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ORIGINAL ARTICLE

Multicentre study of liver metastases from colorectal cancer in pathological livers

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Abstract

Objectives: Resection of colorectal cancer (CRC) liver metastases (LM) in pathological liver (PL) patients (with cirrhosis or hepatopathy) is extremely rare. The aim of this study was to perform a multicentre, retrospective analysis of epidemiology, surgical techniques and outcomes in patients with PL who underwent hepatic resection for CRC-LM.

Methods: A retrospective, multicentre questionnaire was distributed to 15 hepatopancreatobiliary surgical units.

Results: Only six of 15 (40%) HPB units reported any experience in the surgical resection of CRC-LM in patients with PL. Of the 20 patients identified, 10 had underlying cirrhosis and 10 had chronic hepatopathy. Their median age was 66 years (range: 49–81 years). Thirteen patients were male. Liver dysfunction was known preoperatively in 18 patients. All patients had Child–Pugh class A disease. Six patients had synchronous disease. There were a total of 38 lesions among the 20 patients, distributed at a median of one lesion per patient (range: 1–4 lesions). The median size of the lesions was 3.0 cm (range: 1.5–9.0 cm). Preoperative median carcinoembryonic antigen (CEA) was 32.3 ng/ml (range: 1–184 ng/ml). The surgical procedures performed included: sub-segmentectomy (n = 12); left lateral sectionectomy (n = 6); segmentectomy (n = 4); radiofrequency ablation (n = 3), and exploratory laparotomy (n = 4). Morbidity occurred in four patients (Clavien grades I [n = 1], II [n = 2] and IVa [n = 1]). Mortality was nil. An R0 resection margin was achieved in 15 of 16 patients. Twelve patients did not receive chemotherapy. In resected patients, 10 presented with relapse. The median disease-free and overall survival periods were 12.2 and 22.3 months, respectively.

Conclusions: When feasible, liver resection is the best option for CRC-LM in PL patients.

Keywords

cirrhosis, surgery, review

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Introduction

The incidence of colorectal cancer (CRC) liver metastasis (LM) within a cirrhotic or pathological liver (PL) is very low.[1–5] Many theories have been proposed in an effort to explain this low rate of occurrence, including: portal hypertension accompanied by hepatofugal flows; capillarization of the hepatic parenchyma; immune alterations; greater levels of matrix metal proteinase (MMP) inhibitors; tumour necrosis factor-α (TNF-α) or interferon-α (IFN-α) levels, and the destruction of tumour cellularity by cytotoxic T cells triggered by hepatotropic viruses.[1–5] The number of hepatic resections performed in patients with PL for CRC-LM is small. Whether this reflects a lack of underlying hepatic function precluding surgical intervention or whether there is a significant reduction in the referral of these patients to liver units for resection is unclear.

The aim of this study was to perform a multicentre, retrospective analysis of epidemiology, surgical techniques and outcomes in patients with PL who underwent hepatic resection for CRC-LM.

Materials and methods

A retrospective, multicentre study was carried out between 1993 and 2009. Fifteen liver surgical units were approached for consultation. All of them replied, but only six had operated for CRC-LM in patients with PL. Diagnosis was achieved by computed tomography scanning. Patients were included in the study on histological confirmation of cirrhosis or chronic hepatopathy. No patient underwent transarterial chemoembolization before a surgical procedure. The questionnaires distributed to the various centres asked for epidemiological patient data (age; gender), information on the hepatopathy (whether or not the origin of the hepatopathy was known; Child–Pugh score), data on primary tumours (tumour–node–metastasis [TNM]; type of colon surgery performed), data on LMs (number; sizes), surgical procedures (type of surgery according to the Brisbane Classification),[6] postoperative morbidity and mortality rates collected according to the Dindo–Clavien classification,[7] and relapse rates (localization; type of treatment performed; total survival and disease-free rates). The statistical analysis was performed using SPSS Version 16.0 for Mac (SPSS, Inc., Chicago, IL, USA). Variables were expressed as median and range. *P*-values of <0.05 were considered to indicate statistical significance.

Results

During the time period studied, a total of 4015 patients underwent hepatic resection for CRC-LM across all 15 units. Within the six units that performed hepatic resection for CRC-LM in PL patients, a total of 2364 (58.9%) patients underwent resection for CRC-LM. From these six units, 20 patients were identified as having undergone hepatic resection for CRC-LM in a PL. These patients represented 0.84% of all CRC-LM subjects resected across the six units and 0.50% of all liver resections for CRC-LM carried out across the 15 units surveyed. The 20 patients had a combined total of 38 liver lesions. Their median age was 66 years (range: 49–81 years). Thirteen patients were male. The primary tumour was localized in the colon in 14 patients and in the rectum in six. The T stage was pT2 ($n = 1$), pT3 ($n = 14$) and pT4 ($n = 5$). Lymph node involvement was pN0 ($n = 10$), pN1 ($n = 6$) and pN2 ($n = 4$).

Ten of the 20 patients had cirrhosis and 10 had chronic hepatopathy. In 18 patients the degree of hepatic dysfunction was known preoperatively. Causes of hepatopathy included: hepatitis C virus (HCV) ($n = 8$); alcohol ($n = 4$); HCV + HBV infection ($n = 1$), and other causes ($n = 6$). All 10 patients were given Childs–Pugh A scores.

Six patients had synchronous hepatic disease at the time of their primary diagnosis. The median number of LMs was one (range: 1–4). The median size of the lesions was 3.0 cm (range: 1.5–9.0 cm). The median preoperative carcinoembryonic antigen (CEA) level was 32.3 ng/ml (range: 1–184 ng/ml).

In four patients, exploratory laparotomy was the only procedure performed because the extent of resection required and the underlying liver disease would have resulted in insufficient liver remnant in all four cases. Procedures performed in the 16 patients who underwent resection included 12 sub-segmentectomies, six left lateral sectionectomies (one laparoscopic), four segmentectomies and three radiofrequency ablations (RFAs). The latter was employed as a complementary treatment to resection in two patients (segmentectomy of segment VI and RFA of the lesion on segment IV; left lateral sectionectomy plus caudate resection and RFA of the lesion on segment VIII) and as the only treatment in a lesion concerning segment VIII in one patient. Four patients developed postoperative complications (Clavien grades I [$n = 1$], II [$n = 2$] and IVa [$n = 1$]). No patient died in the postoperative period. An R0 resection was achieved in 15 of the 16 resected patients.

Postoperatively, one of the four non-resected patients received further therapy and underwent embolization with irinotecan-loaded beads. Only four of the 16 patients resected received postoperative adjuvant therapy. The median follow-up of the 16 patients who underwent resection was 23 months (range: 5–64 months). Ten of the 16 patients developed recurrent disease in the form of hepatic disease only in four patients, isolated extrahepatic disease in four patients (pulmonary in three, lymph nodes in one) and disseminated disease in two patients. Four (three of whom had undergone resection) of the 20 patients died at 4, 15, 22 and 37 months after surgery, respectively. Median disease-free survival was 12.2 months and median overall survival was 22.3 months.

The patient treated only with RFA died at 4 months. The other two RFA patients (RFA + surgery) suffered a hepatic relapse, but remain alive. The small number of patients treated with RFA does not permit us to draw conclusions on its efficacy as an exclusive or complementary treatment in the management of CRC-LM in patients with PL.

Discussion

Hepatic resection is the most effective treatment in selected patients with CRC-LM.[8] Survival rates at 5 years after resection are reported to range between 25% and 40% and are currently superior to those of any other currently available therapeutic option.[8] It has previously been observed that few patients with cirrhosis or hepatopathy accompanied by CRC-LM are referred for surgery. Several potential reasons for this exist and refer to: a lower incidence of CRC-LM in cirrhotic patients; contraindications to surgery secondary to significant co-morbidity, and the non-referral of operable patients.

At present, oncological liver surgery in patients with cirrhosis can be performed with mortality rates of <5%.[9,10] To achieve these outcomes, a detailed preoperative assessment examining hepatic function, the presence or absence of portal hypertension, grade of

Table 1 Previous series of liver metastases in pathological livers

Study	Cases, *n*	Type of study	LM in NL	LM in PL	Liver disease
Hamaya *et al*., 1975[3]	240 377	Autopsies	43.2%	26.3%	Cirrhosis
Vanbockrijck & Kloppel, 1992[4]	2162	Autopsies	46.4%	33.3%	Cirrhosis
Utsunomiya *et al*., 1999[2]	438	CRC patients	21.2%	8.1%	Infection HBV + HCV
Song *et al*., 2001[1]	512	CRC patients	27.1%	13.5%	Infection HBV
Iascone *et al*., 2005[5]	747	CRC patients	32.0%	4.7%	Cirrhosis

LM, liver metastasis; NL, normal liver; PL, pathological liver; CRC, colorectal cancer; HBV, hepatitis B virus; HCV, hepatitis C virus

cholestasis and remnant liver volume post-resection must be performed.[8,9] Resection surgery can be safely performed in a subgroup of these patients with favourable factors. The extrapolation of this approach to patients with cirrhosis and CRC-LM allows us to infer that a proportion of these patients may also undergo resection.

The perception of a reduced incidence of CRC-LM in PL patients is based on a series of historic publications – commonly of autopsies – that reported a low incidence of LM in PLs (cirrhosis, fatty liver, etc.) (Table 1).[1,2] Many theories have been published in an attempt to explain why patients with cirrhosis or hepatopathy develop fewer LMs than patients with healthy livers.[1–4] So far, there is no convincing explanation. The most plausible theories are as follows:

- Mechanical causes: a cirrhotic liver does not represent a breeding ground for the development of tumour cells because fibrosis and the distortion of small hepatic capillaries which occur in cirrhosis – known as sinusoid capillarization – represent a mechanical obstacle to the establishing of tumours.[1,2,11]
- Immune alterations:[1,2] the capillarization mentioned above triggers changes at adhesion molecules and at the hepatic extracellular matrix, which are key points in the metastatic process.[11] In addition, the cirrhotic liver shows higher levels of MMP inhibitors.[11]
- Hepatofugal flow: a high percentage of cirrhotic patients exhibit hepatofugal flow, which may favour the non-establishment of neoplastic cells in the liver. However, this theory is weakened by the fact that it would suggest a higher number of metastases on other body organs, an occurrence that has not been demonstrated.[11]
- Inferior life expectancy: a lower number of extrahepatic neoplasms and fewer LMs caused by these neoplasms are diagnosed in cirrhotic patients because the life expectancy of such patients is, in all probability, lowered by the presence of cirrhosis.[4,11]
- Viral infection: two Japanese series on the frequency of LM in CRC patients infected with HCV and HBV have resulted in the proposal of a new theory.[1,2] The theory establishes that the rate of occurrence of LMs is altered by the presence of HBV or HCV alone, not by the occurrence of hepatic damage, because when viral replication occurs, the rate of LM is lower, regardless of the damage on the parenchyma.[1,2] According to this theory, viral infection hinders the development of tumour cells because they are destroyed by virus-activated cytotoxic T cells when they reach the hepatic sinusoid. Furthermore, increased production of IFN-α in patients with HBV and HCV infections may diminish the occurrence of metastases by stimulating the cytotoxic capacity of Kupffer cells.[2] HBV replication also increases TNF-α production, which includes an anti-tumour effect.[1]

In 1999, Seymour and Charny carried out a systematic review of the literature dealing with postmortem case studies alone, thus including all published data.[11] This 11-study combination concludes that the chances of metastasis occurring are lower in a cirrhotic liver than in a healthy one, with no differences among races. A study conducted by Hamaya *et al.* stands out from the other case studies included in the review because its authors, referring to a very large series of autopsies ($n = 240\,000$), express the discordant view that although the rate of metastasis in non-cirrhotic livers is higher than that seen in cirrhotic livers, metastases are not as infrequent as clinical practice suggests.[3] The inherent problem in the information collected by Seymour and Charny[11] is that most of it stems from autopsy studies and, as such, includes an obvious bias as cirrhotic patients operated on for CRC exhibit a higher perioperative mortality rate, which means that patients may become subject to autopsy before they have developed an LM.[11]

The current series lends itself to some interesting observations. It is clear that the frequency of surgery for CRC-LM in patients with PL is low. At a technical level, the non-resectability rate of four of 20 patients is higher than the 10% previously published for hepatopathy-free patients[12,13] and in the absence of major hepatectomy.[7] These differences reflect the inherent risk of carrying out major hepatectomies in cirrhotic patients. At present, it appears that non-anatomic resections are as valid in oncological terms as anatomic resections.[14] The four exploratory laparotomies mentioned earlier were conducted in patients with advanced cirrhosis and thus it seems that patients with chronic hepatopathy are likely to demonstrate a resectability rate close to that obtained in hepatopathy-free patients.[13] Low morbidity figures and a null mortality rate represent data similar to those obtained in hepatic metastasis resections on healthy livers. It is also noteworthy that hepatic relapses were not managed by re-resection procedures, as would have been suggested in the case of a healthy liver, but by chemotherapy or radiofrequency, probably because of a lack of functional hepatic reserve.[15]

The percentage of patients undergoing post-resection chemotherapy (25%) is very low compared with that in hepatopathy-free patients, which ranges from 55% to 75%.[12,16] Nevertheless, data on hepatic relapse (38%) and survival rates are acceptable and similar to LM series in which chemotherapy rates are higher. As the current data refer to a retrospective study, the actual reasons for the low rate of chemotherapy cannot be given, but it is the authors' assumption that the hepatopathy was crucial to the decision not to administer chemotherapy.[16] Within the current study, no difference was detected between the degree of hepatopathy and survival, but, given the small number of patients, a risk for type II error exists. Total and disease-free survival rates are similar to those obtained in hepatopathy-free patients.[12]

In conclusion, resection of CRC-LM in patients with PL is very rare. In highly selected patients (patients with chronic hepatopathy or Child–Pugh class A cirrhosis) surgical resection, usually in the form of minor hepatectomy, can be performed with low morbidity and mortality and adequate survival.

Conflicts of interest

None declared.

References

1. Song E, Chen J, Ou Q, Su F. (2001) Rare occurrence of metastatic colorectal cancers in livers with replicative hepatitis B infection. *Am J Surg* 181:529–533.
2. Utsunomiya T, Saitsu H, Saku M, Yoshida K, Matsumata T, Shimada M *et al*. (1999) Rare occurrence of colorectal cancer metastasis in livers infected with hepatitis B or C virus. *Am J Surg* 177:279–281.
3. Hamaya K, Hashimoto H, Maeda Y. (1975) Metastatic carcinoma in cirrhotic liver. Statistical survey of autopsies in Japan. *Acta Pathol Jpn* 25:153–159.
4. Vanbockrijck M, Kloppel G. (1992) Incidence and morphology of liver metastasis from extrahepatic malignancies to cirrhotic livers. *Zentrabl Pathol* 138:91–96.
5. Iascone C, Ruperto M, Barillari P. (2005) Occurrence of synchronous colorectal cancer metastasis in the cirrhotic or fatty liver. *Minerva Chir* 60:185–190.
6. Strasberg SM. (2005) Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 12:351–355.
7. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213.
8. Figueras J, Torras J, Valls C, Llado L, Ramos E, Marti-Rague J *et al*. (2007) Surgical resection of colorectal liver metastases in patients with expanded indications. A single-centre experience with 501 patients. *Dis Colon Rectum* 50:478–488.
9. Llovet JM, Buix J. (2008) Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 48 (Suppl):20–37.
10. McCormack L, Capitanich P, Quiñonez E. (2008) Liver surgery in the presence of cirrhosis or steatosis: is morbidity increased? *Patient Saf Surg* 2:8–17.
11. Seymour K, Charny RM. (1999) Evidence that metastasis is less common in cirrhotic than normal liver: a systematic review of postmortem case–control studies. *Br J Surg* 86:1237–1242.
12. Figueras J, Valls C, Rafecas A, Fabregat J, Ramos E, Jaurrieta E. (2001) Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. *Br J Surg* 88:980–985.
13. Pawlik T, Assumpcao L, Vossen JA, Buijs M, Gleisner AL, Schulick RD *et al*. (2009) Trends in non-therapeutic laparotomy rates in patients undergoing surgical therapy for hepatic colorectal metastases. *Ann Surg Oncol* 16:371–378.
14. Sarpel U, Bonavia AS, Grucela A, Roayaie S, Schwartz ME, Labow DM. (2009) Does anatomic versus non-anatomic resection affect recurrence and survival in patients undergoing surgery for colorectal liver metastases? *Ann Surg Oncol* 16:379–384.
15. Yan TD, Lian KQ, Chang D, Morris DL. (2006) Management of intrahepatic recurrence after curative treatment for colorectal liver metastases. *Br J Surg* 93:854–859.
16. Alberts SR. (2006) Evolving role of chemotherapy in resected liver metastases. *J Clin Oncol* 24:4952–4953.