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ORIGINAL ARTICLE

The influence of steatosis on the short- and long-term results of resection of liver metastases from colorectal carcinoma

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Abstract

We aimed to establish whether the presence of hepatic steatosis influences outcome after resection of colorectal liver metastases (CLM).

Patients and methods: Patients operated between 1990 and 2014 were divided into four groups based on the degree of hepatic steatosis. The association between hepatic steatosis and outcome was analyzed, using a multivariate and a propensity score case-match analysis.

Results: No significant differences were observed between patients with and without steatosis in either mortality or morbidity in the complete series or after matching (3.2% vs. 3.5%/p = 0.845) (32.3% vs 31.4%/p = 0.802). Five-year survival in patients with and without steatosis were 56.5% and 46.5% respectively (p = 0.046). The steatosis had a significant protective effect in the univariate analysis (HR (95% CI) = 0.78 (0.62–0.99) p = 0.048), and was close to significance in the multivariate analysis (HR (95%) = 0.81 (0.63–1.03) p = 0.089). No significant differences were seen with regard to liver recurrence.

Conclusions: The presence of steatosis does not predict short-outcome after resection of CLM, but appears to be a favorable prognostic factor for survival. This protective effect does not depend on a decrease in liver recurrence.

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Introduction

Steatosis is the most common histopathological alteration of the liver. It affects more than 30% of the western population[1–3] and consists of the accumulation of triglycerides inside the liver cells. The reported incidence in patients operated on for liver metastases from colorectal carcinoma (CLM) is highly variable (20–80%).[4–7] The etiology of liver steatosis is multifactorial but in patients with CLM it is often associated with obesity, preoperative chemotherapy (especially regimens that include irinotecan) and alcohol consumption.[8–10]

Some reports have described an association between steatosis and increased postoperative morbidity and mortality, particularly after major resection.[11] It has also been reported that hepatic steatosis may affect the long-term results of resection of CLM.[12–14] As a result of these observations, some authors[5,11,12,14–16] have suggested that a specific surgical strategy should be designed for patients with CLM who present steatosis.

The aim of this study is to analyze the effect of hepatic steatosis on the results of postoperative morbidity and mortality, survival, and liver recurrence in patients who had undergone surgery for CLM in a single-center prospective series.

Patients and methods

A prospectively compiled database including all patients operated upon for CLM between January 1990 and December 2014 was analyzed retrospectively. The data of the patients were anonymized for the purposes of this analysis. Written informed consent was considered not necessary for the study, as it is a retrospective analysis of our usual everyday work. This study was

approved by the Clinical Research Ethics Committee of the University Hospital of Bellvitge. The patients were selected for surgery unless they presented unresectable extrahepatic disease and provided that the planned liver remnant was considered sufficient. The preoperative extension study was performed using multislice CT with intravenous contrast, and from 2000 onwards MRI with gadolinium was added in patients with hepatic steatosis.

Preoperative chemotherapy based on 5FU and folinic acid protocols or oxaliplatin regimens was administered to 43.9% of patients. Fewer than 5% of patients received irinotecan-based protocols.

During surgery an exploratory laparotomy and intraoperative ultrasound were performed to detect any lesions that had gone unnoticed in the preoperative study and the Pringle maneuver was used at the discretion of the surgeon. The ISGLS definition of liver failure[17] was used.

After surgery, all patients were referred to the oncology department where the indication of adjuvant chemotherapy was assessed.

The surgical patients were seen every six months for a physical examination, measurement of carcinoembryonic antigen and imaging study (CT or MRI). Patients with hepatic recurrence were treated with re-resection whenever possible. The degree of liver steatosis was assessed only in the first resection specimen by a specialized pathologist, who was not aware of the anthropometric characteristics of the patients.

Definitions

Liver metastases were categorized as synchronous when diagnosed simultaneously, or within three months of the diagnosis of the primary tumor. Major resection was considered as the removal of three or more segments.

Steatosis was defined as the presence of fat vacuoles affecting more than 5% of liver cells. To assess the influence of the degree of steatosis on the results, a qualitative variable with four grades was created: no steatosis (0–5%), mild steatosis (>5% and <30%) moderate steatosis (30%–60%) and severe steatosis (>60%).

Because of the length of the study period, it was divided into three subperiods: 1990–2004, 2005–2009, and 2010–2014, each including approximately 300 patients. Tumor-free margins of less than 1 mm were considered affected.

Postoperative complications where classified according to Dindo-Clavien system.[18]

Statistical analysis

Qualitative variables were compared between groups using the Chi-square test, and quantitative variables using the Student t test. Survival and tumor recurrence were analyzed using the Kaplan–Meier test and the log-rank test was applied to compare survival between groups.

To avoid the bias related to the different distribution of covariates among patients with and without steatosis, a propensity score analysis was carried out to obtain a one–one match with an acceptable matching difference of up to 0.1. The covariates used in the model are specified in the results section. Once the groups were obtained, the differences in the variables were reanalyzed to confirm that the matching was adequate.

Subsequently, a multivariate analysis of predictors of postoperative mortality and morbidity was performed using the logistic regression model, and prognostic factors for survival and liver recurrence were assessed using the Cox model. The variables that were significant in the univariate analysis ($p < 0.1$) were included in the multivariate analysis. The results are expressed as a hazard ratio (HR) with 95% confidence intervals. The statistical analysis was performed using SPSS version 22.0 software (IBM, Armonk, New York, USA).

Results

During the study period, 1271 CLM interventions were performed in 1163 patients. After excluding patients for whom no data on the percentage of steatosis were available, patients with fibrosis and lost to follow-up, the population was reduced to 934 cases. In this population, the incidence of steatosis was 45% and the mean follow-up time was 47.05 (SD = 41.8) months. Steatosis was mild in 30.2% of patients, moderate in 10.7%, and severe in 4.2%. In the patients who received preoperative chemotherapy (44.2%), the rate of steatosis was similar to that observed in untreated patients (41.9% vs 47.7%, $p = 0.078$).

Postoperative mortality and morbidity

No significant differences in postoperative mortality at 90 days were observed between patients with and without steatosis (Table 1), or between patients with different degrees of steatosis (mild: 3.5%, moderate: 3%, severe: 2.6%, $p = 0.931$).

No significant differences in mortality were observed after major resection (without steatosis: 4.5%, mild: 6.2%, moderate: 5.9%, and severe: 7.1%, $p = 0.867$) even after hilar clamping longer than 20 min (6.2%, 6%, 2.9% and 8.3% respectively, $p = 0.087$).

Patients with severe steatosis had a significantly lower proportion of major resections than patients without steatosis (35.9% vs 52.5%, $p = 0.036$). Only 14 patients with steatosis above 60% underwent major resection. A trend was also seen towards a lower proportion of patients over 70 years (15.4% vs 28.5%, $p = 0.077$) and a less frequent indication of preoperative chemotherapy (31.6% vs 47%, $p = 0.066$). These differences were not observed with the other grades of steatosis.

No significant differences were observed in morbidity either when comparing patients with and without steatosis (Table 1), or