**Table 5** Multivariate Analysis of Predictive for Hepatic Recurrence in Patients with Synchronous Metastases

| Factors | Relative | 95% confidence intervals | | $p$ value[a] |
|---|---|---|---|---|
| | | Lower | Upper | |
| Primary nodal involvement (positive to negative) | 1.49 | 0.90 | 2.46 | 0.124 |
| Tumor (5 cm or less to more than 5 cm) | 1.14 | 0.70 | 1.86 | 0.604 |
| Number of metastases (solitary to multiple) | 1.49 | 1.02 | 2.78 | 0.043 |
| Time of resection (synchronous to interval) | 4.74 | 1.72 | 13.1 | 0.003 |

[a] Cox proportional hazards model

The current study showed that nine of the 21 (43%) patients had new lesions at the time of reevaluation, an incidence greater than that reported by Elias,[15] and similar to our previous finding for the recurrence rate in the remnant liver after hepatectomy for CRLM.[4] One reason for this discrepancy might be the fact that the preoperative radiological techniques such as multidetector row CT have recently been developed and could define the extent of metastases more accurately.[16] However, the current findings suggested the possibility of occult micrometastases in patients with synchronous CRLM. Furthermore, during interval periods, new detectable lesions appeared in preoperatively planned future remnant liver which was determined prior to colorectal surgery, suggesting that occult metastases might cause rapid remnant liver recurrence after simultaneous hepatectomy. In fact, as shown in Fig. 1, a higher rate of rapid remnant liver recurrence was found in patients undergoing simultaneous colorectal and hepatic resection for synchronous CRLM. The current data showed that delayed hepatic resection reduced hepatic relapse and was a significant prognostic factor in hepatic disease-free survival in patients with synchronous CRLM. Taken together, we proposed that delayed hepatic resection for synchronous CRLM may detect the occult micrometastases and may allow curative hepatectomy, thus reducing hepatic recurrence. The results of the current study are consistent with those of Lambert et al.[22] demonstrating that interval resection may be a beneficial strategy for patients with synchronous CRLM.

Although this study was retrospective, there may have been some bias in relation to the variability of surgical approaches. In our study, there is likely to have been little substantial difference in surgical approach between the two groups, except for the development of radiological techniques. One concern regarding this strategy is that additional metastases at the time of reevaluation represent new lesions that have appeared during the interval period. Lambert et al.[22] considered it unlikely that new nodules would develop during interval periods; rather, it likely that occult metastases become detectable. In the current study, interval resection for synchronous CRLM, at least, did not impair survival. Rather, interval resection could allow the detection of occult metastases which might be associated with rapid liver recurrence after hepatectomy. A further advantage of this strategy is the minimization of surgical morbidity and mortality related to resection of the primary tumor, such as anastomotic breakdown which leads to infectious complications and secondary hepatic failure after hepatectomy.[18,23] Overall, from the standpoint of biological features, interval reevaluation may be a beneficial strategy.

Although our surgical indication for hepatectomy is to proceed to surgery regardless of the number of metastases whenever the remnant functional liver volume is preserved and a potentially curative resection can be performed, surgical procedures planned prior to resection of the primary tumor were reconsidered for the 11 patients. There may thus be some debate regarding the timing of resection. One requirement is to clarify how long duration between the first and second operations would be appropriate; another is to determine whether all patients with synchronous CRLM should undergo interval hepatectomy; the third is to determine whether chemotherapy is required during interval periods. Our current strategy was to perform separate surgery for synchronous CRLM, and the median/mean duration between the first and second operations was 2/2.4 months. Allen et al.[24] reported that for patients who underwent the second surgery immediately after recovery from colorectal surgery, the median interval was 7 weeks, similar to that in our study. In another study, it was reported that the interval period was up to 6 months.[25] Since no new extrahepatic metastases were found after colorectal surgery, the current strategy of interval resection may be appropriate. Although we examined predictive factors for early recurrence after simultaneous hepatectomy and interval recurrence during interval periods, we were unable to identify specific predictive factors for the two groups. The real need is to be able to identify which patients will not progress and to operate on them as early as possible, while sparing those who will progress an operation. As we do not have the ability to do this yet, delayed hepatectomy may be a reasonable approach.

Chemotherapy for colorectal carcinoma with agents such as oxaliplatin or irinotecan has greatly improved recently, and the median survival of patients with irresectable advanced colorectal carcinoma has been reported to be over 20 months to date.[26–28] It has been reported that neoadjuvant chemotherapy could downstage irresectable CRLM in selected patients and prolong survival.[29] Such a strategy seems favorable for some patients with irresectable CRLM. In contrast, in patients with resectable CRLM, neoadjuvant chemotherapy still remains controversial. Allen et al.[24] reported that patients who received neoadjuvant chemotherapy experienced similar overall survival as patients who did not. They also demonstrated that subgroups of the patients with disease that did not progress with chemotherapy experienced significantly improved survival.[24] Similarly, Adam et al. reported that responsiveness to neoadjuvant chemotherapy prolongs survival and neoadjuvant chemotherapy may thus be beneficial for patient selection.[30] In the current study, three patients underwent preoperative chemotherapy because of irresectability after reevaluation. Fortunately, our 21 consecutive patients could undergo curative hepatectomy. It is important to note that irresectability is determined by an insufficient hepatic functional volume due to the multiple metastatic nodules, huge ill-located tumors which invade the hepatic hilus of portal pedicles or invade hepatic veins draining the remnant liver, and combined irresectable extrahepatic metastases. Thus, it seems likely that chemotherapy will be needed during interval periods if the observation periods are longer and if patients have either a huge tumor, ill-located tumor, or extrahepatic metastases. Since multiple CRLM was also a significant prognostic factor in our series, patients with synchronous multiple CRLM may need to undergo chemotherapy during interval periods. These data are consistent with the findings of Capussotti et al. indicating that patients with more than three metastases should receive neoadjuvant chemotherapy before liver resection.[31] Additionally, the number of lymph node metastases has been reported to be a survival indicator.[32] Interval resection could allow the evaluation of pathological findings prior to hepatectomy, and thus, patients with N2 in the tumor–node–metastasis (TNM) classification might need to undergo chemotherapy during interval periods. It might remain controversial to receive neoadjuvant chemotherapy instead of interval resection. In our study, rapid recurrence was found in patients with multiple metastases or primary nodal involvement after simultaneous resection. Thus, when patients with multiple metastases or suspicious primary nodal involvement are planned to undergo simultaneous hepatectomy instead of interval resection, neoadjuvant chemotherapy may be required. Rather, in the future, neoadjuvant chemotherapy appears to play an important role in this setting by diminishing occult micrometastases and allowing curative resection. However, care should be taken in administering neoadjuvant chemotherapy for resectable CRLM, since the incidence of surgical morbidity after hepatectomy increases in some patients due to liver damage after neoadjuvant chemotherapy.[33,34]

In conclusion, tumor progression was recognized and occult metastases were detected after interval reevaluation. Delayed hepatic resection may be a useful approach that allows the detection of occult metastases in synchronous CRLM and may reduce rapid remnant liver recurrence after hepatic resection for synchronous CRLM.

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# Risk factors of liver dysfunction after extended hepatic resection in biliary tract malignancies

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**KEYWORDS:**
Biliary tract malignancies;
Extended hepatectomy;
Postoperative hyperbilirubinemia;
Remnant liver volume/entire liver volume ratio;
Indocyanine green retention rate at 15 minutes

**Abstract**

**BACKGROUND:** Postoperative hepatic insufficiency is a critical complication after extended hepatic resection in patients with biliary tract malignancies, the majority of whom suffer from obstructive jaundice. The aim of this study was to assess clinical parameters linked to this type of liver dysfunction.

**METHODS:** A total of 111 patients were retrospectively reviewed. Patient background, pre- and intraoperative parameters, and a ratio of remnant liver volume/entire liver volume (RLV/ELV) as a volumetric parameter were compared between patients with and without postoperative hyperbilirubinemia and subsequent fatal outcome.

**RESULTS:** Logistic regression indicated that only RLV/ELV ratio was an independent factor influencing postoperative hyperbilirubinemia, and RLV/ELV ratio and indocyanine green retention rate at 15 minutes (ICG-R15) were factors affecting survival. Patients with RLV/ELV less than 40% had 7.6 times the risk of postoperative hyperbilirubinemia, while no patients with RLV/ELV greater than 40% and ICG-R15 less than 25% died of liver failure.

**CONCLUSIONS:** The RLV/ELV ratio was the factor with the greatest impact on liver dysfunction after extended hepatectomy in patients with biliary tract malignancies.


Recent reports have suggested that aggressive surgical approaches with extended hepatic resection may result in improved prognosis for patients with biliary tract malignancies, such as hilar cholangiocarcinoma, advanced gallbladder carcinoma, and intrahepatic cholangiocarcinoma.[1–7] With advances in anatomic knowledge of the liver and hepatic hilus, as well as in perioperative management and surgical techniques, the indications for these approaches have been expanded, and the likelihood of curative resection has increased. However, serious complications are sometimes encountered after surgery of this type. Postoperative hepatic insufficiency is one of the most serious complications, because it usually has a fatal outcome.

Many factors linked to postoperative hepatic dysfunction after extended hepatic resection have been reported, including preoperative liver function, remnant liver volume, and amount of blood loss during surgery.[8–13] These analyses have usually been performed in patients with hepatic metastasis[8,13] or hepatocellular carcinoma,[9–11] and few have

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examined these factors in patients with biliary tract malignancies, the majority of whom suffer from obstructive jaundice.[14] Obstructive jaundice is known to be an important risk factor for postoperative liver failure after extended hepatic resection, and, in fact, unexpected liver dysfunction is sometimes experienced after such operations. It may be attributed in such cases to impaired hepatic functional reserve due to chronic cholestasis. Therefore, preoperative biliary drainage is generally provided for such patients, to restore liver function before extended hepatic resection, although its impact on postoperative liver dysfunction remains controversial.

In this study, we analyze various pre- and intraoperative factors to identify patients at risk of developing postoperative liver dysfunction, by reviewing a single-institution study of patients with biliary tract malignancies, especially focused on patients undergoing extended hepatic resection.

## Patients and Methods

### Patients

Between December 1981 and March 2005, a total of 111 patients with biliary tract malignancies underwent extended hepatic resection at Chiba University Hospital. Extended hepatic resection was defined as resection of more than 3 Couinaud segments, that is, extended hemihepatectomy or trisegmentectomy.

The patients were 43 women and 68 men with a mean age of 66.1 years (range 40–83) at the time of surgery. The indications for resection were hilar cholangiocarcinoma in 59 patients, gallbladder carcinoma in 29, and intrahepatic cholangiocarcinoma in 23. Eight patients (7.4%) had chronic viral hepatitis but not cirrhosis, and 69 patients (63%) developed obstructive jaundice with serum total bilirubin levels exceeding 3 mg/dL on admission (range 3.1–38.0 mg/dL). All patients with obstructive jaundice received percutaneous transhepatic or endoscopic biliary drainage preoperatively to relieve cholestasis. Hepatic resection was performed principally after total bilirubin concentration had declined below 3 mg/dL, although 13 patients (19%) still had jaundice at the time of surgery (3.1–5.8 mg/dL) because their jaundice could not be expected to be relieved any longer. The period from insertion of the drainage tube to surgery ranged from 7 to 96 days (mean 45.1). Portal vein embolization was provided prior to hepatic resection for 36 patients (32%). This procedure was introduced to our institution in August 1994. During the study period a total of 42 patients were considered for this approach. However, 6 of these 42 patients did not have hepatic resection, because of peritoneal dissemination (1 patient) or irresectable disease at the laparotomy (2 patients), the revelation of distant metastasis after portal vein embolization (1 patient), failure to relieve jaundice even after biliary drainage (1 patient), and failure to improve calculated future liver remnant volume sufficiently (1 patient). Surgical procedures are listed in Table 1. Bilioenteric anastomosis was performed in 108 patients.

### Postoperative liver dysfunction

Postoperative liver dysfunction after extended hepatic resection was assessed in terms of postoperative hyperbilirubinemia and subsequent fatal outcome. Postoperative hyperbilirubinemia was defined as an increase in serum total bilirubin greater than 10 mg/dL, without a hemolytic or obstructive mechanism, within 2 weeks after surgery.

### Perioperative parameters

To analyze risk factors for developing postoperative liver dysfunction, the following parameters were assessed: (1) patient background and preoperative parameters, including

**Table 1** Types of operative procedures

| | Hilar cholangiocarcinoma (n = 59) | Gallbladder carcinoma (n = 29) | Intrahepatic cholangiocarcinoma (n = 23) |
|---|---|---|---|
| Type of hepatic resection | | | |
| Extended right hemihepatectomy | 28 | 24 | 8 |
| Extended left hemihepatectomy | 25 | 5 | 11 |
| Right trisegmentectomy | | | 3 |
| Left trisegmentectomy | 6 | | 1 |
| Associated procedure | | | |
| Bile duct resection and reconstruction | 59 | 29 | 20 |
| Partial resection of colon | | 3 | |
| Partial resection of duodenum | 1 | 1 | |
| Vascular resection & reconstruction | | | |
| Portal vein | 15 | 6 | 6 |
| Inferior vena cava | | | 5 |
| Hepatic artery | 3 | 1 | 1 |

sex, age, presence of chronic viral hepatitis, presence of obstructive jaundice, serum total bilirubin levels at the time of surgery, the rate of decrease in the level of serum bilirubin ("b value"), hepatic functional reserve tests, preoperative portal vein embolization, and presence of cholangitis before operation; (2) intraoperative parameters, including type of hepatic resection, combined vascular resection and reconstruction, bilioenteric anastomosis, amount of blood loss during surgery, operative time, and total duration of intermittent Pringle maneuver; and (3) volumetric parameters, including ratio of remnant liver volume/entire liver volume (RLV/ELV).

As reported by Shimizu et al,[15] the b value was calculated by the nonlinear least squares method, fitted to the equation $y = ae^{bx}$, where y is the serum total bilirubin level, x is the number of days after drainage, a is represented bilirubin levels on the drainage day, b is the rate of decrease of serum bilirubin, and e is the base of the natural logarithm. Based on these data, we categorized the patients into 3 groups: patients with rapid bilirubin decrease ($b < -.05$), patients with slow bilirubin decrease ($b > -.05$), and patients without obstructive jaundice (b value not available). As hepatic functional reserve tests, both indocyanine green (ICG) clearance test and the galactose tolerance test (GaTT) were performed. The ICG clearance test, by means of a single intravenous injection of ICG .5 mg/kg, was estimated as a serum retention rate at 15 minutes after injection (ICG-R15). On the GaTT, a half-life of serum galactose concentration (GaTT-T/2) was determined after an intravenous injection of 100 mL of D-galactose. These tests were performed just before surgery. Portal vein embolization was provided when extended right hemihepatectomy, or right or left hepatic trisegmentectomy, were planned and the measured future liver remnant volume was expected to be less than 40% of the entire liver volume. This policy was not changed throughout the period since the introduction of this approach. Preoperative cholangitis, occurring within a week before surgery, was diagnosed by means of clinical and hematological findings. When cholangitis had subsided, as a result of antibiotic administration, cholangitis was classified as mild, and when the insertion of an additional drainage tube was required, cholangitis was judged as severe.

For a volumetric analysis, preoperative computed tomography scan images were retrospectively used to calculate the volume of the entire liver and the resected liver. To summarize, serial transverse scans were performed at .8-cm intervals, to include the entire liver, after intravenous bolus injection of contrast medium. The total liver, excluding tumor, was outlined on each slice, and the sum of the slices was calculated by means of integrated software techniques, using density threshold. This was repeated for volume of liver resected. The difference between ELV and volume of liver resected was considered RLV. In patients who underwent portal vein embolization, this analysis was performed just before surgery, since the RLV/ELV ratio was significantly improved after portal vein embolization (Table 2).

**Table 2** Liver volume before and after portal vein embolization

| | Portal vein embolization | | |
|---|---|---|---|
| | Before | After | *P* value |
| RLV/ELV (%) | 33.4 ± 6.5 | 41.7 ± 6.7 | <.0001 |

RLV = remnant liver volume; ELV = entire liver volume.

## Statistics

Logistic regression was performed to identify possible risk factors of postoperative hyperbilirubinemia and subsequent fatal outcome associated with extended hepatic resection in cases of biliary tract malignancies. To reduce the number of variables considered in the model, univariate analysis was initially performed using Mann-Whitney test for continuous variables, and 2-tailed Fisher exact probability test or chi-square test for categorical variables. Only variables with $P < .05$ were considered for the model. Once these potential risk factors were identified, a backward stepwise procedure was used to establish the final model; the odds ratio and 95% confident interval were determined. Statistical calculations were performed using SPSS 13.0 program (SPSS Inc, Chicago, IL).

# Results

## Postoperative outcome

Seventeen of 111 patients (15.3%) with biliary tract malignancies who had extended hepatic resection developed postoperative hyperbilirubinemia. Of these patients, 9 (8.1%) died as a result of subsequent hepatic failure.

## Patient background and preoperative parameters and postoperative outcome

Univariate analysis showed no significant risk factors for postoperative outcome in regard to patient background. Among preoperative parameters, only ICG-R15 was a significant factor for death due to hepatic failure. Factors relating to obstructive jaundice, such as presence of obstructive jaundice, serum total bilirubin levels at the time of surgery, and rate of decrease in the level of serum bilirubin, were not associated with either postoperative hyperbilirubinemia or subsequent fatal outcome. Similarly, preoperative cholangitis did not affect postoperative outcome (Tables 3 and 4).

**Table 3** Risk factors for postoperative hyperbilirubinemia in patients with biliary tract malignancies

| Parameter | No postoperative hyperbilirubinemia (n = 94) | Postoperative hyperbilirubinemia (n = 17) | *P* value |
|---|---|---|---|
| Patient background and preoperative parameters | | | |
| Gender (M/F) | 58/36 | 10/7 | .82 |
| Age (y) | 66.2 ± 8.7 | 65.9 ± 8.6 | .89 |
| Chronic viral hepatitis (+) | 7 | 1 | .81 |
| Obstructive jaundice (+) | 56 | 12 | .75 |
| Serum total bilirubin level at operation (mg/dL) | 1.5 ± 1.1 | 2.0 ± 1.4 | .10 |
| b value (<−.05/>−.05) | 41/16 | 7/6 | .24 |
| ICG-R15 (%) | 12.4 ± 8.1 | 16.6 ± 9.8 | .07 |
| GaTT-T/2 (min) | 21.2 ± 7.4 | 22.7 ± 8.8 | .47 |
| Portal vein embolization (+) | 31 | 5 | .75 |
| Cholangitis (+) (mild/ severe) | 18/7 | 5/1 | .59 |
| Intraoperative parameters | | | |
| Type of hepatic resection (ELH/ERH/TS) | 38/49/7 | 3/11/3 | .15 |
| Vascular resection and reconstruction (+) | 27 | 7 | .30 |
| Bilioenteric anastomosis (+) | 91 | 17 | .46 |
| Blood loss during operation (mL) | 1,769 ± 1,959 | 4,438 ± 5,266 | .01 |
| Operative time (min) | 489 ± 96 | 562 ± 142 | .01 |
| Total duration of intermittent Pringle maneuver (min) | 36.2 ± 9.7 | 38.3 ± 17.6 | .54 |
| Volumetric parameter | | | |
| RLV/ELV (%) | 55.1 ± 16.9 | 42.4 ± 15.7 | .009 |

ELH = extended left hepatectomy; ERH = extended right hepatectomy; TS = trisegmentectomy; RLV = remnant liver volume; ELV = entire liver volume.

## Intraoperative parameters and postoperative outcome

The amount of blood loss during surgery and the operative time were significantly greater among patients who developed postoperative hyperbilirubinemia and who subsequently died than among those without postoperative liver dysfunction. Factors related to surgical procedures were not significantly associated with postoperative liver dysfunction (Tables 3 and 4).

**Table 4** Risk factors for postoperative mortality due to liver failure in patients with biliary tract malignancies

| Parameter | No postoperative fatal outcome (n = 102) | Postoperative fatal outcome (n = 9) | *P* value |
|---|---|---|---|
| Patient background and preoperative parameters | | | |
| Gender (M/F) | 64/38 | 4/5 | .28 |
| Age (y) | 65.8 ± 8.8 | 69.0 ± 6.0 | .29 |
| Chronic viral hepatitis (+) | 7 | 1 | .64 |
| Obstructive jaundice (+) | 62 | 6 | .81 |
| Serum total bilirubin level at operation (mg/dL) | 1.6 ± 1.2 | 1.8 ± 1.3 | .60 |
| b value (<−.05/>−.05) | 44/19 | 4/3 | .58 |
| ICG-R15 (%) | 12.4 ± 8.0 | 19.6 ± 11.2 | .02 |
| GaTT-T/2 (min) | 21.4 ± 4.2 | 21.9 ± 9.8 | .98 |
| Portal vein embolization (+) | 33 | 3 | .81 |
| Cholangitis (+) (mild/ severe) | 19/7 | 4/1 | .16 |
| Intraoperative parameters | | | |
| Type of hepatic resection (ELH/ ERH/ TS) | 41/53/8 | 0/7/2 | .92 |
| Vascular resection and reconstruction (+) | 30 | 4 | .35 |
| Bilioenteric anastomosis (+) | 99 | 9 | .60 |
| Blood loss during operation (mL) | 1,942 ± 2,126 | 4,848 ± 6,862 | .03 |
| Operative time (min) | 494 ± 100 | 573 ± 160 | .04 |
| Total duration of intermittent Pringle maneuver (min) | 36.2 ± 14.1 | 4.3 ± 2.4 | .76 |
| Volumetric parameter | | | |
| RLV/ELV (%) | 54.8 ± 16.9 | 35.1 ± 1.7 | .004 |

ELH = extended left hepatectomy; ERH = extended right hepatectomy; TS = trisegmentectomy; RLV = remnant liver volume; ELV = entire liver volume.

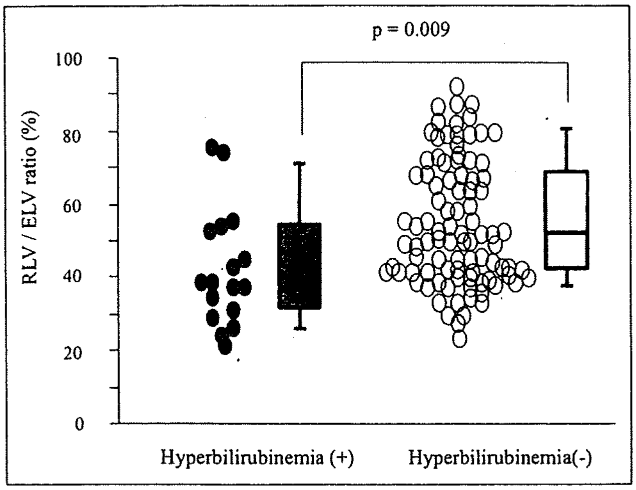


**Figure 1** A comparison of the RLV/ELV ratios of patients with and without postoperative hyperbilirubinemia. Mean RLV/ELV ratio in patients with hyperbilirubinemia was 42.4% ± 15%, while that in patients without hyperbilirubinemia was 55.1% ± 17%. The RLV/ELV ratio in patients with postoperative hyperbilirubinemia was significantly lower than in patients without hyperbilirubinemia (p = 0.009).

## Volumetric analysis and postoperative outcome

The RLV/ELV ratio was significantly lower in patients with postoperative liver dysfunction than in patients without postoperative liver dysfunction ($P < .01$). Mean RLV/ELV ratio in patients with postoperative hyperbilirubinemia was 42.4% ± 15 %, while that in patients without postoperative hyperbilirubinemia was 55.1% ± 17 % (Figure 1). Patients who ultimately died of liver failure had the lowest RLV/ELV ratios, with a mean of 35.1% ± 11%. Peak postoperative serum total bilirubin levels were negatively correlated with RLV/ELV ratio (Figure 2) (Tables 3 and 4).

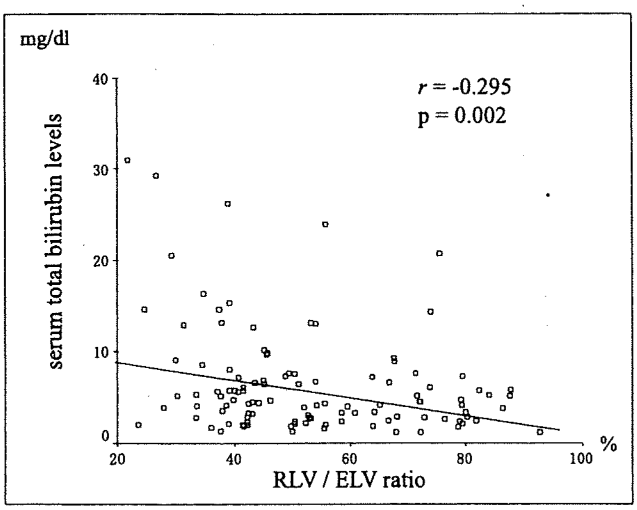


**Figure 2** Relationship between RLV/ELV ratio and peak postoperative total bilirubin levels within 2 weeks after surgery. A significant negative correlation was observed (P = 0.002, r = −0.295).

**Table 5** Multivariate analysis of liver dysfunction

| | *P* value | Odds ratio (95% confidence interval) |
|---|---|---|
| Hyerbilirubinemia | | |
| RLV/ELV ratio | .006 | .938 (.896–.981) |
| Blood loss | .17 | 1.000 (1.000–1.000) |
| Operative time | .09 | 1.006 (.999–1.012) |
| Fatal outcome | | |
| ICG-R15 | .041 | 1.105 (1.004–1.215) |
| RLV/ELV ratio | .005 | 0.864 (.780–.957) |
| Blood loss | .73 | 1.000 (1.000–1.000) |
| Operative time | .17 | 1.008 (0.997–1.018) |

## Logistic regression analysis

Multivariate analysis indicated that only RLV/ELV ratio was an independent risk factor that influenced hyperbilirubinemia after extended hepatic resection, as shown in Table 5. When logistic regression was used, in order to distinguish which patients had died of liver failure, ICG-R15 and, again, RLV/ELV ratio were selected as independent risk factors.

## Determination of the RLV/ELV ratio cut off value affecting postoperative hyperbilirubinemia

According to receiver operating characteristic curve, the best RLV/ELV cutoff value was 40%, with sensitivity 59% and specificity 81%, to distinguish patients with from those without postoperative hyperbilirubinemia. When RLV/ELV ratio was used in the logistic regression model as a categorical variable, instead of a continuous variable, with a cutoff of 40%, it was an independent risk factor that influenced hyperbilirubinemia after extended hepatic resection (odds ratio 7.6; 95% confidence interval, 2.1–27; $P < .002$).

## RLV/ELV ratio and ICG-R15 in patients with fatal outcome

All patients who died of liver failure had a RLV/ELV ratio of less than 40% and/or higher than 25% of ICG-R15 (Figure 3). Conversely, all patients who had RLV/ELV greater than 40% and less than 25% of ICG-R15 tolerated extended hepatic resection.

## Comments

Since extended hepatic resection was first performed to achieve curative resection, which is reported to be a major prognostic factor,[2–5,7] patient survival in cases of biliary tract malignancies has improved greatly. However, the mortality rate after extended hepatic resection is still high, ranging from 0% to 25%.[2,3,16–18] The high mortality rate is

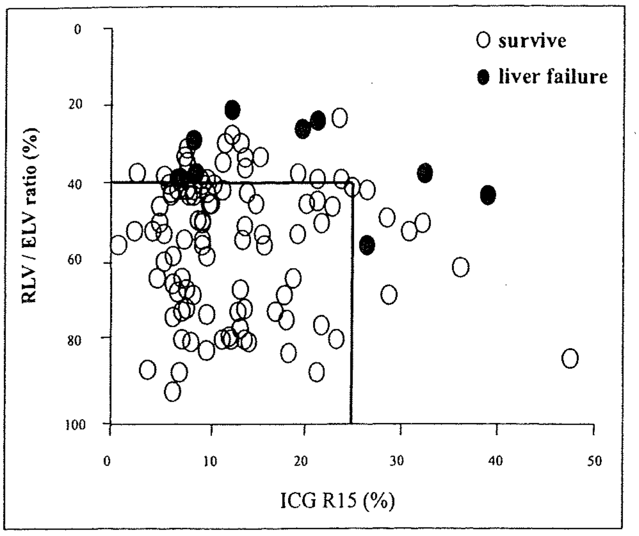


**Figure 3** RLV/ELV ratio and ICG-R15 in patients with fatal outcomes. Open circles: patients who tolerated extended hepatic resection. Filled circles: patients who died of liver failure after extended hepatic resection. All patients tolerated surgery when their RLV/ELV ratio was >40% and ICG-R15 was <25%.

mainly attributable to postoperative hyperbilirubinemia, followed by hepatic failure. Therefore, investigation of factors that influence postoperative liver dysfunction is of great interest for surgeons hoping to improve perioperative outcome in patients with biliary tract malignancies.

Since the majority of patients with biliary tract malignancies have obstructive jaundice, it has been suggested that preoperative cholestasis is associated with postoperative liver dysfunction. Many retrospective clinical reports and experimental data suggest that preoperative obstructive jaundice is related to postoperative morbidity and mortality.[19–21] Based on these facts, routine preoperative biliary decompression, to a serum bilirubin level of 2–3 mg/dL, has been advocated to reduce postoperative complications.[18,20] In the present study, all patients with obstructive jaundice received preoperative biliary drainage, but 13 (19%) of these patients still had jaundice with serum total bilirubin levels greater than 3 mg/dL at the time of extended hepatic resection. However, serum total bilirubin levels at the time of surgery and the rate of decrease in the level of serum bilirubin were not found to be significant risk factors for postoperative liver dysfunction. These results raise the question of whether or not preoperative biliary decompression should be routinely performed before extended hepatic resection, although it is possible that patients in this study who had jaundice at the time of surgery had already received effective relief of cholestasis in spite of their bilirubin levels. There have been few reports on this issue, especially in regard to patients with extended hepatic resections, but Cherqui et al[22] have recently shown that major liver resections without preoperative biliary drainage are safe for most patients with obstructive jaundice.

Our logistic regression model has shown that the RLV/ELV ratio was the strongest risk factor for liver dysfunction after extended hepatic resection in patients, the majority of whom had preoperative jaundice. Recently, with an increase of the number of cases with major hepatic resection and living-related liver transplantation, the importance of volumetric analysis by computed tomography images has been emphasized to avoid postoperative liver dysfunction.[23] Several reports have shown the minimum extent of remnant liver volume compatible with a safe postoperative outcome, with RLV/ELV ratios ranging from 25% to 30%.[8,24,25] A significant correlation between remnant liver volume and postoperative peak bilirubin level has also been reported.[8,25] These results were similar to our current results, although the extent of remnant liver volume in patients who developed postoperative hyperbilirubinemia (mean 42% of RLV/ELV ratio) and subsequent fatal outcome (mean 35% of RLV/ELV ratio) was a bit large in our study. The reason for this might be that, in previous reports, the patients who were assessed mostly had normal liver parenchyma, while in our study, the majority of patients had cholestatic liver. Takahashi et al[26] have also shown that resection of up to 48.7% of the liver was safe and hepatectomy of up to 71.6% was the maximum permissible resection, calculated on the basis of postoperative bilirubin levels, in patients with obstructive jaundice, even after relief of it. Their results and ours suggest that the extent of liver that can be safely resected is limited in the case of cholestatic liver, even after this condition is relieved, and, when the estimated RLV/ELV ratio is ≤40%, which is the critical point for postoperative liver dysfunction as shown in this study, portal vein embolization should be performed before extended hepatic resection to increase the RLV/ELV ratio.

Another significant factor for mortality due to hepatic failure, but not for postoperative hyperbilirubinemia, was ICG-R15. Use of ICG-R15 has been proposed by many institutions as one of the best ways to evaluate the safe limits for hepatic resection.[11,27] However, since such assessment is directly influenced by the severity of jaundice, due to excretory competition with bilirubin, its result must be carefully interpreted in cases of patients with obstructive jaundice. In the present study, this evaluation was conducted principally after the total bilirubin level had declined below 3 mg/dL, even in 8 of 9 patients who died after extended hepatic resection, although 13 patients who had jaundice at the time of surgery had total serum bilirubin levels greater than 3 mg/dL but not beyond 6 mg/dL at the time of ICG-R15 evaluation. Therefore, the results of ICG-R15 in patients with fatal outcomes were relatively reliable, and these results suggested that special attention should be paid to the occurrence of liver failure after extended hepatic resection in patients with high ICG-R15 even after relief of obstructive jaundice, as mentioned by Lee and Hwang[28] (wherein the livers of patients with an ICG-R15 >15% after relief of obstructive jaundice often showed diffuse parenchymal shrinkage, without evidence of liver cirrhosis). This may be an irreversible phenomenon, and hence related to cases of death due to liver failure after extended hepatic resection. In our study, no patients with ICG-R15 less than 25% died of liver failure after extended hepatic resection when their RLV/ELV ratio was greater than 40%.

In addition to preoperative volumetric parameters, intraoperative parameters may also influence postsurgical course. However, our logistic regression model failed to identify any intraoperative parameters associated with postoperative hyperbilirubinemia and also with mortality, although, in univariate analysis, the amount of blood loss during surgery and the operative time were found to be significant factors for postoperative hyperbilirubinemia. These results were similar to those in previous reports by Nagino et al[14] and Fujii et al.[29]

In conclusion, we identified RLV/ELV ratio as having the strongest impact on postoperative liver dysfunction and found that ICG-R15, evaluated after relief of jaundice, had the next strongest relationship to mortality after extended hepatic resection in patients with biliary tract malignancies. To prevent postoperative liver dysfunction, volumetric analysis should be performed in a prospective fashion; based on the results, preoperative portal vein embolization or, if possible, limited hepatic resection after precise estimation of cancer extent[30] should be considered.

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# 多様化する大腸癌肝転移例に対する外科治療

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# 多様化する大腸癌肝転移例に対する外科治療

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**要旨**：大腸癌肝転移は大腸癌症例の予後を規定する重要な因子であり，肝切除はその予後を改善する有効な治療法である．両葉多発肝転移例や大血管浸潤例に対しても，さまざまな外科手術手技を併施し肝切除の適応は拡大されているのが現状である．一方，大腸癌に対する新規抗癌剤併用療法や分子標的治療薬の進歩はめざましく，切除不能肝転移例を切除可能へと移行させる治療戦略となりつつあり，また切除可能例に対してもより根治性を高めることで，予後向上につなげることを目的として術前化学療法が施行されるようになってきている．外科的治療は以前に比してより集学的治療戦略として行われ，今後これらの進歩を踏まえた新たな治療戦略が今後期待される．

**索引用語**：肝転移，血管合併切除，肝切除，予後因子

## はじめに

大腸癌肝転移は大腸癌症例の予後を規定する重要な因子であり，その治療法として肝切除が第一選択であることには議論の余地がない[1)～6)]．大腸癌肝転移症例に対する肝切除の適応は拡大されてきており，両葉多発肝転移例や大血管浸潤例に対しても，術前門脈枝塞栓術による肝実質温存や血管合併切除再建などの積極的な外科治療が施行されるようになってきている[7)～10)]．

一方，進行再発大腸癌に対してFOLFOX，FOLFIRIなど新規抗癌剤併用療法や分子標的治療薬bevacizumab，cetuximabの有効性が報告されており，切除不能進行再発大腸癌症例における生存中央値は20カ月を超す報告がなされるようになってきた[11)～13)]．Adamらは大腸癌肝転移肝切除不能例に対してdownstageを目的としたneoadjuvant chemotherapyにより，1104例中138例（12.5%）に肝切除が施行可能となり，その予後は初回肝切除例と比べても遜色のないことを報告しており[14)]，切除不能肝転移例に対して新規抗癌剤を投与することで切除可能へconvertする新たな治療戦略は切除例数の増加や予後の向上には不可欠であると考えられる．また最近は切除可能例に対してもより根治性を高め予後向上につなげることを期待して術前化学療法が施行されるようになってきており，外科的治療は以前に比してより集学的治療として行われるようになってきた．

## I　外科切除適応

外科切除適応を決定するに当たり実地臨床として考慮する点としては，腫瘍の個数や大きさ・腫瘍の占拠部位・大血管浸潤の有無・肝門グリソン浸潤の有無・肝外転移併存の有無・肝門リンパ節転移の有無が一般的にあげられる[15)～21)]．腫瘍の個数や大きさに関しては，大腸癌取り扱い規約（第7版）において，これらの因子を考慮したH分類が規定されている．以前は腫瘍個数が4個以上の

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**Figure 1.** 肝転移巣による肝切除術式の volumetry のための切除ライン（左3区域切除）.

症例では予後が不良であるとの報告から[19][20]，切除適応となる腫瘍個数に制限をつけることが一般的であった．しかしながら肝切除の安全性の向上と画像診断の進歩から，現在では肝臓外科医からみた手術適応を考える際には，根治的肝切除施行において腫瘍個数には制限をつけていないことが一般的である．これは欧米での切除率25%に対して，本邦ではH1・2で80～90%，H3でも約40%の切除率であることからも理解される．また切除の方法に関しても，海外では葉切除や区域切除が主流であるのに対し，本邦では部分切除が多く行われていることもその一因である．切除適応に当たっての重要な点としては，予測残肝容積の測定結果とICG15分停滞率や肝合成能などからみた肝予備能評価の結果を総合的に判断し，耐術可能の範囲にあるかを判断することである．つまり術式決定に際しては，肝切除後に残る肝実質量が術後の肝不全などの致死的合併症を回避するために機能的に十分に残ることが必要である．肝切除術式を決定する方法としては，ICG15分停滞率・術前総ビリルビン値・腹水の有無から切除可能範囲を予測するいわゆる幕内基準が一般的でかつ簡便である[22]．実際の予測残肝率の測定としては，われわれはFigure 1のように腫瘍の存在範囲より予想される術式を想定して，腫瘍の体積を除いた機能的全肝体積と機能的残肝体積を測定して行っている．また同時に身長・体重より standard liver volume（SLV）を計測する．これらの方法で予測した残肝量が，施設間で差はあるものの全肝およびSLVの30～40%の範囲であれば，一期的に肝切除を施行している．これより少ない場合には門脈枝塞栓術を施行して，2～3週後の残肝量の増大後に手術を施行している．一般に転移性肝癌の場合には肝機能は正常であることが多く，通常は残肝量のみで規定されることが多い．high volume center で行われる転移性肝癌に対する肝切除時の mortality は2%未満であるのが一般的であり，後で述べる血管合併切除などの拡大切除を施行しても，現在はほぼ mortality は0%に近くなっている．

ここで先に述べた切除適応決定因子を検討してみると，腫瘍の個数や大きさ・腫瘍の占拠部位な

どは残肝量不足が切除適応からはずれる主な理由である．残る肝臓の唯一のドレナージとなる肝静脈浸潤例における肝静脈合併切除再建や下大静脈合併切除再建は施設により手技的に可能か否かによって切除適応が決定される．肝門リンパ節転移や制御できない肝外転移併存は一般的には肝切除を施行しても予後が悪く，肝切除の意義が少ないと考えられがちである．抗癌剤・分子標的治療剤の詳細は他稿に譲るが，これらの進歩があっても肝転移が予後規定因子となることが多く，抗癌剤単独での5年以上の生存の可能性はこのような症例に対して極めてまれとなることからも，可及的に肝切除施行を考慮すべきである．そこで，切除不能を決定する際に留意すべき点としては，消化管専門内科医・外科医のみの判断で肝切除不能を判断しないことも必要である．肝切除が施行可能な場合にもかかわらず，腫瘍個数が多いことや腫瘍の大きさが大きいことだけで切除不能と安易に判断してしまうことは，避けなければならない．特に抗癌剤治療が進歩してきている現状であるからこそ逆に，いずれかのタイミングで肝切除が施行可能であれば，予後を延長できる可能性が高くなる．術前抗癌剤併施肝切除については後に述べるが，長期に抗癌剤を投与しSD，PDと判断され紹介された症例でも切除が可能である場合が多いのも事実であり，肝切除を加えることで初回肝切除症例とほぼ同等の予後が期待できる．しかしながら，また同時に長期に抗癌剤の投与を施行した症例では，肝障害のみならず肝切除後の肝再生不全がおこりうることからも，抗癌剤投与と切除をどのタイミングで行うかが今後重要な解決すべき問題点である．

## II　肝切除の手技的問題

肝切除の方法としては，portal triadを処理しその区画を切除する系統的肝切除と腫瘍からの一定のmarginをとり切除を施行する部分切除に分けられる[23)24)]．肝細胞癌では系統的切除を行うことが肝癌診療ガイドラインでも推奨されている[25)]．転移性肝癌でも約30%の症例に微小肝転移が門脈内に存在することが基礎的検討でわかっており，当科では以前は可能な限り系統的肝切除を行っていた．しかしながら現在の両葉多発肝転移症例に対する肝切除例数の増加にともない，根治的肝切除を行いながら術後肝不全を回避するためには，できるだけ肝実質を温存することが必要と考えられ，部分切除を選択することが増えてきている．本邦では先に述べたとおり部分切除を選択する施設が多く，また最近の再肝切除の施行例数の増加にともない安全性からも可及的に肝実質を温存する術式選択が主流となってきている．以上のことからも現在では転移性肝癌では，どちらの切除の方法を選択するかは大きな問題とされない．腫瘍とのmarginに関しては，以前は5ミリ以上，できれば1センチとることが必要と考えられていたが，占拠部位が肝門に近い症例や両葉多発症例において，5ミリ以上のmarginをすべてにとることは不可能である場合も多い．現在，本邦では腫瘍が露出しないように肝切除することで十分であると考えられており，一方欧米でのいわゆるR0手術では1ミリ以上のmarginが必要と考えられている．またKokudoらは基礎的検討を踏まえ2ミリ程度のmarginの必要性を報告しており，肝切除時の腫瘍露出は多変量解析でも予後因子となっていることからも，これが現実的であると考えられる[26)]．いうまでもないが，十分にmarginを取りうる症例でいたずらに縮小することは慎むべきである．

手技的な問題点としては肝静脈合併切除再建や下大静脈合併切除があげられる[27)~30)]．肝静脈合併切除再建の適応となる症例は，一般には限られておりhigh volume centerでも症例数は多くないと思われるが，下大静脈合併切除再建は現在十分安全に施行可能な手技である．Figure 2が当科での下大静脈合併切除施行・未施行の肝切除後の生存曲線であるが，その生存曲線には有意差を認めていないことと術後合併症にも差を認めないことからも，下大静脈浸潤例といえども根治的肝切除が可能である症例は積極的に適応とすべきである．MD-CTやMRIにて癌の浸潤範囲が診断されるが，最終的には術中の判断により浸潤範囲を推定している．下大静脈を切除する際は肝動脈・門脈などの流入血行遮断と肝上・下部での下大静

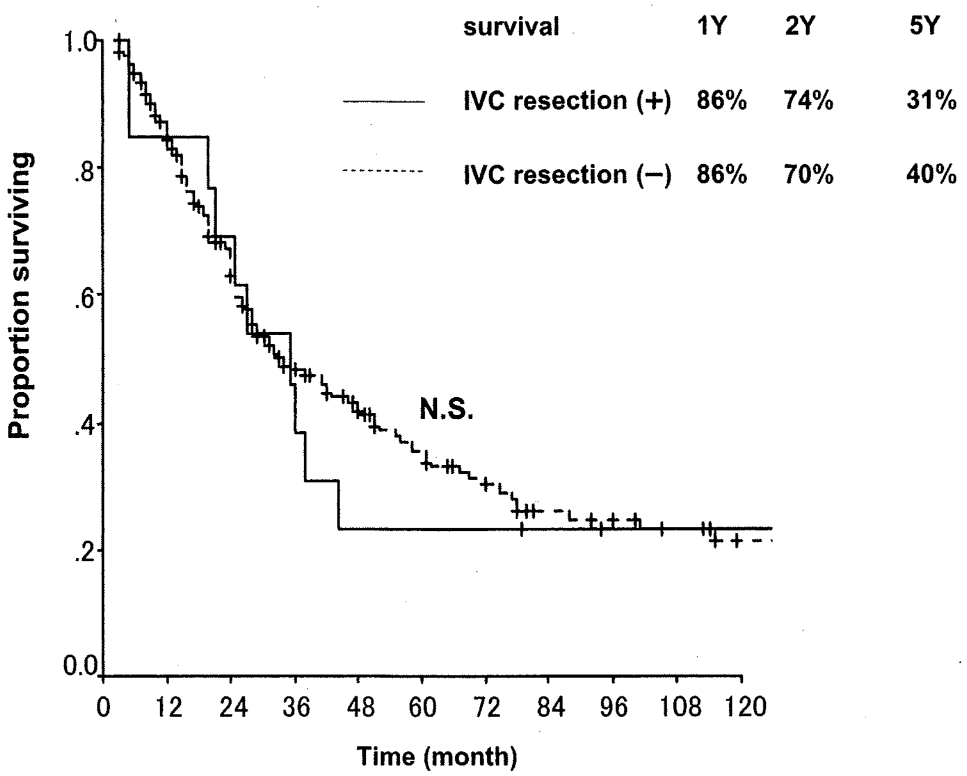


**Figure 2.** 下大静脈浸潤併存肝転移例に対する下大静脈合併切除の有無別の切除後累積生存率.

脈遮断が必要であることが多く，切除方法は部分的に切除か環状に切除かで分けられる[29)30)]．その再建方法は単純縫合閉鎖や自家静脈を用いたパッチ再建やe-PTFEグラフトを用いた全置換に分かれるが[29)30)]，いずれにせよ血管外科手技の発達した今日では，下大静脈浸潤例を切除することは十分に安全に可能である．

両葉多発肝転移例に対して適応は限られているが，two-stage hepatectomyという治療戦略も新たに登場している[31)~33)]．ひとつの例として，まず左肝にある肝転移を切除して術中に多発している右肝に対して，術中右門脈枝塞栓術を施行して残肝量肥大後に右肝切除（右葉切除）を施行して根治的に肝切除を行う方法である．この方法により，肝切除適応はさらに拡大することとなり，化学療法と組み合わせるなど，今後は適応の決定・安全性を含めた症例の集積結果が待たれる治療戦略である．

## III 転移の時期を考慮した肝切除

本邦では一般に大腸癌発見時に存在した肝転移を同時性とし，原発巣切除後に存在するものを異時性肝転移と定義することが多い．本邦では以前より原発巣と同時に肝切除を施行することが多く，当科でも以前は原発巣と同時に切除を行っていた．一方海外では6カ月ないし1年以内までの転移を同時性と考える場合があり，この点で定義に差があるものの，Scheelらは同時性肝転移症例の予後不良の一因として微小肝転移の存在を指摘しており[34)]，われわれのretrospectiveな検討でも転移の時期は独立した有意な予後規定因子であることから，同時性肝転移では微小肝転移の存在が示唆される．つまり切除後残肝に微小肝転移が存在するために，肝再生シグナルとともに肝切除後早期に病変が再発として顕在化する場合があり，このことは消化器専門医にとって，肝切除施行が無用であったと考えさせる一因となる．そこでわれわれは2004年より同時性多発肝転移症例は原則的に原発巣の切除を先行し，一定の観察期間の後に，微小肝転移巣の顕在化の有無と原発巣の治癒切除を病理組織学的に確認した後に，転移

巣を切除する方針へ変更した．観察期間中に約43％の症例で肝転移巣の腫瘍の増大や腫瘍個数の増加が認められ，以前の原発巣との同時切除を施行した症例と比較してみると，術後早期の残肝再発率は有意に抑制された[35]．このように待機的肝切除施行は同時切除にともなう縫合不全などに起因する感染症やそれによる肝不全などの重篤な合併症のリスクが回避できること[36]と，微小転移の出現の有無を確認できることにより根治的肝切除が施行可能となる利点がある[37][38]．特に肝実質を大量に肝切除を行う場合に，感染性合併症は術後の肝不全に対しての危険因子であり注意を要する．また今後は切除不能症例のみならず術前化学療法施行症例の増加が予想され，分子標的治療剤としてbevacizumabを併用投与する場合が考えられる．bevacizumabの出血・縫合不全（創傷治癒遅延）のリスクから考えても，原発巣と分けて肝切除を施行することも新たな治療戦略である．

肝外転移に関して，その中で特に肺転移は外科切除が有効な病変である[16)~18]．以前はその適応はやはり限られていたが，手術術式も鏡視下肺部分切除が一般的な切除の方法であり，現在では術前術後管理の進歩により両葉肺転移症例や多発症例に対しても安全に切除施行可能となり，肺切除の適応は拡大されつつある．同時性肺転移の場合は以前より肝切除と分けて施行されることが多く，肝切除後の根治性確認後に施行されてきた．現在は特に原発巣を含め肝・肺の3臓器に病変がある場合には，1臓器ごとの切除の間に抗癌剤投与を施行しながら根治性・適応を確認して，待機的にselectionを行いながら外科切除を施行していけば治癒にいたる症例も存在するようになっており，制御可能な肺転移併存は肝切除適応外ではなくなっている．

## Ⅳ　術前抗癌剤併施肝切除

他稿に詳述されているとおり大腸癌に対する抗癌剤の進歩はめざましく，これを併用することでその予後は向上できると考えられる．その投与方法としては術前に用いる場合と術後に補助療法として投与する場合に大別される．肝転移に関してはすでにステージⅣであり切除率も低いことから，これまでのところ切除不能症例に対して投与した検討の報告が多い．Adamらの報告[14]のように切除不能の肝転移症例に対して抗癌剤投与により切除可能へとconvertする治療戦略は，肝切除の対象とならない症例において少なくとも10％の症例が肝切除に移行可能となり，これらの対象症例において肝切除を施行した場合の予後は，切除可能症例に対する初回肝切除後の予後とは差異を認めないことから，積極的に行われるべき治療戦略であると考えられる．切除適応基準が施設間でばらつきが多く存在する現状では，いまだ切除不能とされる症例が存在する大腸癌肝転移症例にとって，結果としてこの治療戦略は有益なものであろう．肝切除不能の判断は先に述べたとおり，①腫瘍結節数多発などにより切除後の残肝量が不足する場合，②腫瘍の占拠部位が肝門グリソン鞘のため残肝量不足となる場合や残肝の唯一のドレナージとなる肝静脈に腫瘍浸潤が及びその再建が不能である場合，③切除不能の肝外転移併存の場合，の3点が考えられる．

一方，術前抗癌剤投与による肝障害の報告もなされており，oxaliplatin-basedの投与ではいわゆるblue liver（sinusoidal obstruction syndrome）が，irinotecan-basedではyellow liverつまり脂肪肝の報告がなされている[39]．Vautheyらは FOLFIRIの先行投与によるsteatohepatitisの存在する症例では術後在院死例が多かったことを報告をしているが[40]，われわれはこれまでのところ経験していない．しかしながら，Kaouriら[41]の報告のように抗癌剤の術前投与回数が多いほど術後合併症の頻度が高くなることが報告されており，術前抗癌剤投与と肝障害の観点からは，より効果の早い治療法を選択することが今後重要であろう．FOLFOX，FOLFIRIに分子標的治療薬bevacizumabを併用した治療戦略が現在主流になりつつあり，またbevacizumabの併用によりblue liverの軽減が認められたとの報告もあり[42]，今後投与方法・投与期間を含めさらに詳細な検討が必要となるであろう．本邦ではcetuximabのfirst lineでの投与はまだ認可されていな

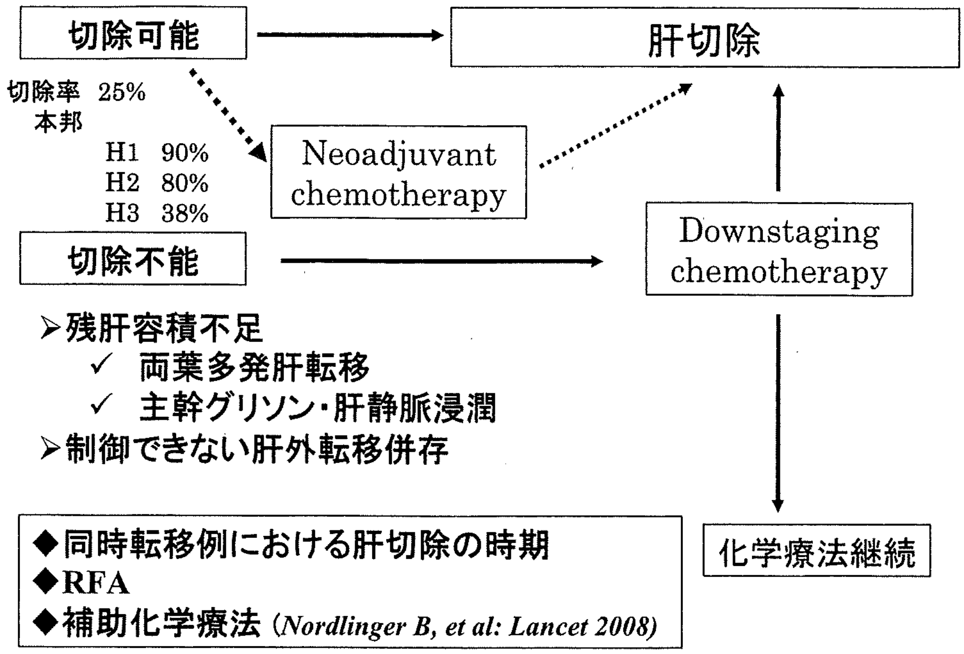


**Figure 3.** 現在の肝転移例に対する治療戦略.

いが，NCCNガイドライン2009においてはfirst lineでの投与が推奨されており，報告をみてもcetuximabの併用は肝切除移行を早期に可能とする可能性が示唆され，今後の検討が待たれるところである．

われわれの経験を踏まえて考えると，一般に抗癌剤投与後の肝切除症例の組織学的効果は画像上Complete response (CR)やPartial Response (PR)の部位においてもGrade　1a～2にとどまっており，腫瘍の切除は必要であることが推測される．ここで肝切除に際して，特に画像上CRになっている病変の扱いが問題になっている[43]．われわれの経験でも瘢痕になっていた部位にはcancer cellは認められないことはあるが，画像上CRとなっている部位が初回肝切除後に再燃し，再肝切除標本においてcancer　cellを認めることは経験されることであり，画像上CRの部分は可及的に切除されることが望ましいと現状では考えられる．実際，画像上CR病変が病理組織学的にCRとなっている頻度は10～20%程度と報告されており[14,43]，また画像上CRとなった部位の経過を観察した報告においても，術中所見で癌の存在を確認し切除を施行した病変と切除を施行せずに術後経過を観察し再燃を認めた病変を合わせると，CR病変全症例の中で83%に癌の存在や再燃があったと報告されている[43]．つまり画像上CR病変であってもどのタイミングかで切除ないしRFA施行が必要になるであろう．これら術前のCT，MRIでのCR病変は実地臨床においては，ソナゾイドを用いた術中超音波検査が今後有効な方法と考えられる．しかしながら，抗癌剤投与が長くなると，術中ソナゾイドを用いた超音波検査でもCR病変は同定ができない場合も考えられ，存在が不明の病変は切除をすることは不可能である．また一方全肝区域に存在する肝転移の場合には，残肝量の問題から画像上CR病変を切除できずに経過観察せざるをえない場合もある．以上の点からも術前抗癌剤投与症例の治療戦略として1つの考え方は，初回肝切除前に切除不能と判断された責任病変がCR/PRとなり切除可能と判断されれば，その時点で切除を考慮することが重要である．現在は再肝切除の手技も確立されており，画像上CR病変に対して再燃後に再度治療を考慮することも1つの戦略であろう．抗癌剤による肝障害の点からも投与を施行してからどのタイミングで肝切除を施行するべきかという問題は，今後詳

細に検討することが必要であろう．

肝切除可能な肝転移症例において，微小転移を消失させ根治性を向上させるという目的で，術前抗癌剤投与を施行後に肝切除を施行するべきかという議論がなされている．術前化学療法の病理組織学的効果が肝切除後の生存期間の予後因子となったとの報告や[44)~46)]，また術前化学療法施行により欧米でのいわゆるR1手術となった肝切除症例の予後とR0症例の予後に差異はなかったとの報告[47)]がなされたことから，術前化学療法施行症例はますます増えてくると考えられる[48)~51)]．現時点での補助療法を含めた大腸癌肝転移例に対する治療戦略をシェーマに示すが（Figure 3），先に述べた微小肝転移の問題を含め，まだ一定の結論は出ていないが，肝切除後の早期肝再発抑制のためには待機的肝切除か術前化学療法併用肝切除を施行するかなど，今後さらなる検討が必要と考えられる．また消化器専門医にとって肝転移はすでにステージIVであることから考えても，新規抗癌剤と分子標的治療剤の投与はますます増えてくると考えられる．肝切除は予後を有意に伸ばしうる治療法であることから肝臓外科医側からみると肝障害や術後の合併症や肝再生の点からも適切な抗癌剤投与方法・期間と切除の可否を含めそのタイミングを考慮することが肝要であることを注記したい．

## おわりに

大腸癌肝転移に対する肝切除は手術手技や周術期管理の進歩により，安全に施行可能であり，肝切除・新規抗癌剤・分子標的薬を合わせた新たな治療戦略は今後ますます進歩していくであろう．

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