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Surgical treatment of hepatocellular carcinoma: Evidence-based outcomes

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Abstract

Surgeons may be severely criticized from the perspective of evidence-based medicine because the majority of surgical publications appear not to be convincing. In the top nine surgical journals in 1996, half of the 175 publications refer to pilot studies lacking a control group, 18% to animal experiments, and only 5% to randomized controlled trials (RCT). There are five levels of clinical evidence: level 1 (randomized controlled trial), level 2 (prospective concurrent cohort study), level 3 (retrospective historical cohort study), level 4 (pre-post study), and level 5 (case report). Recently, a Japanese evidence-based guideline for the surgical treatment of hepatocellular carcinoma (HCC) was made by a committee (Chairman, Professor Makuuchi and five members). We searched the literature using the Medline Dialog System with four keywords: HCC, surgery, English papers, in the last 20 years. A total of 915 publications were identified systematically reviewed. At the first selection (in which surgery-dominant papers were selected), 478 papers survived. In the second selection (clearly concluded papers), 181 papers survived. In the final selection (clinically significant papers), 100 papers survived. The evidence level of the 100 surviving papers is shown here: level-1 papers (13%), level-2 papers (11%), level-3 papers (52%), and level-4 papers (24%); therefore, there were 24% prospective papers and 76% retrospective papers. Here, we present a part of the guideline on the five main surgical issues: indication to operation, operative procedure, peri-operative care, prognostic factor, and post-operative adjuvant therapy.

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Key words: Indication to operation; Hepatocellular

INTRODUCTION

Surgeons may be severely criticized from the perspective of evidence-based medicine because the majority of surgical publications appear not to be convincing^[1]. In the top nine surgical journals in 1996, half of the 175 publications refer to pilot studies lacking a control group, 18% to animal experiments, and only 5% to randomized controlled trials (RCTs).

There are five levels of clinical evidence^[2]: level 1 (randomized controlled trial), level 2 (prospective concurrent cohort study), level 3 (retrospective historical cohort study), level 4 (pre-post study), and level 5 (case report).

Recently, a Japanese evidence-based guideline for the surgical treatment of hepatocellular carcinoma (HCC) was made by a committee (Chairman, Professor Makuuchi and five members). We searched the literature using the Medline Dialog System with four keywords: HCC, surgery, English papers, in the last 20 years. A total of 915 publications were identified and systematically reviewed (Figure 1). At the first selection (in which surgery-dominant papers were selected), 478 papers survived. In the second selection (clearly concluded papers), 181 papers survived. In the final selection (clinically significant papers), 100 papers survived. The evidence level of the 100 surviving papers is shown here: level-1 papers (13%), level-2 papers (11%), level-3 papers (52%), and level-4 papers (24%); therefore, there were 24% prospective papers and 76% retrospective papers.

Here, we present a part of the guideline on the five main surgical issues: indication to operation, operative procedure, peri-operative care, prognostic factor, and post-operative adjuvant therapy.

Figure 1 Selection criteria and proportion of evidence level in surgical treatment of hepatocellular carcinoma. We searched the literature using the Medline Dialog System with four keywords: HCC, surgery, English papers, in the last 20 years. The 915 publications were systematically reviewed by 3 steps. Almost all publications were retrospective (76%), there were only 24 (24%) with a high level evidence.

Figure 2 Algorithm before proceeding to safety hepatectomy for HCC with cirrhotic liver. Makuuchi's criteria include three factors: ascites, total serum bilirubin, and the ICG-R15: indocyanine green 15 min retention rate. This algorithm shows the maximal area for which an operation can be performed safely.

GUIDELINE 1: OPERATIVE INDICATION FOR HCC

Selection criteria in primary HCC

The selection of appropriate candidates for hepatectomy depends on careful assessment of the tumor status and liver function reserve. In order to evaluate tumor status, careful assessment of the liver function reserve is critical in patient selection for hepatectomy to avoid post-operative morbidity and mortality^[3,4]. As selection criteria for operative procedures in patients with HCC and liver cirrhosis, Makuuchi's criteria have been used widely in Japan^[5] (Figure 2). Criteria comprise ascites, total serum bilirubin, and the indocyanine green (ICG) K disappearance rate. In patients without ascites and with total bilirubin of < 2 mg, hepatectomy is indicated. The ICG rate indicates the upper limit of the hepatectomy procedure.

Table 1 The outcome of hepatectomy in major institutions

Author	Criteria	Morbidity (%)	Mortality (%)	5-yr Survival (%)
Blumgart ^[22]	Child	45	4.5	39
Bismuth H ^[7]	Child	40	10.0	48
Belghiti ^[8]	Child	31	6.4	37
Gozzetti ^[9]	Child	36	3.5	43
Bruix ^[10]	Child	-	3.9	51
Fan ^[6]	ICG15	38	2.5	49
Wu CC ^[11]	ICG15	11	2.3	51
Makuuchi ^[7]	ICG15	26	0.0	53

The Child classification is usually used by Western surgeons, while Eastern surgeons rely on the ICG-R15 retention rate to determine the liver function of patients. Operative morbidity rates were similar, but operative mortality rates were lower in the East, and five-year survival rates were higher in the East.

The clinical significance of the ICG clearance test was reported by Lau *et al*^[6]. A prospective study was performed to identify the best test for assessing the adequacy of hepatic functional reserve in patients with HCC before hepatectomy. Each patient was evaluated before operation with regard to the ICG clearance test, the aminopyrine breath test, and the amino acid clearance test. ICG retention at 15 min was significantly associated to whether the patient survived or died.

As shown in Table 1, Eastern surgeons use the Child class and ICG test, while some Western centres rely on liver biochemistry and Child's classification alone to determine the liver function of patients. Operative morbidity rates were similar, but operative mortality rates were lower in the East, and five-year survival rates were higher in the East^[7-11].

In fact, by refining pre-operative and post-operative care and surgical skills, liver resection mortality can be reduced to zero. There were 1056 hepatectomies without operative mortality and less than 3% major postoperative complications in HCC in the last eight years^[12]. Liver resection can be performed without mortality provided that it is carried out in a high-volume centre and the surgeon pays sufficient attention to the liver functional reserve and the volume of liver to be removed. Thus, Makuuchi's criteria and the ICG clearance test are simple and reliable.

Early HCC

Early HCC is a well-differentiated cancer with no substantial destruction of the preexisting hepatic framework^[13]. We performed a prospective study of surgical treatment for stage I HCCs to assess the therapeutic impact of hepatectomy. Stage I HCC was divided into two groups: microscopically early HCCs and others. The rate of microscopic regional spread, the time to recurrence, local recurrence, overall survival, and recurrence-free survival is significantly higher in early HCCs. This study shows that early HCC is a clinical entity with a high rate of surgical cure^[14].

Portal vein tumor thrombus

The presence of portal vein tumor thrombus in a patient with hepatocellular carcinoma is one of the most significant factors for a poor prognosis^[15-18]. In patients with portal vein tumor thrombus (PVTT), the median

Figure 3 Treatment for HCC with portal vein tumor thrombus. Patient survival can be improved by TACE plus hepatectomy, when the number of primary nodules is not greater than two, the portal trunk is not occluded by tumor thrombus, and the indocyanine green retention rate at 15 min is > 20%. Minagawa *et al.* Ann Surg. 2001.

survival was reported to be 2.7 mo, whereas survival in those without PVTT was 24.4 mo. Minagawa *et al.*^[19] reported that hepatic resection followed by pre-operative transarterial chemoembolization (TACE) leads to long-term survival in selected patients (Figure 3). The purpose of pre-operative transcatheter arterial embolization for patients with growth of PVTT is to interrupt the rapid growth of PVTT. They suggest that patient survival can be improved by this combination therapy, when the number of primary nodules is not higher than two, the portal trunk is not occluded by tumor thrombus, and the indocyanine green retention rate at 15 min is > 20%.

Repeat hepatic resection

The cumulative five-year recurrence rates after curative resection for HCC range from 77% to 100% according to the hepatitis virus and the main cause of late death. Some studies have demonstrated that repeat hepatectomy is effective for treating intrahepatic recurrent HCC in selected patients^[20,21]. Using multivariate analysis, the authors showed that repeat hepatic resection is the treatment of choice for patients who have previously undergone resection of a single HCC at primary resection and in whom recurrence developed after a disease-free interval of one year or more and the recurrent tumor had no portal invasion^[22] (Figure 4). For these reasons, repeat resection has been selected as the primary treatment for recurrent HCC under the same indications as for the first hepatectomy.

Transplantation

Liver transplantation is the best option for small HCC in patients presenting with severe deterioration of liver function. Currently, liver transplantation is considered to be the standard treatment for small HCC in patients with cirrhosis or advanced liver disease^[23,24]. Optimal candidates for liver transplantation were identified in the '90 s: patients with single HCC of < 5 cm or with three or less nodules of 3 cm, without extrahepatic or vascular spread^[25]. Liver transplantation eliminates or decreases significantly the risk of developing HCC, and it can prolong the life expectancy of the patient. In Japan,

Figure 4 The result of repeat hepatic resection. Repeat hepatic resection is a satisfactory result in patients previously having undergone resection of a single HCC at primary resection and in whom recurrence developed after a disease-free interval of one year or more and the recurrent tumor had no portal invasion. Minagawa *et al.* Ann Surg. 2003.

the scarcity of donor organs and the waiting time is too long, but living donor-related liver transplantation is rapidly becoming accepted. Moreover, cost-effectiveness analyses have shown that the benefits of living donor liver transplantation are achieved when the waiting time exceeds seven months.

Liver transplantation for HCC of < 5 cm in diameter has been shown to produce favorable survival results, but to extend the patient selection criteria for HCC, further evidence is required.

GUIDELINE 2: OPERATIVE PROCEDURE FOR HCC

Inflow vascular occlusion technique

Minimization of intraoperative blood loss is a widely accepted goal since the amount of blood loss and blood transfusion have been shown to adversely affect patient outcome^[26,27]. Inflow occlusion techniques such as Pringle's maneuver and the hemihepatic vascular occlusion technique have been reported to decrease bleeding during transection of the liver parenchyma without causing damage to the remaining liver, and are widely accepted in conventional hepatectomy^[28].

Makuuchi *et al.* reported that by using the hemihepatic vascular occlusion technique, the amount of blood loss was markedly decreased^[29]. The mean blood loss fell below 1000 mL, and the proportion of non-transfused patients reached 86.9% by 1986. This technique was followed by a prospective study^[30] and RCT^[31]. Man *et al.* evaluated whether vascular inflow occlusion by the Pringle maneuver during hepatectomy is safe and effective in reducing blood loss by RCT^[32]. The findings show a significant effect in less blood loss and better preservation of liver function during liver transection.

Anatomical resection

In 1985, Makuuchi devised "ultrasonically-guided

Figure 5 Anatomical resection in HCC. Overall (A) and disease-free (B) survival in anatomical and non-anatomical resection for single HCC. Both the five-year overall survival and disease-free survival rates in the anatomic resection group were significantly better than those in the non-anatomic resection group. Hasegawa *et al*. Ann Surg. 2003.

systematic segmentectomy,” by which every Couinaud’s segment could be removed completely^[33]. This technique has been widely used around the world and is an essential technique in hepatic resection^[34-40].

Anatomical resection is theoretically effective for eradicating the intrahepatic metastases of HCC with preference for eradicating portal venous tumor extension and intrahepatic metastases. This method is thought to have a beneficial effect on recurrence-free survival after hepatectomy for HCC. In the tumor enucleation group, the five-year survival rate was 35%, and in the segmentectomy group the five-year survival rate was 66% (group difference was significant). The relative risk of death in the segmentectomy group was 0.51, and segmentectomy appears thus to be the better option. The findings are supported by other retrospective studies^[39-41].

Recently, Makuuchi’s group showed that anatomic resection is a reasonable treatment option for HCC^[42]. Both the five-year overall survival and disease-free survival rates in the anatomic resection group were significantly better than those in the non-anatomic resection group (Figure 5). Anatomical resection appeared to have a beneficial effect on recurrence-free survival after hepatectomy for HCC. Thus, systematic anatomical resection is the reasonable option of choice.

GUIDELINE 3: PERI-OPERATIVE CARE FOR HCC

Peri-operative nutritional support

Fan *et al* assessed by RCT whether peri-operative nutritional support improved the outcome in patients undergoing major hepatectomy for HCC associated with cirrhosis^[43]. There was a reduction in the overall post-operative morbidity rate in the peri-operative nutrition group as compared with the control group. The operative morbidity rate was significantly lower in the supporting than in the control group (34% *vs* 55%).

Hemihepatic occlusion technique

Intermittent occlusion of hepatic blood inflow by means of the hemihepatic or total hepatic occlusion technique is essential for reducing operative blood loss, especially in cirrhotic patients^[26-32]. Wu *et al* performed RCT to compare total versus hemihepatic vascular occlusion^[44] (Table 2). There was no difference between the amount of blood loss during liver parenchymal transaction between total and hemihepatic vascular occlusion. However, the blood loss in the declamping period was significantly smaller in the hemihepatic vascular occlusion group due to the difference in operative blood loss and the incidence of blood transfusion. These findings indicate that hemi-hepatic clamping can be recommended for complex central liver resections in cirrhotic patients when the area of transaction is wide.

Blood transfusion

There are frequent recurrences of HCC after resection, especially in patients with cirrhosis. Dr. Yamamoto assessed retrospectively the effect of blood transfusion on HCC recurrence^[45] (Figure 6). Recurrence-free survival was significantly better in the non-transfused than in the transfused group. Multivariate analysis showed that pre-operative blood transfusion was a significant predictor for accelerated recurrence of HCC after hepatectomy ($P = 0.003$). Thus, blood transfusion is avoided as far as possible^[46,47].

Portal vein embolization

Portal vein embolization (PVE) before hepatectomy is intended to induce atrophy of the embolized lobe to be resected, with a compensatory hypertrophy of the counterlobe to be preserved^[48]. To assess whether PVE is clinically useful, we determined the clinical outcome with PVE in 51 HCC patients^[49]. After right lobe PVE, the mean ICG-R15 values rose by 4.3%, and the mean increase of the left lobe was 8%. All patients tolerated PVE well, and hepatic functional data returned to the baseline levels within one week. As a whole, the operative morbidity and mortality rates were the same as in the non-PVE hepatectomy group. The cumulative five-year survival rates were 44% in patients with HCC. PVE is a useful procedure for selected patients who may need extensive hepatectomy for diseased liver.

Table 2 The effect of hemihepatic occlusion in hepatectomy with cirrhotic patients (mean $\pm$ SE)

	Total inflow occlusion group (n = 28)	Hemihepatic occlusion group (n = 30)	P value
Resected liver weight (g)	443.9 $\pm$ 10.7 (150-1670)	422.7 $\pm$ 17.4 (180-1320)	0.29
Overall ischemic time (min)	96.0 $\pm$ 10.9 (62-196)	94.2 $\pm$ 9.9 (64.5-188)	0.28
Liver transection time (min)	86.4 $\pm$ 5.3 (64-171)	84.4 $\pm$ 5.2 (62-174.5)	0.54
Area of liver cut surface (cm ²)	103.1 $\pm$ 8.7 (62-208)	101.2 $\pm$ 6.9 (64-204)	0.86
Overall operative blood loss (mL)	6.82 $\pm$ 0.32 (3.8-11.5)	6.65 $\pm$ 0.26 (3.9-10.8)	0.37
Blood loss during parenchymal transection (mL)	1685 $\pm$ 170 (500-4800)	1159 $\pm$ 221 (400-4200)	0.049
Blood loss in declamping period (mL)	1015 $\pm$ 112 (400-4300)	974 $\pm$ 101 (300-4200)	0.51
Need for blood transfusion (n)	379 $\pm$ 12 (50-890)	179 $\pm$ 18 (50-460)	0.03
	12	5	0.04

Hemihepatic clamping is recommended for complex central liver resections when the area of transection is wide. Wu *et al.* Arch Surg. 2002.

Figure 6 The relation between blood transfusion and recurrence. A close relationship between blood transfusion and recurrence-free survival was shown. Yamamoto *et al.* surgery 1994.

Patients at risk

Treatment	76	63	50	36	23	14	5
Control	74	44	33	24	18	12	5

Time to first recurrence

Figure 7 Prognostic factors in HCC. The eight main prognostic factors (vascular invasion, liver function, the stage of TNM classification, tumor diameter, number of tumor, degree of cirrhosis, Edmondson classification, and pathological type) were identified in twelve major publications. Vascular invasion, pTNM stage, and liver function are the most powerful prognostic factors.

GUIDELINE 4: PROGNOSTIC FACTORS IN HCC

There are many reports on prognostic factors in HCC after hepatectomy. We found 12 publications that focused on prognostic factors in HCC. Shown in Figure 7 are the eight prognostic factors identified: vascular invasion, liver

Figure 8 Adoptive immunotherapy in HCC. Autologous lymphocytes activated in vitro with recombinant interleukin-2 and infused five times during the first month. Adoptive immunotherapy reduces recurrence and improves recurrence-free survival after surgery for HCC. Takayama *et al.* Lancet 2000.

function, pTNM stage, tumor size, number of tumor, degree of cirrhosis, Edmondson's classification, and pathological findings. Vascular invasion was a significant factor in multivariate analysis in ten of twelve publications. Liver function was significant in six publications, tumor stage in five, tumor size and number in four.

Vascular invasion has a high probability in recurrence-free survival, while tumor size is a controversial factor. Three factors, namely vascular invasion, pTNM stage, and liver function are the most powerful prognostic factors.

In a single HCC of < 2 cm in diameter, pathological early HCC showed a lower relative risk of recurrence (0.31) and death (0.26).

GUIDELINE 5: POSTOPERATIVE ADJUVANT THERAPY IN HCC

Resection of hepatocellular carcinoma is potentially curative, but local recurrence is common. In order to reduce the recurrence rate of HCC, effective adjuvant therapy is needed. We found ten publications on RCT in adjuvant therapy^[50-59]. Interventions included transarterial chemoembolization, retinoid therapy, immunotherapy (Figure 8), and interferon treatment^[50-52]. However,

Figure 9 Effects of adjuvant therapy in HCC. Relative risk of recurrence in three RCTs by meta-analysis. The boxes show the relative risk, and the lines indicate 95% CI. A significant relative risk reduction was seen for recurrence (60%, SD 16%). O-E: observed-expected difference by Peto's method. Takayama *et al*. Cancer Reviews 2003.

the sample size was calculated only in three reports^[60] (Figure 9). Eight reports showed positive results, but the quality of these RCTs are different.

Retinoid therapy

Muto *et al* reported that the oral intake of retinoid improves recurrence-free survival^[50]. Cox proportional-hazards analysis demonstrated that, as an independent factor, polyprenoic acid reduced recurrence (relative risk, 0.31; 95% confidence interval, 0.12 to 0.78). Treatment with polyprenoic acid significantly reduced the incidence of recurrence after hepatectomy of the primary HCC as did a percutaneous injection of ethanol.

Intra-arterial ¹³¹I-lipiodol injection

Lau *et al* reported a prospective randomized trial in which they aimed to determine whether one dose of postoperative adjuvant intra-arterial iodine-131-labeled lipiodol reduced the rate of local recurrence and increased disease-free and overall survival^[51]. Patients who underwent curative resection for HCC and recovered within six weeks were given curative resection intra-arterial ¹³¹I-lipiodol treatment. The median disease-free survival in the treatment and control groups was 57.2 (0.4-69.7) and 13.6 (2.1-68.3) mo, respectively ($P = 0.037$). Three-year overall survival in the treatment and control groups was 86.4% and 46.3%, respectively ($P = 0.039$). ¹³¹I-lipiodol had no significant toxic effect, and this treatment decreases the rate of recurrence and increases disease-free and overall survival.

Adoptive immunotherapy

We used adoptive immunotherapy. From an HCC patient, peripheral blood was taken and lymphocytes were cultured in the presence of interleukin-2 for two weeks before assay-activated autologous T-cells were transferred back to the same patient^[52]. Before the start of this RCT, we calculated the sample size of 143 patients to detect 20% improvement of recurrence-free survival at 5% significance and 80% power. After a median follow-up of five years, adoptive immunotherapy improved recurrence-free survival (Figure 8). On multivariate analysis, the relative risk of recurrence was 0.60.

CONCLUSION

Operative procedures are selected by precise pre-operative

evaluation of hepatic functional reserve; thus, we rely on the algorithm (Figure 2) for decision making in surgical treatment. The overall five-year survival after resection of HCC in a high-volume centre is around 50%. However, the disease-free survival after partial hepatectomy is unsatisfactory because of the high incidence of intrahepatic recurrence. As there is no established adjuvant therapy that is proven to be effective in prevention of recurrence, aggressive management of recurrence using various modalities including surgical resection, transarterial chemoembolization, and local ablation is currently the most practical measure in prolonging survival after resection of HCC.

Liver transplantation offers the dual advantages of eradicating the tumor and replacing the diseased liver. This modality has become the treatment of choice, especially for patients with end-stage liver disease, whereby LDLT is a promising treatment for HCC in Japan.

We here presented part of the Japanese guideline, showing that surgery is the primary option of choice for HCC. However, the guideline should be refined using high-level evidence as it becomes available.

REFERENCES

- Horton R. Surgical research or comic opera: questions, but few answers. *Lancet* 1996; **347**: 984-985
- Matsuyama Y. Correcting for non-compliance of repeated binary outcomes in randomized clinical trials: randomized analysis approach. *Stat Med* 2002; **21**: 675-687
- Lai EC, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. *Ann Surg* 1995; **221**: 291-298
- Sitzmann JV, Greene PS. Perioperative predictors of morbidity following hepatic resection for neoplasm. A multivariate analysis of a single surgeon experience with 105 patients. *Ann Surg* 1994; **219**: 13-17
- Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, Kawasaki S. Surgery for small liver cancers. *Semin Surg Oncol* 1993; **9**: 298-304
- Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg* 1997; **84**: 1255-1259
- Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993; **218**: 145-151
- Belghiti J, Di Carlo I, Sauvanet A, Uribe M, Fekete F. A

- ten-year experience with hepatic resection in 338 patients: evolutions in indications and of operative mortality. *Eur J Surg* 1994; **160**: 277-282
- 9 **Gozzetti G**, Mazziotti A, Cavallari A, Bellusci R, Bolondi L, Grigioni W, Grazi GL. Hepatic resection for tumours in cirrhotic livers. *Int Surg* 1987; **72**: 82-86
 - 10 **Llovet JM**, Fuster J, Bruix J. Prognosis of hepatocellular carcinoma. *Hepatogastroenterology* 2002; **49**: 7-11
 - 11 **Wu CC**, Ho WL, Yeh DC, Huang CR, Liu TJ, P'eng FK. Hepatic resection of hepatocellular carcinoma in cirrhotic livers: is it unjustified in impaired liver function? *Surgery* 1996; **120**: 34-39
 - 12 **Imamura H**, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, Takayama T, Makuuchi M. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003; **138**: 1198-206; discussion 1206
 - 13 **Takayama T**, Makuuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takayasu K, Kosuge T, Motoo Y, Yamazaki S, Hasegawa H. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. *Lancet* 1990; **336**: 1150-1153
 - 14 **Takayama T**, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, Kosuge T, Okada S, Takayasu K, Yamasaki S. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. *Hepatology* 1998; **28**: 1241-1246
 - 15 **Okuda K**, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-928
 - 16 **Fujii T**, Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Kosuge T, Takayama T, Makuuchi M, Yamasaki S, Okazaki N. Hepatocellular carcinoma with portal tumor thrombus: analysis of factors determining prognosis. *Jpn J Clin Oncol* 1993; **23**: 105-109
 - 17 **Llovet JM**, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Bru C, Rodes J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62-67
 - 18 **Urata K**, Matsumata T, Kamakura T, Hasuo K, Sugimachi K. Lipiodolization for unresectable hepatocellular carcinoma: an analysis of 205 patients using univariate and multivariate analysis. *J Surg Oncol* 1994; **56**: 54-58
 - 19 **Minagawa M**, Makuuchi M, Takayama T, Ohtomo K. Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. *Ann Surg* 2001; **233**: 379-384
 - 20 **Lange JF**, Leese T, Castaing D, Bismuth H. Repeat hepatectomy for recurrent malignant tumors of the liver. *Surg Gynecol Obstet* 1989; **169**: 119-126
 - 21 **Kakazu T**, Makuuchi M, Kawasaki S, Miyagawa S, Hashikura Y, Kosuge T, Takayama T, Yamamoto J. Repeat hepatic resection for recurrent hepatocellular carcinoma. *Hepatogastroenterology* 1993; **40**: 337-341
 - 22 **Minagawa M**, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. *Ann Surg* 2003; **238**: 703-710
 - 23 **Lo CM**, Fan ST, Liu CL, Chan SC, Wong J. The role and limitation of living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2004; **10**: 440-447
 - 24 **Makuuchi M**, Sano K. The surgical approach to HCC: our progress and results in Japan. *Liver Transpl* 2004; **10**: S46-S52
 - 25 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699
 - 26 **Sitzmann JV**, Greene PS. Perioperative predictors of morbidity following hepatic resection for neoplasm. A multivariate analysis of a single surgeon experience with 105 patients. *Ann Surg* 1994; **219**: 13-17
 - 27 **Jarnagin WR**, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, Corvera C, Weber S, Blumgart LH. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397-406; discussion 406-407
 - 28 **Pringle JH**. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg* 1908; **48**: 541-549
 - 29 **Makuuchi M**, Mori T, Gunven P, Yamazaki S, Hasegawa H. Safety of hemihepatic vascular occlusion during resection of the liver. *Surg Gynecol Obstet* 1987; **164**: 155-158
 - 30 **Belghiti J**, Noun R, Zante E, Ballet T, Sauvanet A. Portal triad clamping or hepatic vascular exclusion for major liver resection. A controlled study. *Ann Surg* 1996; **224**: 155-161
 - 31 **Wu CC**, Yeh DC, Ho WM, Yu CL, Cheng SB, Liu TJ, P'eng FK. Occlusion of hepatic blood inflow for complex central liver resections in cirrhotic patients: a randomized comparison of hemihepatic and total hepatic occlusion techniques. *Arch Surg* 2002; **137**: 1369-1376
 - 32 **Man K**, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Prospective evaluation of Pringle maneuver in hepatectomy for liver tumors by a randomized study. *Ann Surg* 1997; **226**: 704-711; discussion 711-713
 - 33 **Makuuchi M**, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346-350
 - 34 **Takayama T**, Makuuchi M, Watanabe K, Kosuge T, Takayasu K, Yamazaki S, Hasegawa H. A new method for mapping hepatic subsegment: counterstaining identification technique. *Surgery* 1991; **109**: 226-229
 - 35 **Gozzetti G**, Mazziotti A, Bolondi L, Cavallari A, Grigioni W, Casanova P, Bellusci R, Villanacci V, Labo G. Intraoperative ultrasonography in surgery for liver tumors. *Surgery* 1986; **99**: 523-530
 - 36 **Franco D**, Smadja C, Kahwaji F, Grange D, Kemeny F, Traynor O. Segmentectomies in the management of liver tumors. *Arch Surg* 1988; **123**: 519-522
 - 37 **Castaing D**, Garden OJ, Bismuth H. Segmental liver resection using ultrasound-guided selective portal venous occlusion. *Ann Surg* 1989; **210**: 20-23
 - 38 **Kosuge T**, Makuuchi M, Takayama T, Yamamoto J, Shimada K, Yamasaki S. Long-term results after resection of hepatocellular carcinoma: experience of 480 cases. *Hepatogastroenterology* 1993; **40**: 328-332
 - 39 **Yamamoto M**, Takasaki K, Ohtsubo T, Katsuragawa H, Fukuda C, Katagiri S. Effectiveness of systematized hepatectomy with Glisson's pedicle transection at the hepatic hilus for small nodular hepatocellular carcinoma: retrospective analysis. *Surgery* 2001; **130**: 443-448
 - 40 **Takasaki K**, Kobayashi S, Tanaka S, Saito A, Yamamoto M, Hanyu F. Highly anatomically systematized hepatic resection with Glissonian sheath code transection at the hepatic hilus. *Int Surg* 1990; **75**: 73-77
 - 41 **Imamura H**, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S, Makuuchi M, Kawasaki S. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. *Br J Surg* 1999; **86**: 1032-1038
 - 42 **Hasegawa K**, Kokudo N, Imamura H, Matsuyama Y, Aoki T, Minagawa M, Sano K, Sugawara Y, Takayama T, Makuuchi M. Prognostic impact of anatomic resection for hepatocellular carcinoma. *Ann Surg* 2005; **242**: 252-259
 - 43 **Fan ST**, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med* 1994; **331**: 1547-1552
 - 44 **Wu CC**, Yeh DC, Ho WM, Yu CL, Cheng SB, Liu TJ, P'eng FK. Occlusion of hepatic blood inflow for complex central liver resections in cirrhotic patients: a randomized comparison of hemihepatic and total hepatic occlusion techniques. *Arch Surg* 2002; **137**: 1369-1376
 - 45 **Yamamoto J**, Kosuge T, Takayama T, Shimada K, Yamasaki S, Ozaki H, Yamaguchi N, Mizuno S, Makuuchi M. Perioperative blood transfusion promotes recurrence of hepatocellular carcinoma after hepatectomy. *Surgery* 1994; **115**: 303-309
 - 46 **Makuuchi M**, Takayama T, Gunven P, Kosuge T, Yamazaki S, Hasegawa H. Restrictive versus liberal blood transfusion policy for hepatectomies in cirrhotic patients. *World J Surg* 1989; **13**: 644-648

- 47 **Sakamoto Y**, Yamamoto J, Kokudo N, Seki M, Kosuge T, Yamaguchi T, Muto T, Makuuchi M. Bloodless liver resection using the monopolar floating ball plus ligasure diathermy: preliminary results of 16 liver resections. *World J Surg* 2004; **28**: 166-172
- 48 **Imamura H**, Shimada R, Kubota M, Matsuyama Y, Nakayama A, Miyagawa S, Makuuchi M, Kawasaki S. Preoperative portal vein embolization: an audit of 84 patients. *Hepatology* 1999; **29**: 1099-1105
- 49 **Takayama T**, Makuuchi M, Kosuge T, Yamamoto J, Shimada K, Inoue K. Preoperative portal embolization. *Ann Ital Chir* 1997; **68**: 745-750
- 50 **Muto Y**, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, Tanaka T, Tsurumi K, Okuno M, Tomita E, Nakamura T, Kojima T. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 1996; **334**: 1561-1567
- 51 **Lau WY**, Leung TW, Ho SK, Chan M, Machin D, Lau J, Chan AT, Yeo W, Mok TS, Yu SC, Leung NW, Johnson PJ. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; **353**: 797-801
- 52 **Takayama T**, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, Shimada K, Sakamoto M, Hirohashi S, Ohashi Y, Kakizoe T. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. *Lancet* 2000; **356**: 802-807
- 53 **Wu CC**, Ho YZ, Ho WL, Wu TC, Liu TJ, P'eng FK. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. *Br J Surg* 1995; **82**: 122-126
- 54 **Yamasaki S**, Hasegawa H, Kinoshita H, Furukawa M, Imaoka S, Takasaki K, Kakumoto Y, Saito H, Yamada R, Oosaki Y, Arai S, Okamoto E, Monden M, Ryu M, Kusano S, Kanematsu T, Ikeda K, Yamamoto M, Saoshiro T, Tsuzuki T. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. *Jpn J Cancer Res* 1996; **87**: 206-211
- 55 **Izumi R**, Shimizu K, Iyobe T, Ii T, Yagi M, Matsui O, Nonomura A, Miyazaki I. Postoperative adjuvant hepatic arterial infusion of Lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. *Hepatology* 1994; **20**: 295-301
- 56 **Lai EC**, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. *Arch Surg* 1998; **133**: 183-188
- 57 **Kawata A**, Une Y, Hosokawa M, Wakizaka Y, Namieno T, Uchino J, Kobayashi H. Adjuvant chemoinmunotherapy for hepatocellular carcinoma patients. Adriamycin, interleukin-2, and lymphokine-activated killer cells versus adriamycin alone. *Am J Clin Oncol* 1995; **18**: 257-262
- 58 **Ikeda K**, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, Tsubota A, Chayama K, Murashima N, Kumada H. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000; **32**: 228-232
- 59 **Kubo S**, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg* 2002; **89**: 418-422
- 60 **Takayama T**, Makuuchi M. Adjuvant therapy for hepatocellular carcinoma: Is there an effective modality? *Cancer Reviews* 2003; **1**: 237-244

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