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# Differential impact of obesity and diabetes mellitus on survival after liver resection for colorectal cancer metastases

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ARTICLE INFO

*Article history:*
Received 16 March 2015
Received in revised form
27 May 2015
Accepted 29 May 2015
Available online 4 June 2015

*Keywords:*
Colorectal cancer metastases
Liver resection
Obesity
Diabetes mellitus
Outcome
Survival

ABSTRACT

*Background:* Data on the potential effect of obesity and diabetes mellitus on survival after liver resection due to colorectal cancer (CRC) metastases are very limited.
*Methods:* Patients undergoing liver resection for CRC metastases in a European institution in 2004–2011 were retrospectively enrolled. Relevant data, such as body mass index, extent of resection, chemotherapy, and perioperative outcome, were collected from medical records. The relation of obesity and diabetes mellitus with overall and disease-free survival was assessed using adjusted Cox models.
*Results:* Thirty of 207 patients (14.4%) included in the study were obese (BMI $\geq$30 kg/m$^2$) and 25 (12%) had diabetes mellitus. Major hepatectomy was performed in 46%. Although both obese patients and those with diabetes had higher American Society of Anesthesiologist scores ($P < 0.05$ for both), neither obesity nor diabetes was significantly related to primary tumor characteristics, liver metastasis features, extent or radicality of resection, extrahepatic disease at hepatectomy, preoperative or postoperative oncologic therapy, or perioperative outcome ($P > 0.05$ for all). Patients were followed up for a median of 39 mo posthepatectomy (interquartile range, 13–56 mo). After adjustment for confounders, obesity was an independent predictor of improved (hazard ratio, 0.305, 95% confidence interval, 0.103–0.902) and diabetes of worse overall survival (hazard ratio, 3.298, 95% confidence interval, 1.306–8.330). Obese patients with diabetes had also worse disease-free survival compared with the rest of the cohort ($P < 0.05$).
*Conclusions:* After hepatectomy for CRC metastases, obesity does not seem to be associated to poor outcome while diabetes mellitus has a negative impact on prognosis.



## 1. Introduction

Obesity is increasing worldwide and it is a risk factor for colorectal cancer (CRC) development [1]. A significant proportion of patients with CRC, develop liver metastases, and a small fraction may be amenable to curative liver resection. Thus, up to 40% of patients with CRC metastases undergoing hepatectomy may be obese [2–4]. Although several reports have shown that obesity is associated with higher odds of perioperative complications after hepatectomy

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0022-4804/$ – see front matter 
http://dx.doi.org/10.1016/j.jss.2015.05.059

[2,5–7], published data are not unanimous [4,8–10]. Also, in most studies, only a fraction of enrolled patients had undergone hepatectomy due to CRC metastases, as patients with other indications including benign conditions, and with underlying end-stage liver disease were also included [2,5–7,9–11].

Obesity may affect prognosis after cancer diagnosis [1]. In advanced CRC, it has been reported to have a detrimental effect on overall survival and disease recurrence [12,13], but published reports are inconsistent [14]. Data on the impact of obesity on survival after liver resection for CRC metastases are very limited. Although overall survival has been shown to be prolonged with increasing body mass index (BMI) after hepatectomy for various types of cancer [2], this was not confirmed in a recent study in patients undergoing liver resection due to CRC metastases [3]. Finally, diabetes mellitus is frequent in obesity and may have a negative impact on oncologic outcomes in CRC [15], but data on its potential effect on survival after liver resection for CRC metastases are scarce.

The primary aim of the present study was to evaluate the potential role of obesity and diabetes mellitus in survival after liver resection for CRC metastases. Secondarily, we also aimed to assess the potential impact of obesity and diabetes on perioperative morbidity in these patients.

## 2. Patients and methods

### 2.1. Patients

All consecutive patients who underwent liver resection due to CRC metastases at the Skåne University Hospital in Lund, Sweden in 2004–2011 were retrospectively identified through a search of the computerized discharge register of the hospital. Repeat resections were excluded. Medical records were scrutinized, and patients without an available preoperative height and/or weight were also excluded. Relevant data were collected, such as demographics, site, and TNM staging of the primary tumor, number and size of liver metastases, preoperative chemotherapy and its intent (adjuvant after resection of primary CRC or neoadjuvant before hepatectomy), date and extent of liver resection, American Society of Anesthesiologists (ASA) score, postoperative chemotherapy, and its intent (adjuvant after hepatectomy or palliative). Preoperative locoregional treatment, such as portal vein embolization, was also registered. History of diabetes and arterial hypertension were noted. The Charlson comorbidity index was calculated as a measure of the burden of comorbid illness [16], excluding malignant tumors. A resection margin of <1 mm was considered a positive margin, whereas a margin of ≥1 mm was considered a tumor-free margin. Resections of ≥3 liver segments were considered major resections. The cohort was stratified into underweight (BMI <18.5 kg/m$^2$), normal (BMI 18.5–24.9 kg/m$^2$), overweight (BMI 25–29.9 kg/m$^2$), and obese patients (BMI ≥30 kg/m$^2$) according to the World Health Organization criteria. Analyses were performed between obese (BMI ≥30 kg/m$^2$) and nonobese patients (BMI <30 kg/m$^2$). The study protocol was approved by the local ethics committee.

### 2.2. Outcome parameters

The primary outcome end point of the study was overall survival (from hepatectomy until death from any cause). Alive patients were censored at last follow-up. Death *versus* alive status was ascertained through medical records and the regional health care administrations system. Secondary end points were disease-free survival, calculated from the date of liver resection to tumor recurrence or death due to any cause, postoperative mortality, defined as mortality from any cause within 30 and 90 d after liver resection, and postoperative complications. Length of intensive care unit (ICU) stay and total length of stay (LOS), from liver resection until discharge, were also analyzed. Complications were graded according to the Dindo–Clavien classification [17], and those with a score of ≥3 were considered severe. Complications were further classified as non–liver related (cardiovascular, respiratory, infection, bleeding, acute kidney injury, and other) and liver related. Bleeding was defined as need for intraoperative or postoperative blood transfusions. Acute kidney injury was defined as previously described [18]. Liver-related complications included postoperative hepatic failure, defined as peak postoperative total bilirubin >7 mg/dL [19] and/or ascites, and bile leak.

### 2.3. Statistics

Data are presented as mean and standard deviation (SD) or *n* (%) as appropriate. When comparing groups, the chi-square test or Fisher exact test was used for categorical variables, whereas analysis of variance or the Mann–Whitney test was used for continuous variables, as appropriate. Logistic regression analyses were used to adjust for confounders in the relation between, on the one hand, obesity and, on the other hand, complications, prolonged length of ICU stay (≥1 d), and prolonged LOS (≥10 d, i.e., ≥ the 75th percentile of the whole cohort). Confounding factors included age, gender, the ASA score, the Charlson comorbidity index, type of resection, and diabetes, and any parameter in our cohort found to be related to postoperative complications or prolonged ICU stay and LOS in univariate analysis at $P < 0.1$. The relationships of obesity and diabetes with overall and disease-free survival were assessed with survival analysis (Kaplan–Meier), and groups were compared with the log-rank test. Cox regression analysis was used to adjust for confounders, that is, node positive primary, >3 liver metastases, size of the largest ≥5 cm, carcinoembryonic antigen >60 ng/mL, positive resection margin, and extrahepatic disease [20], as well as any parameter found to be related to overall survival (ASA score, the Charlson comorbidity index, the number of perioperative complications, liver-related complications, T stage of the primary tumor, and adjuvant chemotherapy after hepatectomy) or disease-free survival (ASA score, multiple or severe perioperative complications, perioperative bleeding, locoregional treatment after surgery, preoperative chemotherapy, and adjuvant chemotherapy after hepatectomy) in univariate analysis at $P < 0.1$ in our cohort. For overall survival, our data set would have a power of 0.78 to detect a hazard ratio of 0.4 for obesity, given a type 1 error of 5%. Reported $P$ values are two-tailed, and the significance level was set at $P < 0.05$.