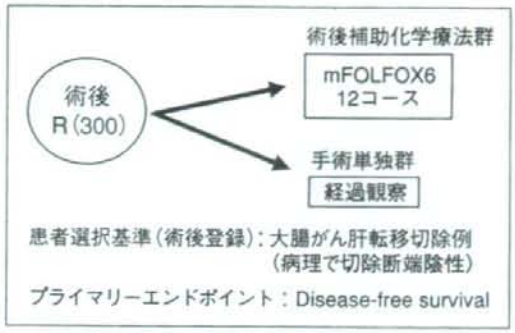


図5 JCOG0603のシェーマ

切除単独が標準治療であった時代と決別する節目として期待されていたEORTC40983であるが，新しい標準治療を確立するには至らなかったことからJCOG0603の重要性はより高まったと考えられる．今後，欧米で切除単独をコントロール群としておいた大規模RCTが改めて行われる可能性は少なく，JCOG0603は切除単独の時代を明確に終らせることが可能な貴重なRCTとして位置づけられる．今後の試験の結果に期待したい．

本邦での切除可能大腸がん肝転移治療への影響

EORTC40983では術前・術後FOLFOX4が有効か否か明瞭にならなかった．したがって，この結果によって切除可能大腸がん肝転移の治療が大きく変化することはなく，また変化するべきではない．一般病院で切除可能肝転移に対し肝切除前・後にルーチンでFOLFOXを使用することは控えるべきである．現時点では切除可能肝転移に対する補助療法はがん診療拠点病院にお

いて臨床試験に参加する形で行われるのが望ましい．

肝転移術後にstage II, III に準じた補助療法や経口抗がん剤を使用している例も多くみられるが，stage II, III の患者と肝転移の患者は腫瘍状況が異なり，stage II, III の臨床試験の結果を肝転移例に外挿する正当性を保証できないので，扱いやすいからといってこれらの薬剤を安易に使用することは慎むべきである．

大腸がん肝転移患者を対象としたRCTは海外でも症例集積に苦労することが多く難しい臨床試験であるが，新しいエビデンスを生み出し現状を打破するため，迅速に推し進めなければならない．

今後の展望「術前・術後化学療法か術後補助療法か？」

現在進行している切除可能大腸がん肝転移のRCTは，英国で進行中のUSCTU-4351(OxMdGまたはCAPOX vs. OxMdG＋セツキシマブまたはCAPOX＋セツキシマブ)のように術前・術後補助療法を行うRCTと前述のJCOG0603等の術後補助療法のみを行うRCTに分かれる．切除可能肝転移に対する治療戦略として，術前・術後化学療法と術後補助療法のどちらが良いのであろうか？

一般に，術前化学療法のメリットは，①早期に強度の高い治療が可能，②組織学的効果判定が可能，③高悪性度の症例を選別可能，といわれている．術前化学療法は，手術による合併症や臓器機能低下に治療開始時期を左右されないため強度の高い化学療法を行うことができる．また，術前化学療法後に腫瘍切除が行われた場合，化学療法に対する組織学的な効果判定が可能でありその後の治療方針を考慮する上で貴重な情報が得られる．化学療法に抵抗性で急激に進行する悪性度の高い腫瘍は切除不能となるため，切除例の予後は改善する．

一方，術前化学療法のデメリットは，①増悪例が切除不能となる可能性，②化学療法の影響による術中・術後合併症増加，が指摘される．①はメリットの裏返しではあるが，術前化学療法中もしくは後に増悪し切除不能となる症例は根治切除の可能性を逃しているのかもしれない．術前化学療法増悪例はその後肝切除をした場合，切除後予後が不良であると報告されている[17]．増悪し切除不能になった症例は，たとえ術前化学療法を行わずに切除を先行していたとしても予後不良であったと推測し，術前化学療法は切除例の選別として有効であるとする向きもある．しかし，化学療法増悪症例には本当に切除適応はないのであろうか？ 現在，肝切除の安全性は高まっており，肝転移に対する外科治療法も再肝切除[18]，2期的肝切除[19]，術前門脈塞栓による拡大手術[20]等のさまざまな治療戦略をとることが可能である．化学療法抵抗性の症例でも切除先行で外科切除を積極的に行うことにより長期生存が期待できる症例もいるかもしれない．

②については化学療法後肝障害がとくに問題となる．オキサリプラチン，イリノテカン併用化学療法に肝障害が発生し術後合併症割合，術後死亡割合が上昇するという報告がある[21][22]．オキサリプラチン併用化学療法と肝類洞閉塞(hepatic sinusoidal obstruction)，イリノテカン併用療法と脂肪肝炎(steatohepatitis)の有意な相関を示す病理組織学的な検討があり[21]，オキサリプラチン，イリノテカン併用化学療法を行う回数が多いほど，また肝切除が大規模であるほど術後の合併症が多くなるのではないかと考えられている[22]．実際，EORTC40983では死亡率こそ差はなかったが，化学療法群で，胆汁漏，肝不全，腹腔内感染症を中心に術後合併症が有意に多かった(表2)．現在，化学療法後肝障害の評価，術後死亡率，罹患率の予測，肝障害の術前評価に基づく治療体系等は確立しておらず喫緊の問題となっている．化学療法肝障害によるリスク(肝切除後死亡率，罹患率の上昇)の大きさ次第では術前・術後化学療法よりも術後化学療法の方が切除可能大腸がん肝転移例には適しているかもしれない．

現時点でどちらの治療戦略が良いのか明らかではない．再発抑制効果に加え，化学療法後肝障害のリスク評価が重要な鍵になると思われる．術前・術後化学療法か術後補助療法か？という命題に明確な解答を与えるには，術前・術後化学療法vs. 術後補助療法のRCTが必要である．現在は，標準治療となる治療の開発，検証が優先されるべきであるが，将来検討が必要な時期が

くるであろう.

おわりに

EORTC40983では術前・術後FOLFOX4の有効性は明確にならなかった. 切除可能肝転移に対する新しい標準治療の確立はJCOG0603をはじめとする今後の国内外臨床試験の結果に委ねられた. 臨床試験の迅速な推進が望まれる.

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症例報告

化学療法が奏効し切除可能となった大腸癌肝転移の1例

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A case report of hepatectomy for initially unresectable colorectal liver metastasis

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Summary : Surgical resection is the most effective treatment for colorectal liver metastases (CRLM), but curative resection can only be performed in 10-20% of all patients presenting with CRLM. An increase in response rate has been obtained by combining 5-FU-FA with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). This improved efficacy has resulted not only in an increased survival for patients with palliative setting, but also in the possibility for patients with initially unresectable CRLM to undergo curative surgical resection after downsizing by chemotherapy. A 69-year-old man was diagnosed with liver metastasis from sigmoid colon cancer which resected 2 years ago. The patient was treated with 5-FU-FA with irinotecan (IFL) as neoadjuvant chemotherapy because liver metastasis was unresectable. Liver metastasis had shrunk after 4 cycles of IFL. Therefore we performed radical left hepatectomy and curative resection with pathological free margin was achieved. The patient survived for 2 years and 10 months after hepatectomy with no evidence of recurrence.

Key words : liver metastasis, hepatectomy, chemotherapy, neoadjuvant
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はじめに

大腸癌肝転移に対する第一選択は肝切除であるが，根治切除可能な症例は 10～20% にすぎない[1,2]。全身化学療法により根治切除可能となった大腸癌肝転移に対する肝切除は近年新たな治療戦略として認識されるようになってきた。われわれは下大静脈浸潤を伴い切除不能であった大腸癌肝転移に対し，化学療法が奏効し切除可能となった症例を経験したので文献的考察を交えて報告する。

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I. 症 例

患者：69歳，男性。
主訴：特になし。
既往歴：特記事項なし。
家族歴：父，胃癌にて死亡。
飲酒歴，喫煙歴：特記事項なし。
現病歴：2002年1月前医でS状結腸癌に対しS