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# Prognostic factors after resection of colorectal cancer liver metastases

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A B S T R A C T

*Introduction:* There are many studies that analyse preoperative factors with a poor prognosis in patients undergoing surgery for colorectal carcinoma liver metastases, in order to avoid unnecessary surgery . However, there are few studies that evaluate the intra- and postoperative prognostic factors. The aim of this study is to analyse pre-, intra-, and postoperative prognostic factors in a series of 210 patients undergoing surgery for colorectal carcinoma liver metastases, with special emphasis on the postoperative factors that can give us information on the aggressiveness of the tumour and the curative effectiveness of the surgery.

*Patients and method:* Between September 1996 and December 2006, 210 patients undergoing surgery for colorectal carcinoma liver metastases in whom we analysed pre-, intra-, and postoperative factors of survival. Mean follow-up was 55 (3) months (range, 12-124 months).

*Results:* The postoperative mortality rate was 1.4% and the morbidity rate was 22%. Actuarial and disease-free survival at 1-, 3-, and 5-years was 89.9% versus 63%, 66.9% versus 32%, and 53.8% vs 23%, respectively. Among the preoperative factors analysed, the age >65 years and LM size >5 cm were independent predictors of poor overall survival, whereas the other 2 significant factors were obtained from those analysed postoperatively: presence of microsatellitosis and postoperative CEA levels (at 1 and 3 months).

*Conclusions:* In patients with colorectal carcinoma liver metastases we must take into account certain postoperative factors that can give us information on the aggressiveness of the tumour and the effectiveness of the surgery.



## Factores pronósticos tras resección hepática de metástasis hepáticas de cáncer colorrectal

*Palabras clave:*
Resección hepática
Factores pronósticos

R E S U M E N

*Introducción:* Numerosos estudios han analizado los factores de mal pronóstico preoperatorios en pacientes sometidos a resección hepática por metástasis hepáticas de cáncer colorrectal (MHCCR) con el fin de seleccionar a los pacientes para tratamiento quirúrgico. Sin embargo, los factores intraoperatorios y postoperatorios han sido poco analizados. El objetivo de este estudio es determinar los factores preoperatorios, intraoperatorios y postope-

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ratorios en una serie de 210 pacientes intervenidos por MHCCR, con especial énfasis en los factores postoperatorios, que podrían informar acerca de la agresividad del tumor y de la eficacia curativa de la cirugía realizada.

*Pacientes y método:* Realizamos un estudio prospectivo en 210 pacientes intervenidos de MHCCR entre septiembre de 1996 y diciembre de 2006, en el que analizamos factores de supervivencia preoperatorios, intraoperatorios y postoperatorios. El seguimiento fue de 55 ± 3 (intervalo, 12-124) meses.

*Resultados:* La mortalidad postoperatoria fue del 1,4% y la morbilidad, del 22%. Las supervivencias actuariales frente a intervalos libres de enfermedad a 1, 3 y 5 años fueron del 89,9 frente al 63%, el 66,9 frente al 32% y el 53,8 frente al 23%, respectivamente. Entre los factores preoperatorios analizados, la edad > 65 años y el tamaño de la metástasis > 5 cm fueron factores de mal pronóstico independientes, mientras que dos factores significativos de mal pronóstico fueron obtenidos del análisis postoperatorio: microsatelitosis y cifras postoperatorias de CEA > 5 ng/ml (a 1 y 3 meses).

*Conclusiones:* En pacientes con MHCCR es necesario tener en cuenta los factores postoperatorios que pueden informarnos acerca de la agresividad del tumor y de la eficacia de la cirugía.



## Introduction

The treatment with intention to cure in patients with colorectal cancer liver metastases (CCLM) is liver resection (LR), in case R0 resection can be achieved with low morbidity and mortality.[1-3] There are many studies[4-11] that have analysed the classical post-operative prognostic factors for survival, in order to avoid unnecessary surgery: factors relating to the patient, to the primary tumour and the liver metastases (LM). However, some authors do not contraindicate surgery in patients with poor prognostic criteria in case R0 resection can be achieved, since certain prognostic factors can only take place after LM resection (histology, morbidity rate, carcinoembryonic antigen [CEA], post-operative period, and adjuvant chemotherapy). While the pre-operative CEA is considered a poor prognostic factor (CEA >10,[11] >30,[5] >50,[7] >200[4] ng/mL), few studies[2-10] have analysed the CEA at 1 to 3 months after operation as a measure of the effectiveness of the surgery, which could be relevant to subsequent treatments.

The aim of this study is to analyse, pre-operative, intra-operative factors and those obtained after LR in a series of 210 patients undergoing LR with CCLM, including histological factors, post-operative morbidity, postoperative CEA levels (at 1 and 3 months), and adjuvant chemotherapy.

## Patients and Method

Between September 1996 and December 2006, we operated on 210 patients diagnosed with CCLM, performing 273 LR. The mean (standard deviation) (range) age was 61 (12) (23-84) years, the majority men (n=140). The mean follow up was 55 (3) (12-124) months.

During this period, a total of 270 patients with CCLM were evaluated in our unit, of whom 176 (65.1%) were initially considered operable. Of these, 162 patients underwent LR (92% resection), and the remaining 14 were administered palliative chemotherapy for inoperable liver disease (n=9) or disseminated disease (n=5). Of the 94 patients who were not initially operable, a total of 48 of these (51%) of cases, 25 with chemotherapy, 8 with portal occlusion techniques (POT), and 15 with POT and chemotherapy. In 23 patients POT was required on the grounds of insufficient residual liver volume (RLV) (preoperative portal embolism [PPE] in 7 cases and resection on 2 occasions in the remaining 16 cases).

In the case of LR of 4 or more segments, helical computerised tomography (CT) was performed for RLV calculation, and insufficient RLV was deemed when <25% in healthy livers and <35% in diseased livers (diabetic or stenosis due to prior chemotherapy).[12]

Of the 210 patients operated, 99 (47.8%) presented synchronic LM. In 41 (19.5%), at the time of the LR, R0 extrahepatic disease was present: 3 cases of relapsing CCR; 8 cases of pulmonary metastases; 8 cases of hilar (N1) lymph node involvement, in which case a lymphadenectomy was performed; 20 cases in which diaphragm and localised peritoneal implants resection were performed (in 2 cases with related intestinal resection), 1 case of pulmonary metastasis and peritoneal implants, and 1 case of hilar lymph node involvement (N1) and peritoneal implants. All the peritoneal implants were localised, without ascites or peritoneal carcinomatosis.

### *Surgical Technique*

In all cases, after exploring the abdominal cavity, intraoperative palpation and ultrasound were performed on the liver. During the parenchema section, we maintained a central venous pressure <4 mm Hg associating a perfusion of nitroglycerine at 1 µg/kg/min. In the LR performed by laparotomy, the parenchematose section was performed with the Cusa Excel surgical aspirator and argon scalpel. In the laparoscopic LR, Ligasure Atlas was used, with a harmonic scalpel and endovascular catheters.[13,14] The Pringle

**Table 1. Univariate Analysis. Preoperative Prognostic Factors. Factors Depending on the Patient and on the Primary Tumour (n=207)**

| | Cases, No. (%) | Survival 1 Year, % | Survival 3 Years, % | Survival 5 Years, % | Survival, Mean (SD), mo | Log-Rank | *P* |
|---|---|---|---|---|---|---|---|
| Patient dependent factors | | | | | | | |
| Age | | | | | | | |
| ≤65 y | 121 (58.5) | 90.9 | 71.9 | 60.6 | 74.7 (5.7) | 3.98 | .05 |
| >65 y | 86 (41.5) | 88.1 | 55.1 | 39.6 | 60.7 (8.1) | | |
| Sex | | | | | | | |
| Male | 137 (66.2) | 89.1 | 64.6 | 53.1 | 70 (5.7) | 0.67 | NS |
| Female | 70 (33.8) | 91.3 | 71.1 | 44.6 | 69 (7.5) | | |
| Preoperative morbidity | | | | | | | |
| Yes | 89 (42.9) | 86.5 | 66.7 | 59 | 66.7 (7.2) | 0.99 | NS |
| No | 118 (57.1) | 92.2 | 67 | 51 | 69 (5.6) | | |
| Factors depending on the primary tumour | | | | | | | |
| Location | | | | | | | |
| Colon | 116 (56) | 87.8 | 63.2 | 49.5 | 67.1 (7) | 1.05 | NS |
| Rectum | 91 (44) | 91.4 | 69.6 | 57 | 70.3 (6) | | |
| T CCR | | | | | | | |
| T1-T2 | 28 (13.5) | 85.7 | 61.1 | 55 | 77 (11.5) | 0.01 | NS |
| T3-T4 | 179 (86.5) | 90.4 | 67.8 | 53.3 | 66.4 (4.9) | | |
| Lymph node involvement | | | | | | | |
| N0 | 75 (36.2) | 90.7 | 67.2 | 59.1 | 71 (6.9) | 0.13 | NS |
| N1-N2 | 132 (63.8) | 89.3 | 66.7 | 50.5 | 64 (5) | | |
| Differentiation | | | | | | | |
| Good | 22 (10.6) | 81 | 75.9 | 63.2 | 82.9 (12) | 0.99 | NS |
| Moderate | 175 (84.5) | 90.9 | 65.6 | 52.4 | 69.3 (5.3) | | |
| Poor | 10 (4.9) | 90 | 70 | 42 | 58.4 (12) | | |

CCR indicates colorectal cancer; T, TNM classification.

manoeuvre was performed in 63 patients with a mean of 10 (2) (5-22) min.

A total of 273 LR were performed in 153 patients: 1 LR; in 41 patients with intrahepatic relapse, 88 LR (in 36, 2 LR; in 4, 3 LR; and in 1, 4 LR). The remaining 32 LR were resections in 16 patients on 2 occasions. In 28 patients, laparoscopic LR was performed; 126 were major LR and 147 were minor LR. In 19 cases, intraoperative radiofrequency was added to complete the R0 resection.

The mean surgical time was 194 (88) min. Of the 210 patients, a total of 50 (23%) received transfusions. Twenty-one percent of 273 resections needed transfusions, with an average of 832 (539) (300-3600) mL. Vascular occlusion of the residual liver was not used in any of the major resections with hemihepatic vascular control, in order to minimise the risk of post-operative liver failure.

### *Follow-up*

The same surgical team followed-up all the patients at 1 month, at 3 months and, after the first year, every 6 months, with a prospective protocol. No patients were lost from the follow up. In all cases, the preoperative CEA levels were measured on the day before surgery, and post-operatively at 1 month and at 3 months of intervention. The patients were referred to the oncology units 1 month postoperatively for subsequent treatment with adjuvant chemotherapy.

### *Statistical Method*

The prognostic variables analysed are presented in Tables 1-5.

The data were processed with SPSS 11.5 statistical programme for Windows. Survival rates were calculated using the Kaplan-Meier estimation method, and the survival curves were compared with the log-rank test or with the Breslow test. The survival data of each group were summarised by the survival rates at 1, 3, and 5 years with their 95% of confidence intervals (CI). The possible prognostic survival factors were analysed excluding the patients who died in the immediate post-operative period and were evaluated with the proportional Cox regression risk. We present the results of the prognostic survival factors, statistically significant selected with the odds ratio of each category and its 95% of CI (a *P* value less than .05 was considered significant).

## Results

Three patients died in the immediate post-operative period (1.4%): 2 of them due to pneumonia (*Morganella morganii* and *Pseudomonas aeruginosa* respectively) and 1 from heart failure. Morbidity was 22% (46 patients). Survival at 1, 3, and 5 years was 89.9%, 66.9%, and 53.8% respectively. Disease-free survival at 1, 3, and 5 years was 63%, 32%, and 23% respectively (Figure). The average hospitalisation was 9.8 (7) (3-72) days.

**Table 2. Univariate Analysis. Preoperative Prognostic Factors. Factors Dependent on Hepatic Metastases, Tumour Markers, and Extrahepatic Disease (n=207)**

| | Cases, No. (%) | Survival 1 Year, % | Survival 3 Years, % | Survival 5 Years, % | Survival, Mean (SD), mo | Log-Rank | P |
|---|---|---|---|---|---|---|---|
| Factors dependent on the metastasis | | | | | | | |
| Presentation | | | | | | | |
| Metachronic | 108 (52.2) | 87.9 | 63.2 | 48.3 | 60.9 (5.5) | 0.69 | NS |
| Synchronic | 99 (47.8) | 91.6 | 70 | 58 | 72 (6.1) | | |
| ATPM (n=108) | | | | | | 0.03 | NS |
| 6-12 mo | 39 (18.8) | 92 | 70.6 | 65.2 | 73 (9.3) | | |
| 12-24 mo | 39 (18.8) | 94.7 | 74 | 63 | 73.8 (8.4) | | |
| >24 mo | 30 (14.4) | 86.7 | 58 | 44 | 61.8 (10.5) | | |
| Distribution | | | | | | | |
| Unilobular | 134 (64.7) | 88.7 | 64.8 | 51.9 | 72 (5.5) | 0.66 | NS |
| Bilobular | 73 (35.3) | 91.8 | 70.9 | 49.6 | 62 (6.2) | | |
| Size | | | | | | | |
| <5 cm | 127 (61.4) | 91.3 | 74.1 | 61 | 79 (5.9) | 8.4 | .004 |
| ≥5 cm | 80 (38.6) | 87.5 | 55.7 | 41.5 | 56 (6.5) | | |
| Number | | | | | | | |
| <3 cm | 140 (67.6) | 89.4 | 68 | 54 | 70 (5) | 0.706 | NS |
| ≥3 cm | 67 (32.4) | 91.7 | 62 | 53.4 | 54 (6.3) | | |
| Tumour markers | | | | | | | |
| Pre-operative CEA | | | | | | | |
| ≤5 ng/mL | 127 (61.4) | 91.3 | 74.1 | 61 | 79 (5.9) | 8.4 | .004 |
| >5 ng/mL | 80 (38.6) | 87.5 | 55.7 | 41.5 | 56 (6.5) | | |
| Post-operative CEA | | | | | | | |
| <20 ng/mL | 123 (59.4) | 91.1 | 62.6 | 51.4 | 69.2 (6.4) | 0.09 | NS |
| ≥20 ng/mL | 84 (40.6) | 88 | 73.6 | 57.9 | 69.8 (6.7) | | |
| Extrahepatic disease[a] | | | | | | | |
| Yes | 41 (19.8) | 88.9 | 59.7 | 54.8 | 57.7 (7.6) | 0.73 | NS |
| No | 166 (80.2) | 92.9 | 68.5 | 53.4 | 72.9 (5.2) | | |

[a]Includes liver disease detected intraoperatively and previously undetected disease detected in the abdominal examination.
ATPM indicates average time to presentation of the metastasis.

### *Prognostic Survival Factors (n=207)*

*Univariate analysis:* the statistically significant poor prognosis factors were age >65 years (*P*=.05) (Table 1) and the size of the metastasis >5 cm (*P*=.004) (Table 2). There were no intra-operative poor prognosis factors (Table 3). Postoperative poor prognosis factors were microsatellites of the main lesion (*P*=.003) microscopic vascular metastastic venous invasion (*P*=.05) (Table 4) and raised postoperative CEA levels at 1 month and 3 months (*P*=.0001 and *P*=.0001) (Table 4). The following were poor prognostic factors: sex, location of the CCR, degree of parietal CCR infiltration, level of CCR cellular differentiation, lymph node involvement in the primary tumour (N1-N2), synchronic presentation of the metastatis, the synchronous presentation of the metastases, unilobular or bilobular location, the presence of more than 3 metastases, raised preoperative CEA levels, the presence of extrahepatic disease, invaded margin of resection, the level of cellular differentiation of the metastasis, resection type (major or minor), the performance of further resections, intraoperative transfusion, surgery duration, the presence of morbidity, and having administered or failed to administer adjuvant chemotherapy.

*Multivariate analysis*: among the preoperative factors analysed, age >65 years and the size of the LM >5 cm were independent poor prognosis factors (*P*=.043 and *P*=.019, respectively), while the other statistically significant factors were obtained from those analysed in the postoperative period: microsatellitosis (*P*=.038) and raised CEA levels at 1 and 3 months (*P*<.001 and *P*<.001, respectively) (Table 5).

## Discussion

Numerous authors[15-32] have described a series of post-operative poor prognostic factors for avoiding unnecessary surgery. These poor prognostic factors are used to prepare a series of scales, which contraindicate surgery in cases in which poor prognostic factors result in a nil survival rate at 5 years. The most commonly used of these is the Fong et al[4] classification (carried out on 1001 patients operated on for CCLM). Patients with a poor prognosis would be candidates for chemotherapy, especially when, as Adam et al[32] considered, the disease was in progression. However, there are many discrepancies in the literature with regard to the significant factors obtained, and it is difficult to rule out

**Table 3. Univariate Analysis. Intraoperative Factors (n=207)**

| | Cases, No. (%) | Survival 1 Year, % | Survival 3 Years, % | Survival 5 Years, % | Survival, Mean (SD), mo | Log-Rank | P |
|---|---|---|---|---|---|---|---|
| Resection type | | | | | | | |
| Major | 105 (50.7) | 90.5 | 65 | 51.9 | 67.3 (6) | 0.50 | NS |
| Minor | 102 (49.3) | 89 | 69 | 56 | 67.7 (5.9) | | |
| New resection | | | | | | | |
| Yes | 41 (19.8) | 86 | 67 | 58 | 56 (5.3) | 0.01 | NS |
| No | 166 (80.2) | 91 | 67 | 52.9 | 69 (5.1) | | |
| Transfusion | | | | | | | |
| Yes | 50 (24.2) | 88 | 60 | 57 | 71 (7.8) | 0.16 | NS |
| No | 157 (75.8) | 90 69 | 69 | 50 | 61 (4.5) | | |
| Surgical time | | | | | | | |
| <180 min | 78 (37.6) | 88.5 | 63.8 | 51.1 | 68.6 (8.7) | 0.045 | NS |
| ≥180 min | 129 (62.4) | 90.6 | 69 | 55.4 | 68.3 (5.6) | | |

**Table 4. Univariate Analyis. Posoperative Prognostic Factors (n=207). Histological Factors, Morbidity, Tumour Markers, and Chemotherapy (n=207)**

| | Cases, No. (%) | Survival 1 Year, % | Survival 3 Years, % | Survival 5 Years, % | Survival, Mean (SD), mo | Log-Rank | P |
|---|---|---|---|---|---|---|---|
| Histological factors | | | | | | | |
| Microsatellitosis | | | | | | | |
| Yes | 32 (15.5) | 81.3 | 47 | 33.6 | 35.3 (4.5) | 9.13 | .003 |
| No | 175 (84.5) | 91.4 | 70.7 | 58 | 73.8 (5) | | |
| Margin | | | | | | | |
| ≥1 cm | 98 (47.3) | 88.2 | 68.6 | 61.3 | 71 (6.9) | 0.60 | NS |
| 2-9 mm | 68 (32.9) | 90.7 | 67.7 | 53.2 | 68 (6.2) | | |
| Invaded | 41 (19.8) | 90.2 | 61.3 | 42.9 | 51 (6.5) | | |
| Vascular invasion | | | | | | | |
| Yes | 29 (14) | 86.2 | 53.6 | 38.3 | 40 (5.1) | 3.89 | .05 |
| No | 178 (86) | 90.4 | 69.2 | 56.3 | 73 (5.1) | | |
| Differentiation level | | | | | | 2.12 | NS |
| Good | 20 (9.7) | 95 | 68.6 | 63.3 | 77 (1) | | |
| Moderate | 183 (88.4) | 89 | 66.6 | 51.2 | 65 (5.2) | | |
| Poor | 4 (1.9) | 75 | 75 | 75 | 58 (17) | | |
| Morbidity | | | | | | | |
| Yes | 46 (22.2) | 75 | 52 | 32 | 41 (16) | 2.46 | NS |
| No | 161 (77.8) | 92 | 61 | 54 | 94 (10) | | |
| Tumour markers | | | | | | | |
| Post-operative CEA at 1 month | | | | | | 18.04 | .001 |
| ≤5 ng/mL | 155 (74.9) | 92.9 | 73 | 60.2 | 78 (5.5) | | |
| >5 ng/mL | 52 (25.1) | 80.8 | 43.6 | 32.7 | 40 (5.9) | | |
| Post-operative CEA at 3 months | | | | | | 21.22 | .001 |
| ≤5 ng/mL | 129 (62.3) | 96.1 | 76.2 | 66.3 | 81.9 (5.9) | | |
| >5 ng/mL | 78 (37.7) | 79.5 | 48.6 | 32.9 | 45.5 (5.9) | | |
| Chemotherapy | | | | | | | |
| Yes | 181 (87.4) | 90.1 | 67.7 | 54.4 | 63 (4) | 0.02 | NS |
| No | 26 (12.6) | 88 | 61.8 | 50.6 | 77 (12) | | |

CEA indicates carcionembryonic antigen.

surgery in cases where R0 resection can be achieved. In our series, age >65 years was a statistically significant factor for poor prognosis, as it also occurs in other series,[4,5,16] although we do not consider this as a formal contraindication for us or for other authors. The size of the primary metastasis >4 cm,[4] >5 cm,[4,5,17] >8 cm,[6] or > 10 cm[20] has been considered as a poor prognostic factor. The results obtained in our series are similar to those described by authors that describe a worse prognosis when the lesion is >5 cm. Other authors[7,8] did not find significant differences regarding a tumour size smaller or larger than 5 cm.

Other preoperative factors analysed in our series were not statistically significant. Thus, the presence of positive lymph nodes in the primary colorectal tumour, a poor prognosis factor according to some authors,[4,5,15] is not repeated in other series.[7,8,16,17] The CCR that invade the serose (T3-T4) may

**Table 5. Multivariate Analysis (Cox Regression Model). Poor Prognostic Factors**

| Prognostic Factors | Value | OR | 95% CI | *P* |
|---|---|---|---|---|
| Age | ≥65 y | 1.6 | 1.014-2.526 | .043 |
| Size of the LM | ≥5 cm | 1.694 | 1.090-2.631 | .019 |
| Microsatellitosis | Yes | 1.794 | 1.030-3.124 | .038 |
| Post-operative CEA (1 mo) | >5 | 2.341 | 1.471-3.727 | .001 |
| Post-operative CEA (3 mo) | >5 | 3.104 | 1.562-4.302 | .001 |

CEA indicates carcinoembryonic antigen; LM, liver metastases.

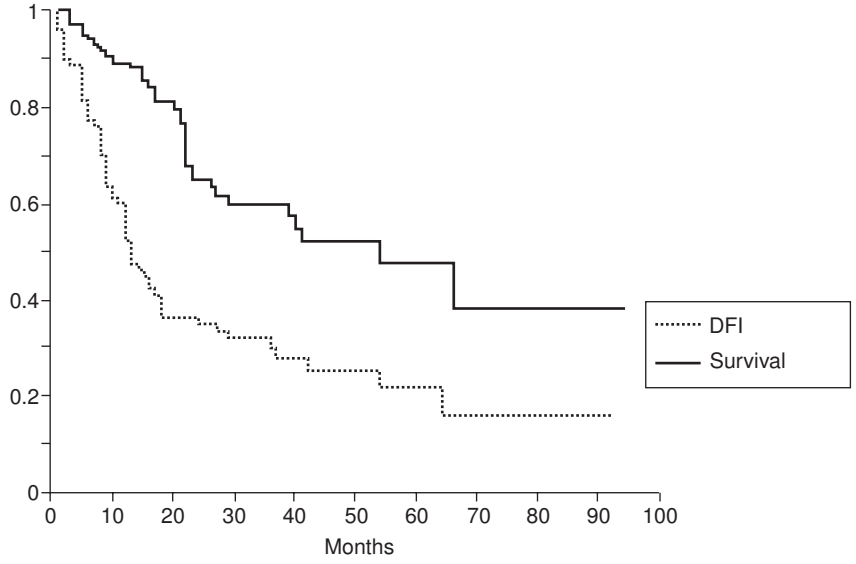


**Figure 1 – Survival and disease free interval in our series.**

have a worse prognosis,[6,17,18] although other authors[19,20] do not share these findings. A short interval between the surgery on the primary tumour and the appearance of synchronised LM,[1,2,6,7,19] before 12 months,[2,5-7,17] 24 months,[6] or 30 months[1] is considered a poor prognostic factor. The number of LM >1 was a factor for poor prognosis[4]; others[10] consider poor prognosis a number >3 and, recently, >8 LM.[16] Bi-lobular location is considered a factor of poor prognosis by some authors,[1,4,5,9] but this is not significant in other series.[7,15,18,21] Despite resectable extrahepatic disease detected preoperatively contraindicated surgery per se in the series of Fong et al,[4] they were not a contraindication for surgery for us or other authors, provided that the entire disease would be R0 once resectioned.[22,23] The same criteria was followed with the resection of relapsing livers,[24] given that patients with LR 2 and 3 presented a survival rate similar to the first LR.

There is also a series of intraoperative factors (surgical techniques used and transfusion) that can influence survival,[8] but which have not been statistically significant in our series or for other authors.[1,7,20] In accordance with the majority of authors,[25-27] we considered that non–palpable lesions, deep lesions or lesions close to the large vessels should be treated more radically by segmentary resection or routine surgical resection of the liver, and, in the case of multiple superficial lesions, or when there are doubts regarding the hepatic reserve, limited resection is advisable, the margin taking precedence over the technique chosen.

Adjuvant chemotherapy was not a prognostic factor for survival in our study, or in other series.[5,6,15,17] In contrast, Figueras et al[31] showed that the adjuvant chemotherapy is a good prognostic factor for survival (with a chemotherapy regimen comprising 5-fluorouracil and folinic acid, in a non-randomised study). With current neoadjuvant chemotherapy, we can achieve down-staging of the liver disease[32] making between 10%-20% of initially inoperable patients operable, with a 5-year survival rate in 22%-40%. Some authors suggest sequential inverted treatment in this type of patients.[33,34] Given the lack of prospective randomised study, provided that the metastases are operable, and regardless of the number of lesions, our criteria is to remove all macroscopic disease to continue with adjuvant chemotherapy, given that it is not known which patients will respond to this treatment (between 30%-50% of patients do not respond to current chemotherapy).

On the other hand, some factors obtained in the post-operative period could give guidance regarding the prognosis and efficiency of the surgery performed. These factors are the histological study of the resection sample (microscopic vascular invasion, microsatellitosis, and resection margin) and the early post-operative measurement of post-operative CEA concentrations. A resection margin of <1 cm has been related to a larger number of local recurrences and lower survival rates,[4,8,15,28] although in our series this did not have a statistically significant effect on survival. This is a controversial aspect.[29,30] Some authors currently[29] relate the recurrence to the distance from the resection margin: 13% recurrence rate when the edge was <2 mm, 2.8% with 2-4 mm, and 0 when this was >5 mm.[30] Microscopic venous invasion was a poor prognosis factor for survival for Shirabe et al[27]: lesions >4 cm were the most frequent conditions. In our series, 29 cases presented vascular invasion, which was a poor prognosis factor in the univariate study. The presence of microsatellites has been related to recurrences in the incision line, very common when the resection border is <5 mm. In our series, 32 patients presented microsatellites and had a significantly lower rate of survival than those not presenting them (33.6% against 58% respectively), which was a significant factor in the univariate and multivariate analysis, respectively.

The preoperative CEA limits of >5, >50, >100, or >200 ng/mL were a poor prognostic factor in numerous series.[1-5,7,35] In ours, there were no statistically significant differences among the patients with raised (n=164) and normal CEA (n=43). Some authors[36-38] measure immediate postoperative CEA to evaluate the effectiveness of the surgical treatment and relate this to the relapse and the survival. Ueno et al,[36] in a retrospective study on 68 patients undergoing surgery for CCLM, analysed post-operative CEA at 1 and 3 months from surgery and found that raised post-operative figures of CEA were related to greater recurrence of the disease. Hohenberger et al[37] analysed pre- and post-operative CEA in 166 patients undergoing surgery for CCLM; the pre-operative figures were not statistically significant, while raised postoperative levels were the negative predictive factor with the greatest influence in terms of survival. Gervaz et al[38] analysed the post-operative values of CEA and the resection margins in a series of 49 patients with CCLM resection, and determined that the raised values were a poor prognostic factor and that the resection margins did not influence these, even when they were invaded. In our series, the 5-year survival rate among those who had normalised post-operative figures at 1 month was significantly higher (60.2%) than that of the patients who maintained raised CEA figures (32.7%) at 1 and 3 months. In these cases, the search for residual diseases (lesions <1 cm that may go unnoticed), the possibility of further surgery or more aggressive chemotherapy are factors that must be taken into account in the follow up.

In conclusion, in the literature there is no evidence that enables us to rule out patients with CCLM for surgery, on the basis of preoperative poor prognostic factors, provided all the disease can be resectioned by R0, on the basis that in our series the most relevant factors for poor prognosis are obtained postoperatively.

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