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Liver resection for hepatic metastases: 15 years of experience

Giulio Belli, Alberto D'Agostino, Fabio Ciciliano, Corrado Fantini, Nadia Russolillo, and Andrea Belli

Department of General and Hepato-Pancreato-Biliary Surgery, S. Maria di Loreto nuovo Hospital, Naples, Italy

Abstract

Background/Purpose. Liver metastases, especially those from primary colorectal cancers, are treatable and potentially curable. Imaging techniques such as computed tomography, magnetic resonance, and ultrasonography have advanced in recent years and led to increased sensitivity and specificity in the diagnosis of liver metastases. Liver surgery also has been revolutionized in the past two decades. Dissection along nonanatomical lines has permitted the resection of multiple lesions that previously might have been considered unresectable.

Methods. From 1986 to 2000, 181 patients underwent liver resection for hepatic metastasis from colorectal cancer. Of these, 56 patients underwent systematic anatomical major hepatic resection and 125 underwent nonanatomical limited resection.

Results. Operative morbidity and mortality rates were higher in patients in whom anatomical procedures were performed. The overall 5-year survival rate of the 181 patients was 39.8%.

Conclusions. An aggressive surgical procedure in patients with hepatic colorectal metastases is safe, and may prolong overall survival, and therefore should be considered in all patients with metastases confined to the liver.

Key words Hepatic metastases · Colorectal cancer · Liver resection

Introduction

Hepatic metastasis is the main cause of death in patients with colorectal cancer. In the patient with metastatic disease confined to the liver, resection offers the best chance of cure. In recent reports, the 5-year survival rate after liver resection in patients with metastatic colorectal cancer has improved, being up to 49%.[1–6] Advances in hepatic resection techniques have dramatically evolved during the past two decades, with a decline in perioperative morbidity and mortality. Intraoperative mortality has been reported to be around 4%.[2]

Resectability is usually determined by the absence of extrahepatic disease, by th number of liver deposits, and by the ability to obtain free resection margins. Recently it has been demonstrated that the presence of more than four metastases does not automatically preclude resectability.[7–11] Dissection along nonanatomical lines has permitted the resection of multiple lesions that previously might have been considered unresectable.

The aim of this study was to describe the long-term results of surgical procedures for colorectal liver metastases and to determine whether the changes in surgical techniques have had an impact on mean survival rate and on recurrence percentages.

Patients and methods

Between January 1986 and December 2000, 181 consecutive patients underwent potentially curative hepatic resection of metastases from colorectal cancer at two institutions, the Department of General Surgery and Organ Transplantation, Federico II University, School of Medicine, Naples, Italy, and the Department of General and Hepato-Pancreato-Biliary Surgery, S. Maria di Loreto Nuovo Hospital, Naples, Italy. Of these patients, 56 underwent systematic anatomical major hepatic resection and 125 underwent nonantomical resection to remove all intrahepatic tumors with sufficient free margins (Table 1). Hepatectomy procedures were selected based on tumor size, location (proximity to hepatic pedicle), or number of lesions.

Statistical analysis included Fisher's exact test, the χ^2 test, or Student's *t*-text where appropriate. A value of $P < 0.05$ was accepted as statistically significant.

Offprint requests to: G. Belli
Via Cimarosa 2/a, 80127 — Naples, Italy

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Survival time was calculated from the date of resection to date of death. Survival curves were generated by using the Kaplan-Meier method and were then compared with the log-rank test (univariate analysis). As prognostic factors, we examined age, sex, number of lesions, tumor distribution (lobar, bilobar), tumor size, extrahepatic disease, tumor-free margin, preoperative serum carcinoembryonic antigen (CEA) levels, surgical procedure, primary tumor site, and temporal relationship with the primary tumor (Table 2).

In the retrospective analysis, we considered two periods: 1986–1995 and 1996–2000. This study has emphasized the evolution in the operative approach for surgical treatment of hepatic metastases in the past 5 years (Fig. 1).

Table 1. Operative procedures for liver resection

Operative procedure	Number of patients
Major hepatic resection	56 (30.9%)
One segmentectomy	31 (55.4%)
Bisegmentectomy	21 (37.5%)
Trisegmentectomy	4 (7.1%)
Nonanatomical resection	125 (69.1%)
Total	181 (100%)

Results

The overall 1-, 3-, and 5-year survival rates of the 181 patients were 91.2%, 55.3%, and 39.8% respectively (Fig. 2).

Among the factors studied, univariate analysis showed a significant difference in survival rate based on tumor size (Fig. 3), number of tumors (Fig. 4), temporal relationship, presence of extrahepatic disease, surgical margins (Fig. 5), and preoperative CEA serum level (Fig. 6). Age (Fig. 7), sex (Fig. 8), primary tumor site, and surgical procedure (Fig. 9) did not significantly affect the patient's survival.

In 56 patients, anatomical hepatic resections were performed: 31 segmentectomies, 21 bisegmentectomies, and 4 trisegmentectomies. The anatomic nomenclature of Couinaud was used to define the various types of liver resection.[12] In this series, "segmentectomy" was defined as major hepatic resection removing at least one whole segment according to the Couinaud classification. For example, complete resection of segment 4 plus partial resection of adjacent segment 3 was considered as "one segmentectomy".

Since 1992, intraoperative ultrasonography (IOUS) was performed in all hepatic operations.

Table 2. Univariate analysis of prognostic factors

Prognostic factors		Number of patients	Survival rate (%)			*P* value[a]
			1 year	3 years	5 years	
Overall survival		181	91.2	55.3	39.8	
Age (years)	≤70	96	90.7	50.8	40.6	0.11
	>70	85	89.7	50.1	38.9	
Sex	Male	118	88.6	50.6	41.1	0.32
	Female	63	86.9	52.5	40.3	
Number of lesions	1	109	96.8	61.9	43.1	0.04
	2–4	45	81.2	40.7	34.2	
	>4	27	80.6	39.9	31.6	
Tumor distribution	Unilateral	123	91.6	49.9	34.5	0.32
	Bilateral	58	86.4	42.5	30.9	
Size of tumor	≤5 cm	130	97.7	54.7	46.9	0.02
	>5 cm	51	81.6	47.2	35.1	
Extrahepatic disease[b]	Absent	175	90.8	54.1	41.4	0.001
	Present	6	88.8	45.7	30.7	
Tumor-free margin	<1 cm	105	93.0	56.2	36.9	0.04
	≥1 cm	76	94.5	58.9	44.2	
Preoperative CEA[c]	<50 mg/ml	110	88.7	52.3	49.6	0.033
	≥50 mg/ml	71	81.4	41.6	33.7	
Type of resection	Anatomical	56	87.2	56.9	43.2	0.56
	Nonanatomical	125	96.8	51.9	39.8	
Primary tumor site	Colon	109	90.8	55.2	35.2	0.40
	Rectum	72	88.9	50.3	37.4	
Temporal relationship	Metachronous	112	91.5	60.5	48.7	0.04
	Synchronous	69	93.6	58.3	37.8	

[a] Log rank
[b] Pulmonary localization
[c] Carcinoembryonic antigen

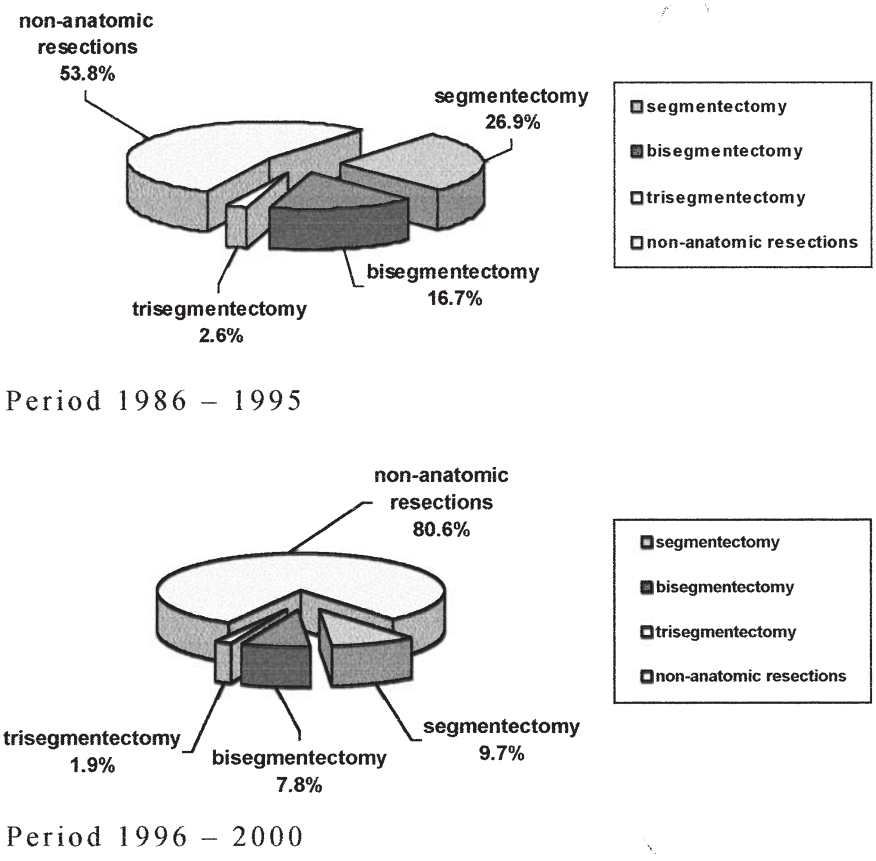

Fig. 1. Differences in surgical procedures performed between the two periods considered: 1986–1995 and 1996–2000

Fig. 2. Actuarial 5-year survival of patients who underwent resection for hepatic metastases from colorectal cancer

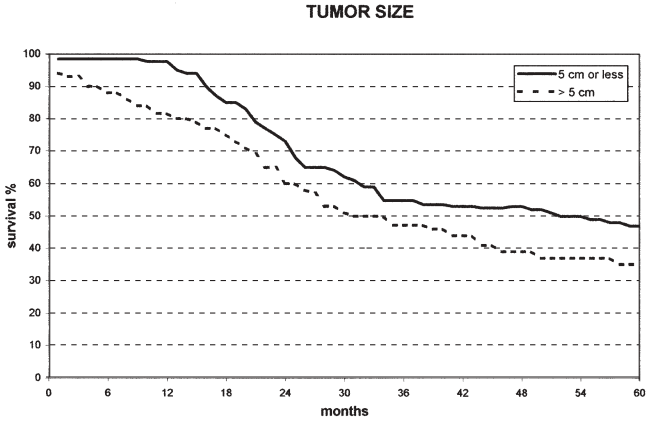

Fig. 3. Patient survival after resection for hepatic metastases according to size of tumor. There was a significant difference in patient survival between tumors of 5 cm or less (*solid line*; $n = 130$) and those of more than 5 cm (*dashed line*; $n = 51$; $P = 0.02$)

The hepatic parenchyma was trnasected by the forceps fracture method and, more recently, with other new devices such as the TissueLink Floating Ball, Ultracision, and Ligasure.[13] Vascular inflow occlusion was obtained in all major hepatic resections. Liver ischemia to periods of 15 min, followed by 5 min of perfusion, which was repeated if necessary, was performed in selected patients for nonanatomical resections.

There were 19 (10.5%) postoprative complicaations. The operative mortaility rate (death within 30 days from the surgical procedure) was (2.8%) (five patients).

In the group of patients who underwent anatomical resection, two patients died of liver-related postoperative complications, such as liver failure and coagulopathy, and one died of heart failure. In the group of

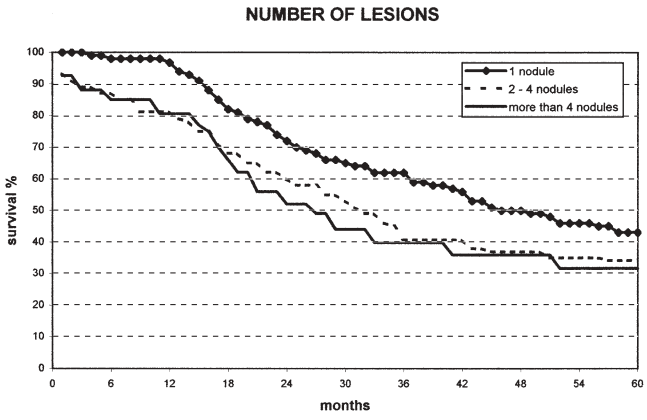

Fig. 4. Patient survival after resection for hepatic metastases according to number of lesions ($P = 0.02$, logrank)

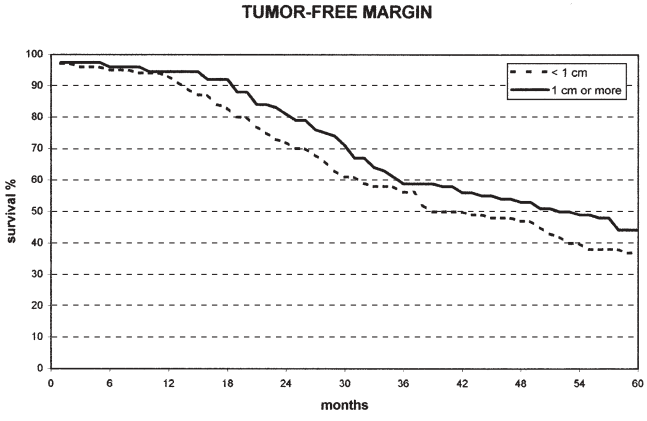

Fig. 5. Patient survival after resection for hepatic metastases according to surgical tumor-free margins. There was a significant difference in patient survival between tumor-free margins of 1 cm or more (*solid line*; $n = 76$) and those of less than 1 cm (*dashed line*; $n = 105$; $P = 0.04$)

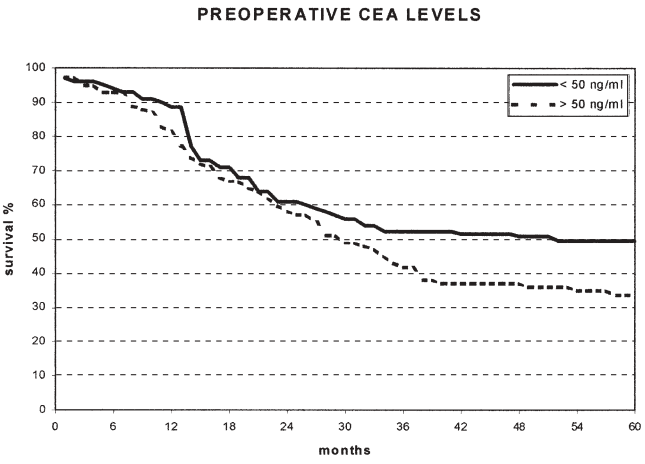

Fig. 6. Patient survival after resection for hepatic metastases according to preoperative carcinoembryonic antigen (*CEA*) serum level. There was a significant difference in patient survival between levels of CEA of 50 ng/ml or more (*dashed line*; $n = 71$) and levels of less than 50 ng/ml (*solid line*; $n = 110$; $P = 0.033$)

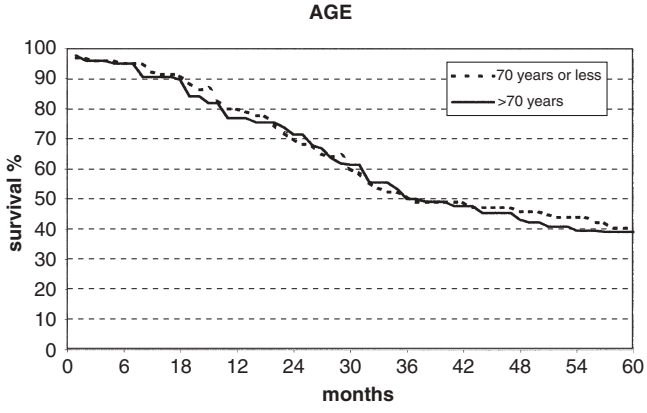

Fig. 7. Patient survival after resection for hepatic metastases according to age. There was no significant difference in patient survival between those aged 70 years or less (*dashed line*; $n = 96$) and those aged more than 70 years (*solid line*; $n = 85$; $P = 0.11$)

patiets who underwent nonanatomical resection, one died of coagulopathy and one died of pulmonary embolism.

There were 8 operative complications from 1986 to 1995, and 11 from 1996 to 2000.

There were complications in nine patients (16.1%) who underwent anatomical resection, and in 10 patients (8.0%) who underwent nonanatomical resection (Table 3).

Overall tumor recurrence in the remnant liver was observed in 53 patients. The percentage was 30.4% in the group treated from 1986 to 1995 and 28.3% in the group treated from 1996 to 2000.

Discussion

Advances in surgical techniques have extended the frontiers of resectability for liver tumors.[14] Recognition of the segmental basis of liver anatomy has led to the evolution of segment-based tumor resection. The availability of new surgical procedures,[15–20] such as the vascular occlusion Pringle maneuver, has reduced the morbidity associated with liver resection; total vascular exclusion has now become widely adopted when operating on difficult lesions, due to its minimum blood loss. Such procedures make easier the excision of lesions involving the vena cava or those lying near the junction of the hepatic veins.

Complete resection with clear margins, containing not less than 1 cm of nonmetastatic hepatic tissue, has been shown to be a good predictor of long-term survival, even if survival after surgery is not always dependent on this pathological parameter.[21–23]

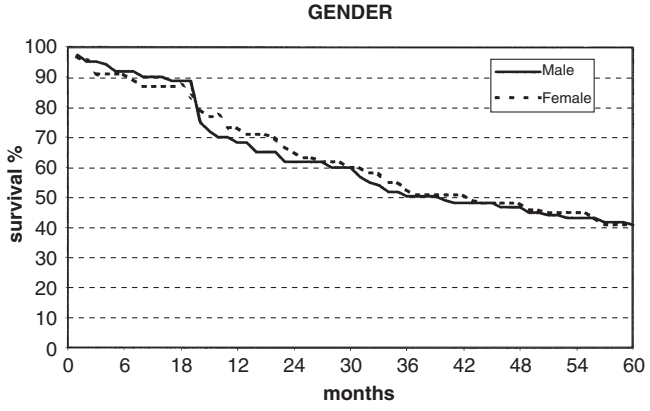

Fig. 8. Patient survival after resection for hepatic metastases according to gender. There was no significant difference in patient survival between male patients (*solid line*; $n = 118$) and female patients (*dashed line*; $n = 63$; $P = 0.32$)

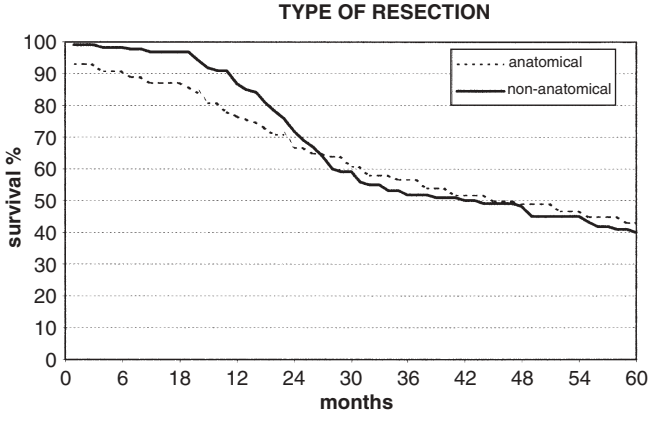

Fig. 9. Patient survival after resection for hepatic metastases according to type of resection. There was no significant difference in patient survival between anatomical (*dashed line*; $n = 56$) and non-anatomical resection (*solid line*; $n = 125$; $P = 0.56$)

Also, in our experience, this factor significantly affects either the prognosis or the disease-free survival (Fig. 5). On the other hand, Yamamoto et al.[24,25] has shown that the occurrence of satellite nodules around the main metastatic lesion is rare and, therefore, wedge resection is justified, even with a tumor-free margin of less than 0.5–1 cm, but with exposure of neither the tumor nor the cut surface.

If we consider the surgical procedure, our experience is in accordance with many reports:[21–23] it confirms, that for liver metastasis, the type of resection does not significantly affect patient survival (Fig. 9).

In our experience, the routine use of ultrasound-guided resection procedures has eliminated incomplete tumor removal.

Many authors have considered tumor size as an adverse factor in prognosis after surgery.[2,7,8] Also, in our experience, patients with a lesion larger than 5 cm had

Table 3. Operative morbidity and mortality after liver resection

	Anatomical resection ($n = 56$)	Nonanatomical resection ($n = 125$)
Postoperative complications		
Bile leakage	2	4
Subphrenic abscess	1	2
Jaundice	1	—
Ascites	1	1
Pleural effusion	1	1
Heart failure	1	—
Coagulopathy	1	1
Hepatic failure	1	—
Pulmonary embolism	—	1
Total	9 (16.1%)	10 (8.0%)
Mortality		
Operative death[a]	3 (5.4%)	2 (1.6%)

[a] Death within 30 days after surgical procedure

life expectancies worse than those with a smaller lesion (Fig. 3).

We observed a significant difference in survival rate when patients were grouped according to the number of lesions (Fig. 4). Therefore, the presence of multiple liver metastases seems to be, by itself, a poor prognostic factor. However, the relevance of the number of lesions to patient survival has been controversial in the surgical community. For some authors,[2,9,26–28] the cutoff number of four metastases represents the boundary between patients with an acceptable outcome and those with a particularly poor prognosis.

With regard to unilateral or bilateral tumor distribution, there seems to be agreement that this factor has no prognostic value.[27,28] In our series, 58 patients (32.0%) had bilateral metastases, but no statistically significant difference regarding distribution was observed in long-term or disease-free survival. This supports our current approach, which is to treat all lesions with wedge resection, regardless of their distribution.

The finding that a high CEA serum level was associated with a poor prognosis illustrates that this elevated marker level reflects a high incience of subclinical extrahepatic disease, because neither the maximum rise nor the number of nodules were meaningful prognostic variables.[27–29]

Also, our experience in the series showed a statistical relathipship between preoperative CEA serum level and survival rates (Fig. 6).

Some authors believe that the prognosis of patients with synchronous metastases is worse than the prognosis of those with metachronous presentation,[27,30,31] and our experience is in agreement with this belief.

The adverse consequences of percutaneous biopsy are now recognized. A reflex exists among many

radiologists, gastroenterologists, oncologists, and even some surgeons, that a lesion, even an obvious metastasis, identified on imaging the liver, must be biopsied. This is depsite the fact that such a biopsy is virtually never necessary for making a diagnosis. It is now known that patients being subjected to a needle biopsy will develop tumor seeding of the biopsy tract.[32]

The optimal management of all patients identified as having colorectal liver metastases on imaging should be discussed with a multidisciplinary team, which includes a specialist liver surgeon.

The use of IOUS is mandatory in all hepatic surgery, because it is able to identify nonpalpable lesions and demonstrate the tumor and its relation to the intrahepatic vasculature.

In contrast to liver resection, the case for alternative ablative therapy is less convincing.[33,34] Ablative therapy takes numerous forms: cryotherapy, radiofrequency ablation, and laser hyperthermia all use thermal energy of some kind to ablate tumor and liver substance. In our opinion, these kinds of alternative therapy are to be used only when surgery is not available.

In conclusion, indications for liver resection for metastases from colorectal cancer are currently accepted according to the possibility of treatment. Therefore, a specific scientific background and adequate training in hepatic surgery, including the ability to perform IOUS, and its availability, are mandatory for performing safe and effective treatment.

References

1. Nakamura S, Suzuki S, Konno H (1999) Resection of hepatic metastases of colorectal carcinoma: 20 years' experience. J Hepatobiliary Pancreat Surg 6:16–22
2. Harmon KE, Ryan JA Jr, Biehl TR, Lee FT (1999) Benefits and safety of hepatic resection for colorectal metastases. Am J Surg 177:402–404
3. Iwatsuki S, Esquivel CO, Gordon RD, Starzl TE (1986) Liver resection for metastatic colorectal cancer. Surgery 100:804–810
4. Fuhrman GM, Curley SA, Hohn DC, Roh MS (1995) Improved survival after resection of colorectal liver metastases. Ann Surg Oncol 2:537–541
5. Scheele J, Stangl R, Altendorf-Hofmann A (1990) Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 77:1241–1246
6. Rodgers MS, McCall JL (2000) Surgery for colorectal liver metastases with hepatic lymph node involvement: a systematic review. Br J Surg 87:1142–1155
7. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF (1997) Liver resection for colorectal metastases. J Clin Oncol 15:938–946
8. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, Matsubara T, Takahashi T, Nakajima T, Muto T (2001) Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma. Am J Sug 181:153–159
9. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Cancer 77:1254–1262
10. Ohlsson B, Stenram U, Tranberg KG (1998) Resection of colorectal liver metastases: 25-year experience. World J Surg 22:268–277
11. Nordlinger B, Jaeck D, Guiguet M, Vaillant JC, Balladur P, Schaal JC (1992) Resection chirurgicale des metastases hepatiques. In: Monographies de l'Association Francaise de Chirurgie. Traitement des metastases hepatiques des cancer colorectaux. Springer, Berlin Heidelberg New York Tokyo Paris, pp 129–146
12. Couinaud C (1957) Le foie, etude anatomiques et chirurgicales. Masson, Paris, pp 400–409
13. Hodgson WJ, Morgan J, Byrne D, Del Guercio LR (1992) Hepatic resection for primary and metastatic tumors using the ultrasonic surgical dissector. Am J Surg 163:246–250
14. Rees M, Plant G, Wells J (1996) One hundred and fifty hepatic resections: evolution of technique towards bloodless surgery. Br J Surg 83:1526–1529
15. Rees M, Plant G, Bygrave S (1997) Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 84:1136–1140
16. Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 116:703–711
17. Hughes KS, Simon R, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG (1988) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Surgery 103:278–288
18. Irie T, Itai Y, Hatsuse K, Mochizuki H (1999) Does resection of small liver metastases from colorectal cancer improve survival of patients? Br J Radiol 72:246–249
19. Jarnagin WR, Fong Y, Ky A, Schwartz LH, Paty PB, Cohen AM (1999) Liver resection for metastatic colorectal cancer: assessing the risk of occult irresectable disease. J Am Coll Surg 188:33–42
20. D'Angelica M, Brennan MF, Fortner JG, Cohen AM, Blumgart LH, Fong Y (1997) Ninety-six 5-year survivors after liver resection for metastatic colorectal cancer. J Am Coll Surg 185:554–559
21. Elias D, Cavalcanti A, Sabourin JC, Lassau N, Pignon JP, Ducreux M (1998) Resection of liver metastases from colorectal cancer: the real impact of the surgical margin. Eur J Surg Oncol 24:174–179
22. Cady B, Jenkins RL, Steele GD Jr, Lewis WD, Stone MD, McDermott WV (1998) Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. Ann Surg 227:566–571
23. Shirabe K, Takenaka K, Gion T, Fujiwara Y, Shimada M, yanaga K (1997) Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. Br J Surg 84:1077–1080
24. Yamamoto J, Sugihara K, Kosuge T, Takayama T, Shimada K, yamasaki S (1995) Pathologic support for limited hepatectomy in the treatment of liver metastases from colorectal cancer. Ann Surg 221:74–78
25. Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H (1999) Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. Br J Surg 86:332–337
26. Imamura H, Kawasaki S (1999) Treatment strategy for multiple hepatic metastases of colorectal carcinoma. J Hepatobiliary Pancreat Surg 6:23–29
27. Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J, Imamura I (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer. Ann Surg 231:487–499
28. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for

metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230:309–318
29. Hohenberger P, Schlag PM, Gerneth T, Herfarth C (1994) Pre- and postoperative carcinoembryonic antigen determinations in hepatic resection for colorectal metastases. Predictive value and implications for adjuvant treatment based on multivariate analysis. Ann Surg 219:135–143
30. Schlag P, Hohenberger P, Herfarth C (1990) Resection of liver metastases in colorectal cancer — competitive analysis of treatment results in synchronous versus metachronous metastases. Eur J Surg Oncol 16:360–365
31. Vogt P, Raab R, Ringe B, Pichlmayr R (1991) Resection of synchronous liver metastases from colorectal cancer. World J Surg 15:62–67
32. Belli G, Ciciliano F, Iannelli A, Marano I (1999) Hepatic needle tract implantation of hepatocellular carcinoma 6 years after fine needle aspiration biopsy. HPB Surgery 2:91–93
33. Siperstein A, Garland A, Engle K (2000) Local recurrence after laparoscopic radiofrequency thermal ablation of hepatic tumors. Ann Surg Oncol 7:106–113
34. Poston GJ (2001) Cryotherapy for colorectal liver metastases. Hepatogastroenterology 48:323–324