at the end of the 24-week drug-free follow-up period. HCV RNA was assessed by qualitative reverse transcription polymerase chain reaction (TaqMan RT-PCR). SVR represented a negative HCV RNA at 24-week follow-up without treatment after the end of active treatment. Transient viral response (TR) was defined as positive HCV RNA at 24-week follow-up after a negative HCV RNA at the end of active treatment. Complete early viral response (cEVR) was defined as negative HCV RNA at week 12 of active treatment. Partial early viral response (pEVR) was defined as HCV RNA ≥ 2 log10 drop from baseline at week 12 of active treatment. Null response (NR) was defined as HCV RNA that never dropped by ≥2 log10 from baseline at week 12 of active treatment.

Histopathological stage was assessed before treatment and determined based on the histological scoring system of Desmet *et al.* [38].

Assessment of hepatocellular carcinoma recurrence

The concentrations of serum tumour markers α-fetoprotein (AFP) and des-γ-carboxy prothrombin were measured once a month after hepatic resection or radiofrequency ablation. Follow-up US was performed every 3 months; and CT or MR imaging was performed every 6 months. IFN therapy was discontinued upon suspicion of HCC recurrence.

Statistical analysis

Nonparametric tests (chi-square test and Fisher's exact probability test) were used to compare the clinical and laboratory parameters of the two groups. Univariate and multivariate logistic regression analyses were used to determine those factors that significantly contributed to early viral dynamics. The odds ratio and 95% confidence intervals (95% CI) were also calculated. All P values <0.05 using two-tailed tests were considered significant. Variables that achieved statistical significance ($P < 0.05$) or marginal significance ($P < 0.10$) on univariate analysis were entered into multiple logistic regression analysis to identify significant independent predictive factors.

Cumulative survival and recurrence rates were calculated from the initial date of hepatic resection or radiofrequency ablation and assessed by the Kaplan–Meier life-table method, with differences evaluated by the log rank test. All statistical analyses were performed using PASW 18 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Table 1 shows the baseline characteristics of the patients treated with PEGIFN/RBV after hepatic resection or radiofrequency ablation for HCC. The median age of the patients (55 men and 23 women) was 66 years. The median body mass index was 22.4 kg/m^2. The median pretreatment serum HCV RNA viral load was 6.0 log IU/mL. Most patients were infected with HCV genotype 1 ($n = 58$) followed by genotype 2 ($n = 20$). IL-28B genotype (rs8099917) was TT ($n = 51$), GG+TG ($n = 25$) and no date ($n = 2$).

Table 1 The baseline characteristics of the all 78 patients treated with PEGIFN/RBV

	$n = 78$
Gender (male/female)	55/23
Age (years)*	66 (48–83)
Body mass index (kg/m^2)*	22.4 (15.6–40.1)
IL28B genotype (TT/GG+TG/ND)	51/25/2
White blood Cell (×10^3/μL)*	4.2 (2.4–7.5)
Haemoglobin (g/dL)*	13.3 (8.7–18.1)
Platelet count (×10^4/mm^3)*	11.1 (3.9–20.5)
T-bilirubin (mg/dL)*	0.7 (0.2–2.8)
Alanine aminotransferase (IU/L)*	44 (8–189)
Prothrombin time activity (%)*	87 (58–121)
Albumin (g/dL)*	4.0 (2.7–5.2)
γ-glutamyl transpeptidase (IU/L)*	45 (12–371)
HbA1c (%)*	5.3 (3.9–10.8)
Indocyanine green retention rate (%)*	15.4 (3.5–45.4)
Fibrosis stage (F1-3/F4/ND)	20/19/39
Genotype (1/2)	58/20
HCV viral load (Log IU/mL)*	6.0 (2.1–7.2)
Tumour stage (I/II/III/IV)†	28/27/23/0
α-Fetoprotein (ng/mL)*	11 (0.5–286)
Des-γ-carboxy prothrombin (mAU/mL)*	29 (10–4550)
Tumour size (mm)*	21 (7–110)
Number of tumour*	1 (1–4)
Hepatic resection/radiofrequency ablation	28/50

ND, not done; HCV, hepatitis C virus; PEGIFN/RBV, pegylated interferon-alpha plus ribavirin combination therapy. *Data are median and (range). †Tumour staging was defined based on the Liver Cancer Study Group of Japan/Tumor-Node-Metastasis staging system of the Liver Cancer Study Group of Japan.

Efficacy and tolerance of therapy and adverse events

Figure 1 shows the effects of PEGIFN/RBV treatment according to genotype. The SVR rate was 33.3% (26/78) for all patients. The PRGIFN/RBV treatment protocol could not be completed by 32 (41%) patients; 17 (53%) of the 32 developed HCC recurrence. In 58 patients with genotype 1, PEGIFN and RBV were discontinued in 29% (17/58) patients because of HCC recurrence and because of other reasons in another 9 (15.5%) [general fatigue ($n = 3$), cancer of the

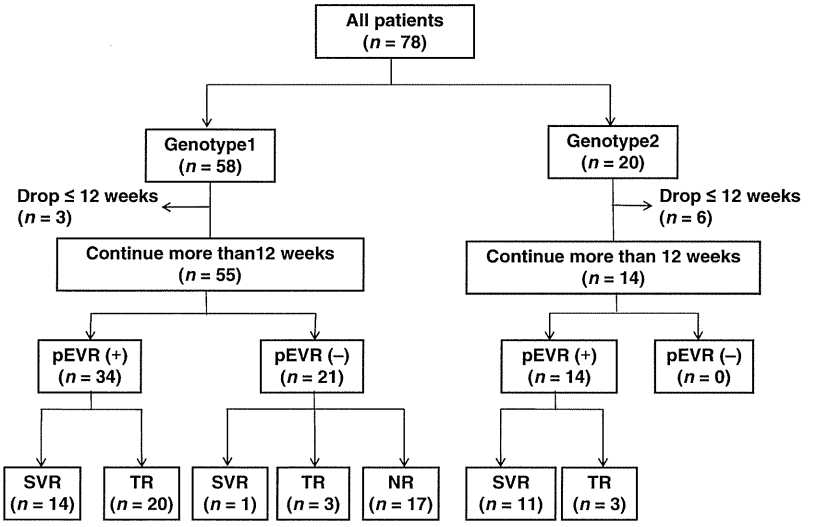

Fig. 1 Flow diagram showing the course of Peg-related interferon plus ribavirin therapy after curative treatment for hepatitis C virus (HCV)-related hepatocellular carcinoma. According to HCV genotype, 78 patients treated with pegylated interferon-alpha plus ribavirin combination therapy were divided into three groups, namely the sustained virological response, transient response and null response. *n*, number of patients.

throat (n = 1), vomiting (n = 1), itching (n = 1), pulmonary haemorrhage (n = 1), jumpiness (n = 1), sarcoidosis (n = 1)] within 48 weeks. Thus, PEGIFN and RBV treatment could be achieved in 55% (32/58) of the patients. Furthermore, 95% (55/58) of the patients continued the treatment for more than 12 weeks. Among 55 patients, 34 achieved pEVR, including 21 patients achieved cEVR, 14 achieved SVR and 20 showed TR. In the other 21 patients who did not achieve pEVR, one patient achieved SVR and three patients showed TR while 17 patients showed NR. Thus, the SVR rate was 25.8% (15/58) for patients infected with HCV genotype 1.

Among the 20 patients infected with genotype 2, 6 discontinued treatment because of side effects [general fatigue (n = 3), thrombocytopenia (n = 1), diabetes mellitus (n = 1), bleeding from oesophageal varices (n = 1)] within 12 weeks. The remaining 14 (70%) patients completed the treatment protocol. All 14 patients achieved pEVR, including 11 who showed SVR and three achieved TR. Thus, the SVR rate was 55.0% (11/20) for patients infected with genotype 2 (Fig. 1).

Relationship between IL-28B and viral response in patients infected with hepatitis C virus genotype 1

In patients infected with HCV genotype 1, number of patients with TT genotype of IL-28B was 44 (TT group) and GG+TG was 14 (GG+TG group). The SVR rate of the TT group [34.3% (n = 14/41)] was higher than that of the TG+GG group [7% (n = 1/14), P = 0.08, Fig. 2A]. The pEVR rate of TT group [73.1% (n = 30/41)] was also significantly higher than that of the TG+GG group [28.5% (n = 4/14), P = 0.009, Fig. 2B]. The NR rate of the TT group [19.5% (n = 8/41)] was significantly lower than that of the TG+GG group [64.2% (n = 9/14), P = 0.005, Fig. 2C].

Determinants of sustained viral response in patients infected with hepatitis C virus genotype 1

Next, we analysed the factors that determine SVR using data of 55 patients infected with HCV genotype 1 who continued PEGIFN/RBV therapy for more than 12 weeks (Table 2). Univariate analysis identified five parameters that correlated with SVR: pEVR (P = 0.004), viral load (<6.0 g/dL; P = 0.008), completion of therapy (P = 0.06), IL-28B genotype (TT genotype; P = 0.08) and gender (man; P = 0.043). Multivariate analysis identified pEVR as the only significant and independent factor that influenced the SVR: (odds ratio, 14.73, 95%CI 1.7–123.2, P = 0.013).

Determinants of partial early viral response in patients infected with hepatitis C virus genotype 1

Next, we analysed the factors that determine pEVR using data of 55 patients infected with HCV genotype 1 who continued PEGIFN/RBV treatment for >12 weeks. Univariate analysis identified three parameters that correlated with pEVR: IL-28B genotype (TT genotype; P = 0.009), gender (man; P = 0.005) and viral load (<6.0 g/dL; P = 0.068) (Table 3). Multivariate analysis identified two parameters that independently influenced the pEVR: gender (male; odds ratio 8.72, 95%CI 2.1–41.6, P = 0.001) and IL-28B genotype (TT genotype; odds ratio 7.93, 95%CI 1.7–36.0, P = 0.007, Table 4). Mutations of aa 70 and aa 91 in the core region of the HCV protein and fewer mutations in its ISDR region were not significantly different between the pEVR and non-pEVR groups among patients infected with HCV genotype 1b in our study.

Determinants of null response in patients infected with hepatitis C virus genotype 1

Next, we analysed the factors that determine the NR in patients infected with HCV genotype 1 (n = 55). Univariate

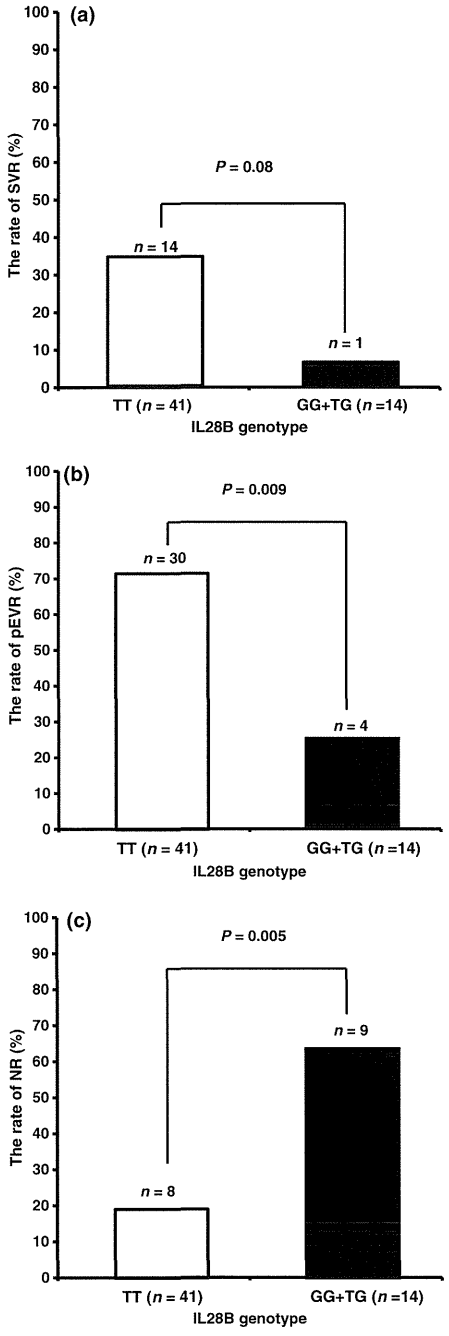

Fig. 2 Relationship between IL-28B and viral response in patients infected with hepatitis C virus genotype 1. (a) Sustained viral response rate, (b) Partial early viral response rate, (c) null response rate.

analysis identified three parameters that influenced NR: IL-28B genotype (genotype; GG+TG, $P = 0.005$), AFP (>30 ng/dL; $P = 0.054$) and gender (male; $P = 0.022$) (Table 5). Multivariate analysis identified two parameters that independently influenced the NR: IL-28B genotype (genotype GG+TG; odds ratio 7.8, 95%CI 1.81–34.4, $P = 0.006$) and AFP (>30; odds ratio 5.6, 95%CI1.40–22.8, $P = 0.015$) (Table 6). Mutations of aa 70 and aa 91 in the core region of the HCV protein and fewer mutations in its ISDR region were not significantly different between the NR and SVR+TR groups among patients infected with HCV genotype 1b.

Survival rates

The overall survival rate was significant different between patients of the SVR and non-SVR groups ($P = 0.034$). The survival rate of the SVR groups was 100% at 1 year, 100% at 3 years and 100% at 5 years. In contrast, the rates of the non-SVR group were 100%, 96% and 74%, respectively (Fig. 3).

Comparison of the first and second recurrence rates of hepatocellular carcinoma

Finally, we compared the overall cumulative rates of the first and second recurrence of HCC between the SVR and non-SVR groups (Fig. 4). The 1-, 3- and 5-year rates of the first recurrence of HCC in the SVR and non-SVR group were not different (0% *vs* 6.7%, 38.1% *vs* 37% and 48% *vs* 68%, respectively, Fig. 4A, $P = 0.41$). The 1-, 3- and 5-year rates of the second recurrence in the SVR and non-SVR groups were 0% *vs* 0%, 41% *vs* 64% and 48% *vs* 78%, respectively (Fig. 4(B), $P = 0.054$). These results demonstrated that patients of the SVR group tended to have a better chance of escaping a second HCC recurrence compared with those of the non-SVR group.

DISCUSSION

Several recent studies have reported that IFN therapy can prevent HCC recurrence and improve survival, especially in patients with SVR, even when administered after curative treatment for HCV-related HCC [10–21,31,39]. While there are a few reports of the use of PEGIFN/RBV after curative treatment for HCV-related HCC [30,31], none have discussed the SVR rate and the factors that determine the viral response to PEGIFN/RBV in such patients. In the present study, we reported the viral response and determinants (specially SNPs) of viral response with PEGIFN/RBV after treatment of HCC.

In our study, the SVR rate was 33.3% (26/78) for all patients, while that for patients with genotype 1 was 25.8% (15/58) and genotype 2 was 55.0% (11/20). These SVR rates are lower than that of patients with chronic hepatitis. The lower rate in the present study was probably because of the low number of patients who completed the therapy. The reason for the latter was the relatively high rate of HCC recurrence [53% (17/32)].

One of the major reasons of the low SVR rate was probably of discontinuation of therapy because of HCC recurrence.

Table 2 Univariate analysis of factors associated with SVR in 55 patients with genotype 1 continued PEGIFN/RBV >12 weeks

	SVR (n = 15)	TR+NR (n = 40)	P
Gender (male/female)	1/14	25/15	0.043
Age (years)*	65 (54–74)	65 (53–83)	0.94
Body mass index (kg/m^2)*	21.2 (18.4–28.5)	23.0 (18.7–40.1)	0.174
White blood Cell ($\times 10^3/\mu$L)*	5050 (4390–6130)	4280 (2470–6660)	0.8
Haemoglobin (g/dL)*	13.7 (11.2–14.8)	13.4 (9.3–18.1)	0.96
Platelet count ($\times 10^4$/mm^3)*	12.5 (3.9–19.6)	10.0 (4.7–20.8)	0.138
T-bilirubin (mg/dL)*	0.7 (0.4–1.8)	0.7 (0.2–1.7)	0.58
Alanine aminotransferase (IU/L)*	33 (12–189)	45 (17–166)	0.25
Prothrombin time activity (%)*	88 (80–106)	86 (64–121)	0.49
Albumin (g/dL)*	4.1 (3.7–4.9)	4.0 (2.7–4.9)	0.52
Fibrosis stage (F1-3/F4/ND)	2/2/11	10/15/15	1.0
γ-glutamyl transpeptidase (IU/L)	43 (12–87)	46 (15–294)	1.2
HbA1c (%)	5.1 (4.2–10.2)	5.4 (3.9–10.8)	0.41
Indocyanine green retention rate (%)	17.7 (7.5–37.8)	17.4 (3.5–45.4)	0.92
HCV viral load (Log IU/mL)	5.59 (4.3–7.1)	6.23 (1.2–7.2)	0.08
HCV Core70(mutant/wild)	8/7	23/17	1.0
HCV Core91 (mutant/wild)	5/10	21/19	0.23
HCV ISDR (0–1/>2)	9/6	26/14	0.75
α-Fetoprotein (ng/mL)*	6.9 (5–286.8)	19.7 (5–63240)	0.11
IL28B genotype (TT/GG+TG)	14/1	27/13	0.08
pEVR (yes/no)	14/1	20/20	0.004
Dose of PEGIFN at administration (μg/kg)*	80 (40–100)	80 (50–120)	0.74
Dose of RBV at administration(mg)*	600 (200–800)	600 (200–1000)	0.26
Therapy were completed (yes/no)	12/3	20/20	0.06

ND, not done; HCV, hepatitis C virus; ISDR, interferon sensitivity-determining region; NR, null response; PEGIFN/RBV, pegylated interferon-alpha plus ribavirin combination therapy; pEVR, partial early viral response; SVR, sustained viral response; TR, Transient viral response. *Data are median and (range).

Alternatively, the low rate could be because of a high proportion of patients with advanced liver fibrosis. In fact, 19 (11.5%) patients were classified as F4 stage, and the median of platelet count was 11.1×10^4/mm^3. These reasons may explain the low IFN therapy continuation rate (55.2%) and the low SVR rate.

We analysed the factors that affect SVR in 55 patients infected with HCV genotype 1 who were able to continue therapy for more than 12 weeks. Multivariate analysis identified a single parameter that independently influenced the SVR: pEVR. Among the 55 patients, 34 (61.8%) achieved pEVR. Among the pEVR group, 14 (41.1%) patients achieved SVR. Recent studies reported the importance of the response guide-based therapy in the treatment of chronic hepatitis; i.e. 70–80% of patients of the cEVR group achieved SVR [40–43].

On the other hand, gender (male) and IL-28B genotype (TT) were identified as significant and independent predictors of pEVR. These factors are probably also significant and independent predictors of SVR in patients with chronic hepatitis C.

Thus, male patients with IL-28B genotype TT were more likely to achieve pEVR even when PEGIFN/RBV treatment was introduced after curative treatment for HCV-related HCC.

Evidence suggests that the SVR rate could be improved by IFN therapy (long-term low-dose IFN of 72 weeks instead of 48 weeks). In fact, Pearlman *et al.* [43] reported that the SVR rate was superior in patients treated for 72 *vs* 48 weeks (38% *vs* 18%, respectively; P = 0.026) in the pEVR groups. Furthermore, the SVR rate could be improved by combination therapy for HCC and HCV. For example, to achieve SVR, it might be better to restart PEGIFN/RBV therapy immediately after curative treatment of HCC.

On the other hand, multivariate analysis identified IL-28B genotype (GG+TG) as an independent parameter that influenced the NR. In this group, it is better to select low-dose intermittent IFN therapy than PEGIFN/RBV based on the SVR. In fact, it is reported that low-dose intermittent IFN therapy after hepatectomy for HCC improved liver function of patients with HCV-related HCC, and the preservation of hepatic function increased the chance of successful treatment against recurrence [10]. In contrast, mutations of aa 70 and aa 91 in the core region of the HCV protein and fewer mutations in its ISDR region were not significant and independent predictors of pEVR and NR.

Table 3 Univariate analysis of factors associated with pEVR in 55 patients with genotype 1 continued PEGIFN/RBV >12 weeks

	pEVR (n = 34)	non-pEVR (n = 21)	P
Gender (male/female)	29/5	10/11	0.005
Age (years)*	67 (54–83)	63 (53–72)	0.977
Body mass index (kg/m^2)*	23.6 (18.7–40.1)	22.2 (18.4–30.0)	0.151
White blood Cell ($\times 10^3/\mu$L)*	5150 (4390–6660)	3610 (2470–4930)	0.8
Haemoglobin (g/dL)*	13.8 (10.2–18.1)	12.3 (9.3–17.4)	0.745
Platelet count ($\times 10^4$/mm^3)*	11.1 (3.9–20.8)	10.0 (4.7–18.2)	0.126
T-bilirubin (mg/dL)*	0.7 (0.2–1.8)	0.7 (0.5–1.7)	0.53
Alanine aminotransferase (IU/L)*	44 (17–189)	37 (12–134)	0.319
Prothrombin time activity (%)	88 (68–114)	85 (64–121)	0.41
Albumin (g/dL)*	4.0 (3.4–4.9)	4.0 (2.7–4.9)	0.405
Fibrosis stage (F1-3/F4/ND)	8/8/18	9/4/8	0.43
γ-glutamyl transpeptidase (IU/L)	52 (12–219)	26 (15–294)	0.172
HbA1c (%)	5.5 (4.2–8.8)	5.0 (3.9–10.8)	0.49
Indocyanine green retention rate (%)	17.4 (3.5–37.8)	18.7 (7.6–45.4)	0.92
HCV viral load (Log IU/mL)	6.04 (4.3–7.2)	6.23 (1.2–6.7)	0.068
HCV Core70(mutant/wild)	19/15	13/8	0.78
HCV Core91 (mutant/wild)	13/21	13/8	0.17
HCV ISDR (0–1/>2)	19/15	14/7	0.24
α-Fetoprotein (ng/mL)*	9.1 (5.0–909.2)	42.0 (5.0–63240)	0.116
IL28B genotype (TT/GG+TG)	30/4	11/10	0.009
Dose of PEGIFN at administration (μg/kg)*	80 (40–120)	80 (50–100)	0.689
Dose of RBV at administration (mg)*	600 (200–1000)	600 (200–800)	0.20
Therapy were completed (yes/no)	21/13	11/10	0.4

HCV, hepatitis C virus; PEGIFN/RBV, pegylated interferon-alpha plus ribavirin combination therapy; pEVR, partial early viral response. *Data are median and (range).

Table 4 Multivariate analysis of factors associated with pEVR

Factor	Category	Odds ratio (95%CI)	P
Gender	Female	1	0.001
	Male	8.72 (2.1–41.6)	
IL28B genotype	GG+TG	1	0.007
	TT	7.93 (1.7–36.0)	

pEVR, partial early viral response.

Achieving SVR by PEGIFN/RBV treatment, even when administered after curative treatment for HCV-related HCC, could prevent HCC recurrence and improve survival. Although achieving SVR had no impact on the occurrence of HCC at the initial site, patients of the SVR group tended to show a lower rate of second HCC recurrence in this and another study [31]. It was reported that IFN therapy had no impact on the occurrence of HCC shortly after IFN therapy was started. It was speculated that IFN therapy does not suppress latent HCC. In our study, although the first recurrence rate of HCC was similar between patients with and without SVR, the second HCC recurrence rate tended to be lower in patients with SVR than in those without SVR (P = 0.054). Therefore, efforts should be directed to achieve SVR by PEGIFN/RBV therapy after curative treatment of HCV-related HCC, whenever possible. Importantly, the SVR rate for PEGIFN/RBV combination therapy was better than that for IFN monotherapy. On the other hand, the high rate of incomplete PEGIFN/RBV therapy (44.8%) was one of the causes of the high HCC recurrence rate and the advanced liver fibrosis. Our study identified factors that affect the viral response to PEGIFN/RBV therapy, and the identification of these factors should help in the selection of patients who will best benefit from such therapy.

On the other hand, the SVR rate was 55.0% (11/20) in patients infected with HCV genotype 2. Although the sample size was small, 78.5% (11/14) patients who showed pEVR achieved SVR. Therefore, continuation of treatment is likely to result in achievement of SVR even when PEGIFN/RBV treatment is started after curative treatment for HCV-related HCC. Efforts should be made to achieve SVR by PEGIFN/RBV therapy in patients infected with HCV genotype 2 after curative treatment for HCV-related HCC. Recently, the relationship between IL-28B and the effect of PEGIFN/RBV

Table 5 Univariate analysis of factors associated with NR in 55 patients with genotype 1 continued PEGIFN/RBV >12 weeks

	NR (n = 17)	TR+SVR (n = 38)	P value
Gender (male/female)	8/9	31/7	0.022
Age (years)*	66 (53–83)	67 (48–80)	0.75
Body mass index (kg/m^2)*	22.2 (19.3–30.0)	21.2 (15.6–28.5)	0.86
White blood Cell ($\times 10^3/\mu$L)*	5050 (4390–6130)	4280 (2470–6660)	0.6
Haemoglobin (g/dL)*	12.6 (9.3–17.4)	13.7 (8.7–15)	0.66
Platelet count ($\times 10^4$/mm^3)*	10.1 (4.7–18.2)	12.1 (3.9–19.6)	0.43
T-bilirubin (mg/dL)*	0.7 (0.4–1.7)	0.8 (0.4–2.3)	0.45
Alanine aminotransferase (IU/L)*	45 (19–134)	45 (12–189)	0.75
Prothrombin time activity (%)*	86 (64–121)	88 (69–112)	0.79
Albumin (g/dL)*	3.8 (2.7–4.9)	4 (3.4–5.2)	0.106
Fibrosing stage(F1-3/F4/ND)	3/8/6	9/9/20	0.21
γ-glutamyl transpeptidase (IU/L)*	52 (12–219)	26 (15–294)	0.113
HbA1c (%)*	5.3 (4–10.8)	5.2 (4.2–8.8)	0.99
Indocyanine green retention rate (%)	18.7 (7.6–45.4)	15.4 (8–29.2)	0.21
HCV viral load (Log IU/mL)*	6.28 (2.1–6.7)	6.18 (1.2–6.7)	0.25
HCV Core70 (mutant/wild)	11/6	20/18	0.55
HCV Core91 (mutant/wild)	10/7	16/22	0.38
HCV ISDR (0–1/>2)	12/5	21/17	0.23
α-Fetoprotein (ng/mL)*	45.3 (5–63240)	10 (0.5–909.2)	0.054
IL28B genotype (TT/GG+TG)	8/9	33/5	0.005
Dose of PEGIFN at administration (μg/kg)*	80 (40–120)	80 (50–100)	0.34
Dose of RBV at administration (mg)*	600 (200–1000)	600 (200–800)	0.77
Therapy were completed (yes/no)	9/8	23/15	0.76

HCV, hepatitis C virus; ISDR, interferon sensitivity-determining region; NR, null response; PEGIFN/RBV, pegylated interferon-alpha plus ribavirin combination therapy; SVR, sustained viral response; TR, Transient viral response. *Data are median and (range).

Table 6 Multivariate analysis of factors associated with NR

Factor	Category	Odds rate (95%CI)	P value
IL28B genotype	TT	1	0.006
	GG+TG	7.8 (1.81–34.4)	
AFP	<30	1	0.015
	>30	5.6 (1.40–22.8)	

AFP, α-fetoprotein; NR, null response.

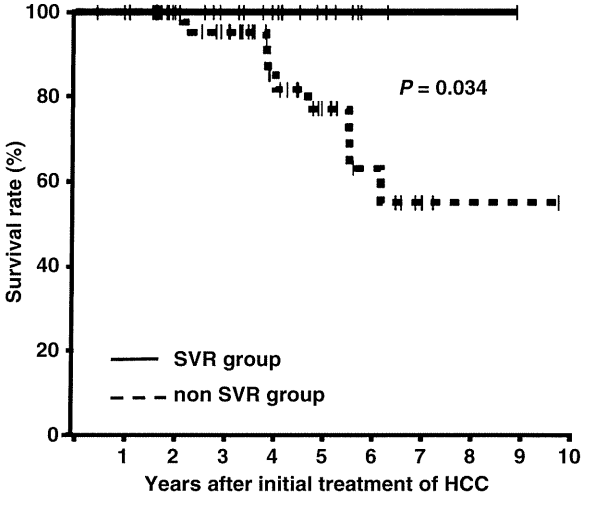

Fig. 3 Comparison of cumulative survival rates in the sustained viral response (SVR) and non-SVR groups. The cumulative survival rate was significantly higher in the SVR group than in the non-SVR group (P = 0.034).

therapy in patients with HCV genotype 2 was reported in two independent studies [28,29]. Further studies of larger sample size are needed to confirm the relationship between IL-28B genotype and the viral response to PEGIFN/RBV after treatment of HCV-related HCC in patients infected with HCV genotype 2.

Our results suggest that IL-28B genotype could be potentially used as a marker for the viral response to PEGIFN/RBV therapy. Furthermore, PEGIFN/RBV therapy should be recommended after curative treatment for HCV-related HCC for patients who are likely to achieve pEVR [those with IL-28B genotype (TT)]. In addition, the SVR rate might improve by IFN therapy and combination therapy HCC and HCV. On the other hand, it might be better to

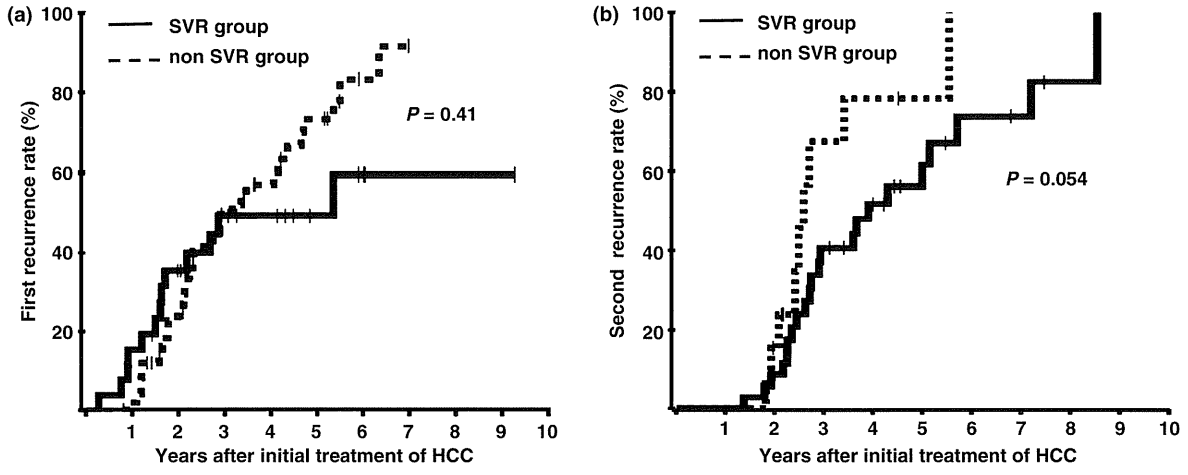

Fig. 4 Cumulative recurrence rates after curative treatment of hepatocellular carcinoma. (a) Rates of first recurrence for the sustained viral response (SVR) and non-SVR groups ($P = 0.41$). (b) Rates of second recurrence for the SVR and non-SVR groups. The second recurrence rate for the SVR group tended to be lower than that for the non-SVR group ($P = 0.054$).

administer low-dose intermittent IFN therapy for patients considered to show NR [those with IL-28B genotype (GG+TG)]. This therapy might result in the improvement of liver function and prevention of HCC recurrence, even if not to obtain SVR.

In conclusion, with regard to the prognosis of patients who undergo curative treatment for HCC, it is desirable to achieve SVR with interferon therapy even after treatment of HCC. IL-28B genotype could potentially be a suitable marker for the response to PEGIFN/RBV combination therapy after treatment of HCV-related HCC.

DISCLOSURES

The authors declare no conflict of interest.

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Liver: Nonanatomical Resection

21

Fumihiko Fujita, Susumu Eguchi, Yoshitsugu Tajima, and Takashi Kanematsu

21.1 Introduction

The first laparoscopic procedure, a laparoscopic cholecystectomy (LC), was initially performed in Europe in the mid-1980s [1, 2]. More complex procedures, like laparoscopic liver surgery, have developed more slowly in the years thereafter. The first laparoscopic hepatectomy was initially performed for benign liver disease in 1991; however, this procedure has been slow to gain acceptance for malignant disease processes [3, 4]. Since 1995, several reports of laparoscopic hepatectomies for liver cancer have been published [5, 6]. Laparoscopic liver surgery had been limited initially to tumors located in peripheral segments of the liver [7]. Some authors report using this procedure for successful anatomical lobe resections or living donor hepatectomies for liver transplantation [8–11].

Hepatocellular carcinoma (HCC) and metastatic liver cancer, especially colorectal cancer, are the two most frequent liver malignancies. Both disease processes can be treated with laparoscopic partial hepatectomy depending on their location. Especially for HCC, anatomic resection techniques are recommended in order to prevent dissemination of cancer cells into the portal vein. These techniques should also be applied if laparoscopy is used to perform a hepatectomy [12, 13]. A Glissonean pedicle transection is recommended as well to prevent cancer cells from being disseminated during a hepatectomy. This technique is thought to improve the postoperative survival in patients with HCC [14]. On the other hand, patients with HCC commonly have a history of chronic hepatitis and liver cirrhosis with an incidence of 74.1% and 63.3%, respectively [15]. This contributes not seldom to severe liver cirrhosis or a poor liver reserve in that subset of patients; hence, a partial, nonanatomic hepatectomy may be more suitable for these patients than major liver resections. HCC can be a secondary cause of viral infections, including hepatitis B virus (HBV) or hepatitis C virus (HCV). Unfortunately, if present, these viral infections seem to increase the incidence of recurrence after surgical resection of the liver. Especially in such cases, laparoscopic procedures may be best suited in order to avoid an unnecessary exploratory laparotomy if only a biopsy or a nonanatomical liver resection is planned.

Metastatic disease to the liver from colorectal cancer is a well-accepted indication for liver resection and it has been demonstrated to improve overall patient survival [16]. Laparoscopic partial hepatectomies are accepted indications for the treatment of liver metastasis, but its successful completion very much depended on the location of the tumor. Mala et al. compared the short-term outcome of laparoscopic and conventional liver resections in patients with colorectal liver metastasis and concluded that the laparoscopic procedure was superior to the traditional open approach in terms of shorter hospital stay and reduced postoperative pain [17].

21.2 Non-surgical Therapies for Liver Malignancies

Optimal treatment strategies for patients with advanced and unresectable HCC are still under investigation [18, 19]. The prognosis of patients with

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unresectable disease, multiple intrahepatic metastases, and major portal vein thrombosis is much worse, and most of these patients die within several months [20, 21]. Given this dismal outcome, the development of effective chemotherapeutic agents or targeted molecular therapies is urgent and mandatory. Transarterial embolization (TAE) or transarterial chemoembolization (TACE) are the most used treatment options for patients with unresectable HCC. In addition, if cirrhotic patients have a poorly preserved liver function, hepatic arterial infusion chemotherapy (HAIC) is another modality used [19, 22, 23]. The chemotherapeutic agents used, either individually or in combination, are Cisplatin, 5-Fluorouracil (5-FU), Epirubicin, Doxorubicin, and Mitomycin-C [19]. Of these agents, 5-FU and Cisplatin are the most commonly applied to treat HCC [24]. Several molecular targeted therapies with drugs like Sorafenib are in trial and the results are awaited with much anticipation.

21.3 Minimally Invasive Approach to Liver Malignancies

21.3.1 Microwave Coagulation Therapy (MCT)

This technique has been widely applied for the treatment of malignant liver disease. A monopolar antenna is inserted into the area harboring cancer and induces tissue necrosis by coagulation [25]. Microwave coagulation therapy (MCT) is applicable for small HCC's with a maximum diameter of less than 2 cm. The big advantage of MCT is that it can be repeated several times over the course of the disease [26]. MCT is especially recommended for patients with poor hepatic reserve, and can be performed via either an open or laparoscopic approach [27, 28]. Sadamori et al. analyzed the serum levels of Interleukin-6, cytokine antagonists, and C-reactive protein, which reflect the severity of surgical stress, between patients following laparoscopic and open MCT, and they concluded that laparoscopic MCT could be recommended for patients with poor hepatic reserve when their indocyanine green retention rate at 15 min (ICG R15) is over 30% [26].

21.3.2 Radiofrequency Ablation (RFA)

Radiofrequency ablation (RFA) is often used percutaneously. As a guidance tool either ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) can be used [29]. RFA has specific characteristics which makes it suitable to treat liver malignancies. It is easy to apply, very effective, and can be repeated if necessary [30, 31]. In comparison to MCT, it coagulates the target point more widely. In general, RFA is indicated for tumors with a maximum diameter of less than 3 cm.

21.4 General Aspects in Laparoscopic Hepatectomies

21.4.1 Preoperative Considerations

The absence of coagulopathy and a sufficient hepatic reserve are important prerequisites. The amount of ascites, the serum level of total bilirubin, and the indocyanine green (ICG) clearance test results are important factors to determine the best surgical strategy. Portal vein pressure is also a useful measurement to evaluate the extent of liver cirrhosis and to determine the area of liver to be resected.

21.4.2 Indications for Laparoscopic Hepatectomy

Indications for laparoscopic hepatectomy should be the same as those for open hepatectomy. Tumor location is still one of the major drawbacks to successful completion of laparoscopic hepatectomy. In general, tumors located in lateral segments (Couinaud segments 2 and 3 and 6) and on the surface of the liver are more suitable for a laparoscopic partial hepatectomy because of their easy access [6, 11, 32]. On the other hand, tumors located in the posterior or superior portion of the right lobe are associated with poor visualization and control of bleeding might be difficult. For those tumors, Huang et al. recommended a hand-assisted laparoscopic approach [33].

21.5 Complications in Laparoscopic Liver Surgery

21.5.1 Intraoperative Bleeding

Intraoperative bleeding is one of the major complications associated with laparoscopic major hepatectomies or even smaller wedge resections. Several authors have reported to intermittently apply the Pringle maneuver for vascular control to reduce blood loss especially during the parenchymal part of the transection [34–36]. In the event of a hemorrhage from the parenchyma of the liver, gauze can be placed over the bleeding site for temporary packing. This packing can usually be removed after 10–15 min. If hemostasis cannot be achieved, a suture or clip can be applied, but the surgeon should consider converting to open surgery under those conditions.

21.5.2 Gas Embolism

In order to obtain good visualization, establishing a pneumoperitoneum using carbon dioxide (CO_2) is recommended especially because of the solubility of CO_2. However, laparoscopic liver surgery using CO_2 carries a high risk of inducing gas embolism [37–39]. Although an accidental gas embolism is rare [40, 41], some authors recommend a gasless laparoscopic technique while resecting the hepatic parenchyma [5, 6, 42]. In addition, the elevated intra-abdominal pressure caused by CO_2 insufflation bears not only the risk of air embolism but also significantly decreases portal blood velocity [39]. Careful monitoring for a gas embolism and meticulous dissection of the liver are crucial preventive measures.

21.5.3 Trocar Site Metastasis

The possibility of port-site recurrence remains one of the main controversies in the use of laparoscopic surgery for malignancies [43–46]. Clinical evidence demonstrated the incidence of wound recurrences to be similar between laparoscopic and conventional procedures [35, 44, 47]. Lang et al. also concluded that laparoscopy does not increase the risk of either port-site or peritoneal metastases in patients with HCC [48]. Vittimberga et al. reported that the immune response is better preserved after laparoscopic surgery than compared with an open procedure. This would result in less port site recurrences [49].

21.6 Surgical Technique

21.6.1 Operating Room Setup and Patient Positioning

The patient is placed in supine position, with split-leg technique. The surgeon positions himself between the legs with one assistant on each side of the patient. Two monitors are placed at the head of the table and as close as possible to the surgeon (Fig. 21.1). For lesions in segment 6, the patient is placed in the left lateral decubitus position in order to expose the lateral aspect of the right lobe of the liver.

21.6.2 Trocar Placement

Four, sometimes five trocars are generally used. A set of two 5-mm and three 12-mm trocars, placing the camera trocar slightly supraumbilical, is used for our preferred setup (Fig. 21.2). Pneumoperitoneum using CO_2 is established and abdominal pressure monitored and maintained below 8 mmHg at all times to reduce the risk of gas embolism. An abdominal wall lift technique is sometimes used in order to reduce the risk of gas embolism (Fig. 21.3). We prefer a laparoscope with a flexible tip.

21.6.3 Diagnostic Laparoscopy and Determination of the Dissection Line

The liver is examined under direct visualization in conjunction with intraoperative ultrasound to confirm the number and size of the lesions to resect. It is important

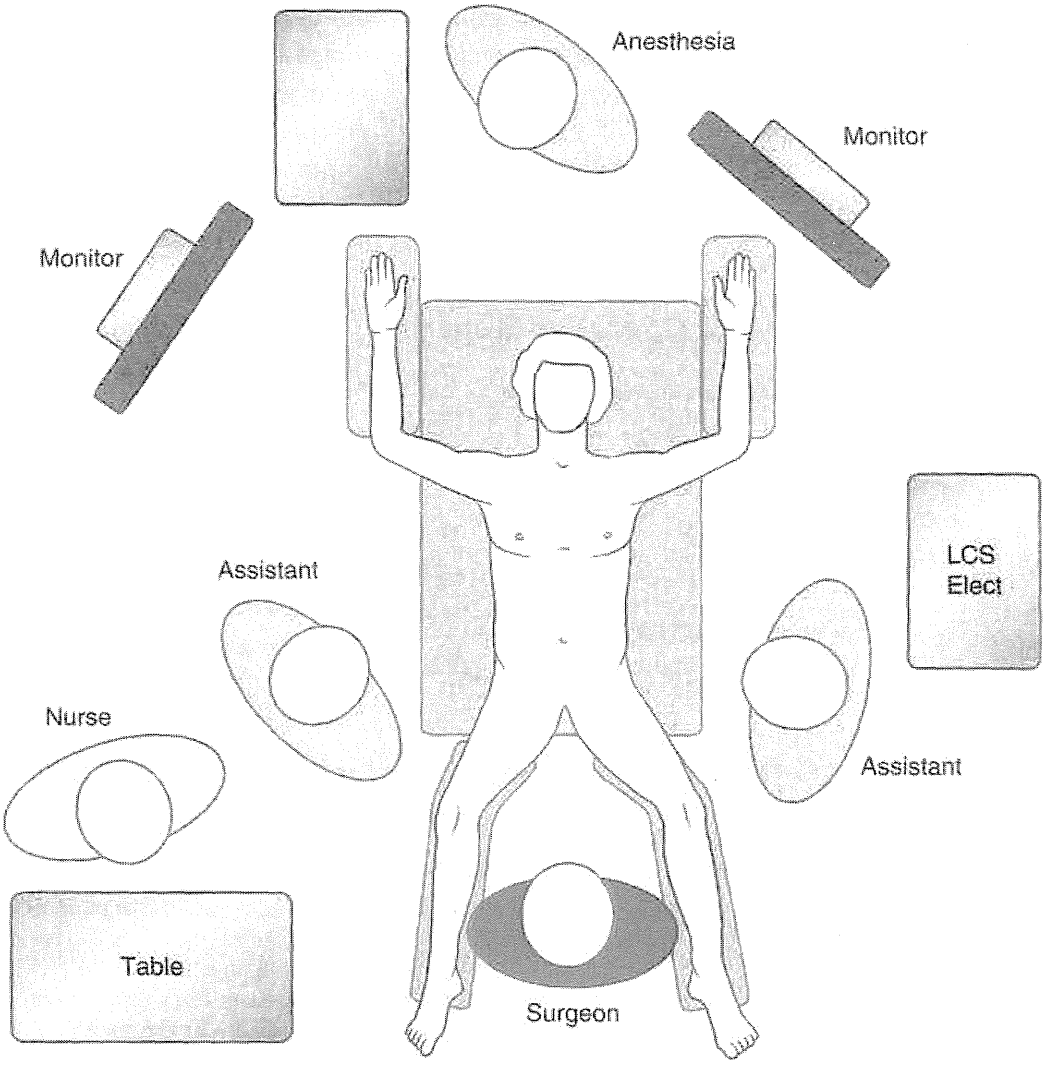

Fig. 21.1 Patient positioning and operating room setup. *Su* surgeon, *As* assistant, *Ns* nurse, *Anes* anesthesiologist. (Drawing by Hippmann GbR, Schwarzenbruck, Germany)

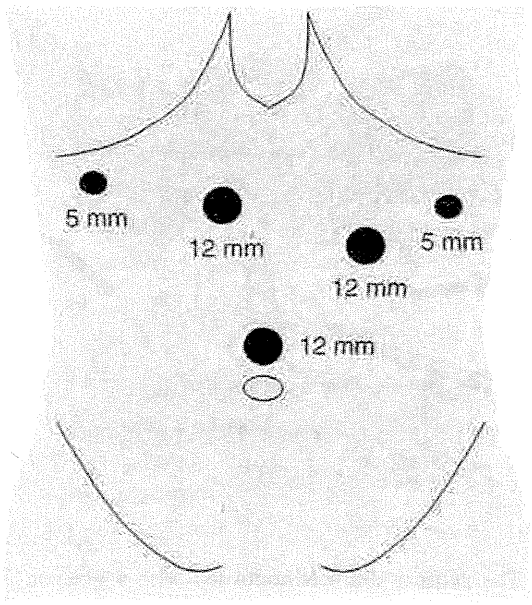

Fig. 21.2 Trocar placement

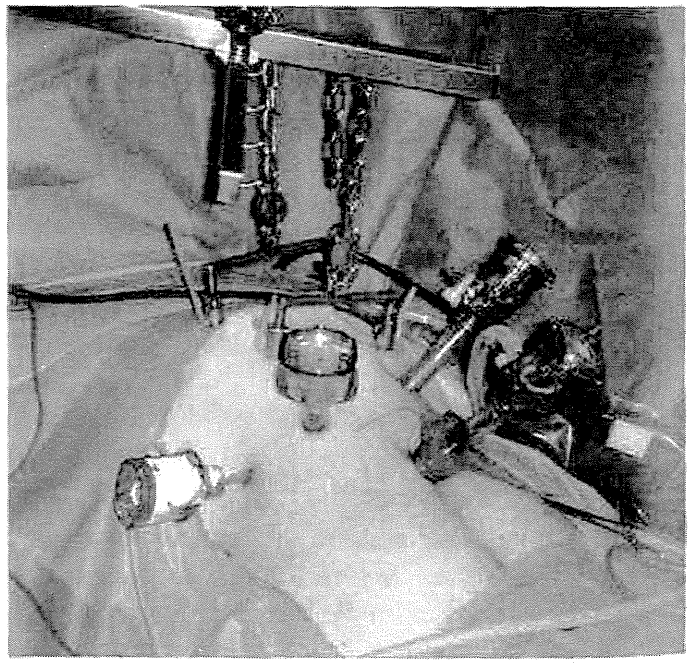

Fig. 21.3 Abdominal wall-lift technique is an alternative to pneumoperitoneum when dissecting the parenchyma of the liver. It is thought to reduce the risk of CO_2 gas embolism

to define their relationship to the intrahepatic vascular structures. In cases where a left lateral segmentectomy or wedge resection is planned, we determine and mark the transecting line on the surface of the liver using intraoperative ultrasound prior to starting the dissection (Fig. 21.4).

21.6.4 Dissection – The Operative Steps

As an initial step, we divide the falciform ligament, and the dissection is then carried on, down to the level of the inferior vena cava. After that, a small hole is made in the coronary ligament, which is located on the extended transecting line. The left triangular ligaments are usually preserved (Fig. 21.5). A penrose drain is inserted into the abdominal cavity and one side of it fixed to the abdominal wall. The other side is passed through the hole in the coronary ligament and positioned behind the posterior surface of the lateral segment of the liver (Fig. 21.6). During the hepatic parenchymal dissection, this penrose drain plays an important role in lifting up the liver and exposing the dissection plane (Figs. 21.7 and 21.8). The preserved

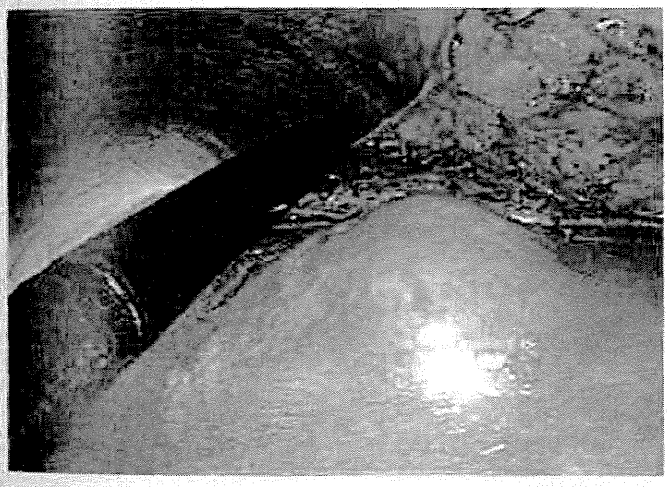

Fig. 21.4 Laparoscopic ultrasound is the key imaging modality to locate the target lesions and to define the dissection line

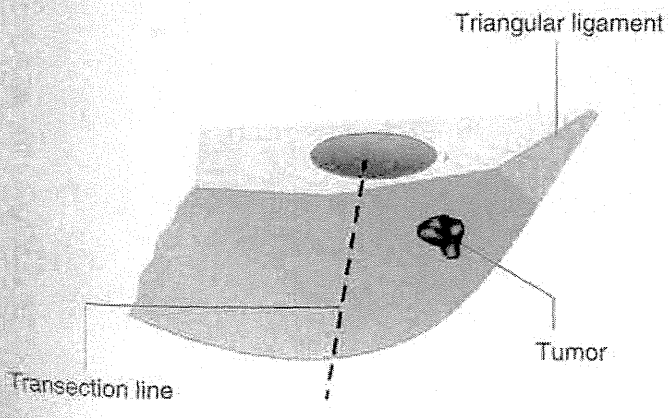

Fig. 21.5 The transection line is determined using intraoperative ultrasound. A hole is made in the coronary ligament that is located on the extended transecting line. This will help for further exposure. (Drawing by Hippmann GbR, Schwarzenbruck, Germany)

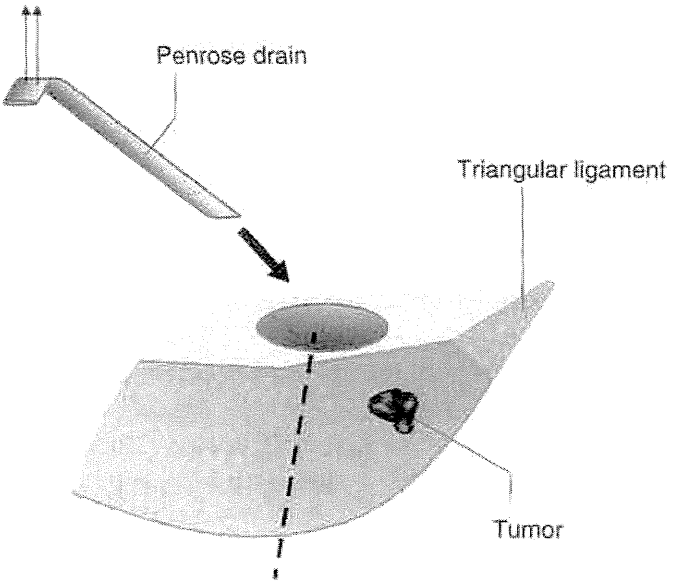

Fig. 21.6 A penrose drain is passed through the divided coronary ligament. One side is fixed to the abdominal wall. The triangular ligament is usually preserved, and helps to prevent the penrose drain from slipping out. (Drawing by Hippmann GbR, Schwarzenbruck, Germany)

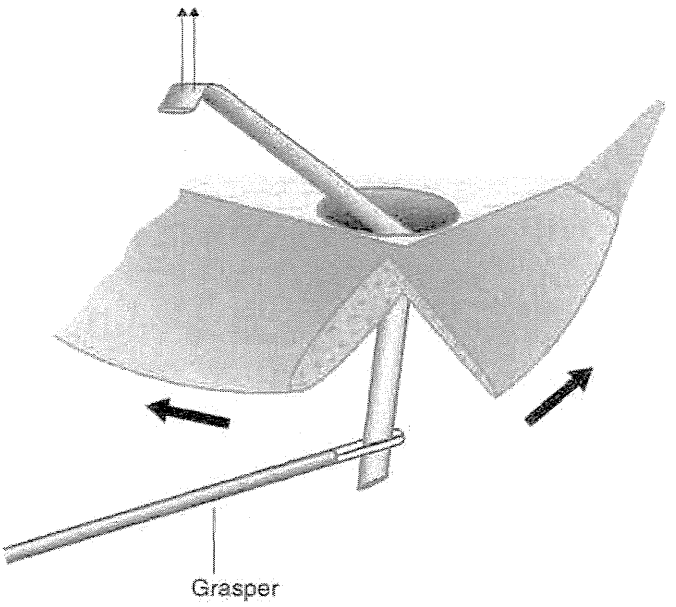

Fig. 21.7 The penrose drain is controled with a grasper. The transecting plane opens up nicely and we obtain great exposure. (Drawing by Hippmann GbR, Schwarzenbruck, Germany)

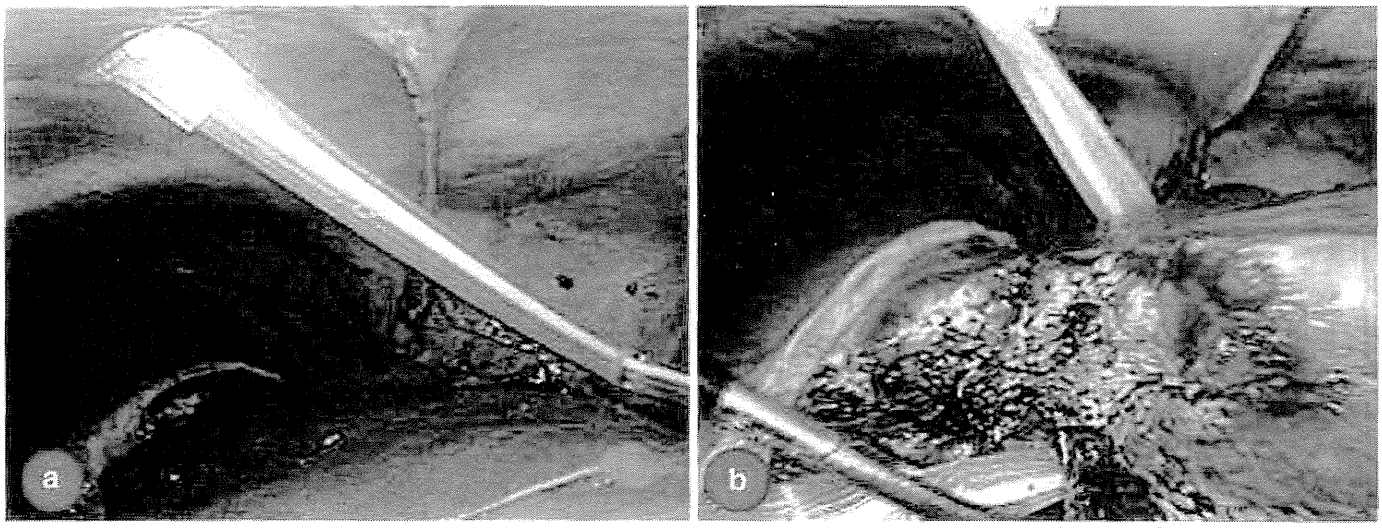

Fig. 21.8 (a) One side of the penrose drain is fixed to the abdominal wall. (b) The penrose drain allows good exposure of the transection plane, contributing to less intraoperative blood loss and safe dissection

left triangular ligaments are useful in preventing the penrose drain from slipping out.

We regularly use the harmonic scalpel (Ultracision; Ethicon Endo-Surgery) to perform the hepatic transection. This is a surgical device utilizing ultrasonic energy to cut and coagulate tissues. This device is sufficient to seal and divide vascular and biliary structures up to 3 mm in diameter. Other larger structures should only be divided after initial clipping. The TissueLink® device, an instrument using monopolar energy, is also used to dissect the parenchyma of the liver. This device provides excellent coagulation and limits bleeding to a great extent [40]. The surface of this radiofrequency device is covered by a continuous flow of saline, to keep the tissue temperature at or below 100°C without producing any char [50]. An important step at this point of the operation is to maintain constant contact with the liver tissue while dissecting the parenchyma. Smaller vessels can be divided safely using the TissueLink device only. Because the TissueLink device has a characteristic mode of action during parenchymal dissection, the vascular and biliary structures are preserved and they are sealed by shrinking the natural collagen in tissue [51] (Fig. 21.9). This sealing is effective for structures up to 3 mm in diameter. Larger structures should be secured with clips before division as we would do when using the harmonic scalpel. Portal pedicles and major hepatic veins are divided by applying a linear stapler using a vascular white load. When dividing the major hepatic veins, make sure that these structures are circumferentially freed off parenchyma in order to safely apply the stapler (Fig. 21.10).

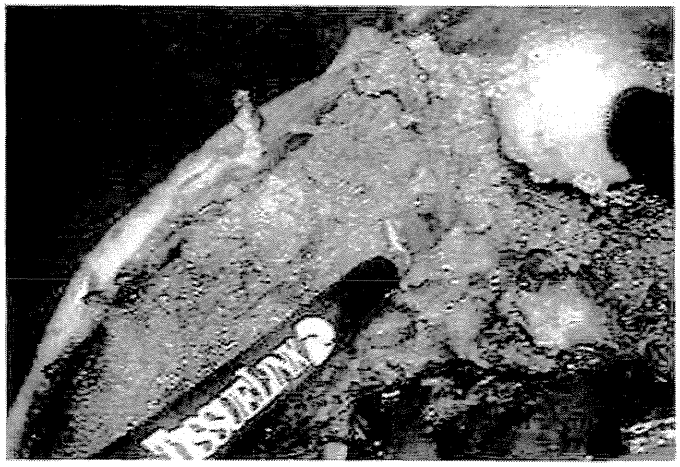

Fig. 21.9 TissueLink™ is used to dissect the parenchyma of the liver. The blunt force applied greatly reduces intraoperative blood loss

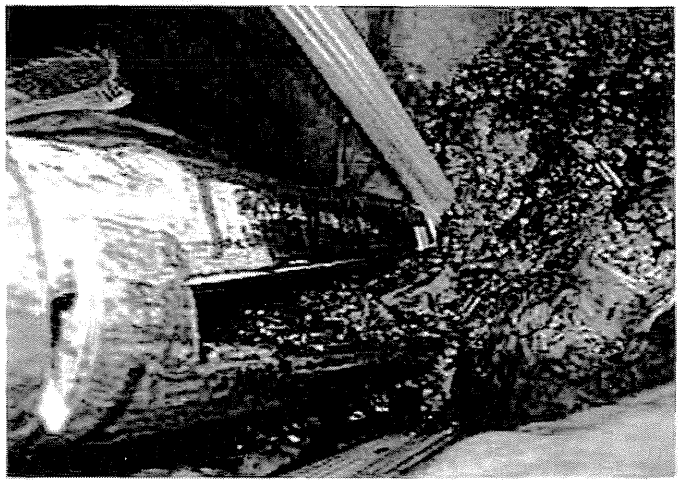

Fig. 21.10 The left hepatic vein is divided with a linear stapler. Make sure that the entire vein is freed off the parenchyma. Blind stapler application may cause major bleeding

21.6.5 Retrieval of the Specimen

The resected specimen is placed in an impermeable retrieval bag and externalized without fragmentation through a separate incision made in the suprapubic region. After retrieval of the specimen, we close this incision immediately and reestablish the pneumoperitoneum. The surgical field is now irrigated and checked for any bleeding or bile leakage. Residual fluid is removed by suction.

21.7 Hand-assisted Technique (HALS)

Hand-assisted laparoscopic surgery (HALS) can overcome some disadvantages associated with a total laparoscopic approach. In 2000, Fong et al. reported preliminary results using HALS for liver resections [36]. Recently, more authors reported the advantages of a HALS approach to the liver [10, 33, 34, 52, 53]. The benefits of HALS are mainly in facilitating manual retraction, in assessing safe resection margins using tactile feedback, and safe parenchymal dissection [10, 34]. The assisting hand can be used for blunt dissection, and to place stapling devices more precisely [34]. Cushieri et al. reported shorter operative times using HALS [52]. The most important advantage seems to be superior control of bleeding, because the fingers can be used to grasp the bleeding vessels immediately. HALS may be converted to an open procedure more easily, whenever it becomes necessary. In this case, we are able to extend the incision for the hand port to a full laparotomy incision much faster. Although HALS usually requires a larger incision of 6–8 cm when compared to a totally laparoscopic procedure, this wide incision will be used to deliver the specimen.

21.8 Future Trends

Will laparoscopic liver surgery become the "gold standard" for all types of liver procedures?

Laparoscopic techniques will probably take the place of open techniques with regard to wedge resections and segmentectomies for focal lesions. Most hepatobiliary surgeons already accept laparoscopic partial hepatectomies for benign liver tumors in various locations. However, for malignant disorders, many surgeons may choose a laparoscopic approach only for tumors located in peripheral segments. In cases, where the extent of the resection is bigger than just a wedge or one segment, an open approach may be chosen in many surgical departments because of safety concerns or out of technical reasons. Recent advancements in technology have made laparoscopic liver surgery safer. New instruments such as TissueLink™ or harmonic scalpel can reduce the amount of intraoperative blood loss. Laparoscopic liver surgery for major hepatectomies may be easily accepted by many surgeons in the near future as technology evolves and surgeons acquire advanced skills through specialized training. Laparoscopic procedures for malignant lesions should only be performed by surgical experts and the same oncological rules should apply when compared to an open resection.

Quick Reference Guide

1. Patient positioning and port placement are dependend on tumor location.
2. Maintain intra-abdominal pressure as low as possible while still achieving adequate visualization. A pressure of less than 8 mmHg should be used to reduce the risk of gas embolism.
3. Laparoscopic ultrasonography is useful to confirm the location of the tumor and to determine the dissection line.
4. Stitches placed on both sides of the dissection line can help to provide good counter traction while dissecting the parenchyma of the liver.
5. Appropriate devices should be selected to dissect the parenchyma of the liver. This can greatly reduce intraoperative blood loss.
6. The harmonic scalpel is used to incise the capsule of the liver and to seal vessels or intrahepatic bile ducts up to 3 mm in diameter. The TissueLink® device is used to dissect the parenchyma of the liver
7. Vessels or intrahepatic bile ducts more than 3 mm in diameter should be clipped before they are divided.
8. If bleeding occurs from the cut edge of the liver, immediate packing with gauze should be the

first choice. Thereafter, clips or stitches should be applied.

9. It is necessary to obtain great visualization when approaching the hepatic vein. If a linear cutting stapler is used to divide the hepatic vein, the surrounding parenchyma should be dissected carefully before firing the device.
10. Upon completion of the operation, confirm that there is no bleeding or bile leakage at the cut surface.

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J Hepatobiliary Pancreat Sci (2011) 18:170–175
DOI 10.1007/s00534-010-0322-0

ORIGINAL ARTICLE

Technical refinements of bile duct division in living donor liver surgery

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Published online: 31 August 2010

Abstract
Background/purpose In spite of the great risk involved, the donor bile duct division procedure has not been thoroughly addressed in the literature. The purpose of this study is to show the appropriate approach to bile duct division in living donor hepatectomy.
Methods Of 87 living donor liver surgeries, we performed bile duct division by marking the cutting point using a small vascular clip under ordinary cholangiography in the first 37 patients, while the current procedure was used in 50 patients by encircling the cutting point using a radiopaque marker filament under real-time C-arm cholangiography.
Results Regarding the procurement of the 51 right lobe grafts, the incidence of multiple bile ducts in the graft was significantly reduced by our novel procedure [20/28 (71%) vs. 7/23 (30%), $P < 0.01$, Fisher's test]. Overall, there were no biliary strictures after surgery in any of the donors, with a median follow-up period of 43 months (range 8–136).
Conclusions Our procedure of bile duct division in living liver donor surgery enabled us to avoid the biliary stricture while cutting the bile duct of the donor with great accuracy.

Keywords Liver transplantation · Living donor · Bile duct

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Introduction

Living donor liver transplantation (LDLT) has been established as an effective modality for the treatment of various end-stage liver diseases. However, compared to deceased donor liver transplantation, more technical and ethical dilemmas exist, primarily because it is difficult to strike a balance between donor safety and recipient benefit. Regarding biliary reconstruction in this context, the recipient requires a large, single bile duct orifice in order to reduce the risk of post-surgical biliary complications [1, 2]. Thus, while it is desirable to cut the bile duct as close as possible to the hepatic hilum during donor surgery, this leads to significant concerns about biliary stricture in the donor. Donor safety should be the top priority in LDLT, and therefore the bile duct must be cut with great caution and according to the most appropriate procedure. In spite of the great risk involved, the donor bile duct division procedure has not been thoroughly addressed in the literature. The aim of this study was therefore to describe our technical refinements to the procedure of bile duct division in living donor liver surgery.

Patients and methods

Patients

Eighty-seven living donor hepatectomies for primary liver transplantation were performed at our institution from August 1997 to April 2008. The living donors consisted of 44 males and 43 females with a median age of 39 (range 19–67). The following types of grafts were procured: 9 left lateral segments, 2 left lobes without the middle hepatic vein (MHV), 8 extended left lobes with the MHV, 12

extended left lobes with the caudate lobe, 51 right lobes without the MHV, and 5 right posterior segments. These cases were divided as follows into two groups according to the treatment period: group A (August 1997 to December 2004, $n = 37$) and group B (January 2005 to April 2008, $n = 50$) (Table 1). Preoperative evaluation of the biliary anatomy was performed by magnetic resonance cholangiopancreatography in both groups. In group A, we adapted a right lobe graft only for adult-to-adult LDLT, but thereafter we used various types of grafts (e.g., left liver grafts and right posterior segment grafts), primarily to enhance donor safety. Moreover, we altered the bile duct division procedure. Initially, we carried out ordinary cholangiography after the cholecystectomy via a catheter that had been placed at the cystic duct, and the bile duct was cut prior to parenchymal transection by marking the cutting point using a small vascular clip (Fig. 1). However, we frequently encountered patients with multiple bile ducts during right lobe graft procurement, such that we adapted the previous procedure to arrive at the current approach to bile duct division, as described below. This procedure was adapted in group B.

Surgical procedure of bile duct division

During hilar dissection, the gall bladder was dissected away from the liver, and the hepatic artery and portal branch were fully exposed and isolated from the hilar plate. Particular attention was paid to retaining the surrounding tissue of the hilar plate without exposing the bile duct; in order to avoid heat injury, electric cautery should not be used at this step. At the final step of the subsequent parenchymal transection, the hilar plate was fully exposed and encircled with a radiopaque marker filament obtained from surgical gauze (Fig. 2a). Real-time cholangiography using C-arm fluoroscopy was then performed via the catheter, which was placed in the cystic duct (Fig. 2b). To verify the optimal point for cutting the bile duct, the radiopaque filament was retracted (Fig. 2c), and the C-arm was rounded to adjust the apparatus to the accurate angle. After confirmation of the accurate cutting point, parenchymal transection was further advanced using a liver hanging-maneuver technique [3] with preservation of the hilar plate. We then interposed the surgery after completion of the liver parenchymal transection. When the surgeon for

Table 1 Characteristics of donor and recipient

	Group A ($n = 37$)	Group B ($n = 50$)	P value
Donor			
Age	39 (21–67)	37 (19–64)	NS
Gender	Male 16, female 21	Male 28, female 22	NS
Graft			
RL	28	23	NS
LL + CL	0	12	<0.01
LL	0	10	<0.01
LLS	9	0	<0.01
RPS	0	5	<0.01
Multiple ducts in RL graft	20/28 (71%)	7/23 (30%)	<0.01
Biliary stricture	0	0	NS
Recipient			
Age	41 (0–65)	57 (11–68)	NS
Gender	Male 20, female 13	Male 32, female 18	NS
Disease			
BA	8	1	<0.01
Viral cirrhosis	11	33	<0.01
With HCC	5	27	
W/o HCC	6	6	
FHF	7	2	<0.01
Others	11	13	NS
Biliary reconstruction			
HJ	13	7	<0.05
DD	24	43	
Biliary stricture	9	8	NS
Follow-up period	79 months (52–136)	24 months (8–48)	<0.01

Statistical analyses were performed with Fisher's test

RL right lobe, *LL* left lobe, *CL* caudate lobe, *LLS* left lateral segment, *RPS* right posterior segment, *BA* biliary atresia, *HCC* hepatocellular carcinoma, *FHF* fulminant hepatic failure, *HJ* hepaticojejunostomy, *DD* duct to duct