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Equivalent survival in patients with and without steatosis undergoing resection for colorectal liver metastases following pre-operative chemotherapy☆

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Abstract

Background: We previously reported that the presence of steatosis did not adversely influence survival in patients undergoing resection for colorectal liver metastases (CLM) without pre-operative chemotherapy. Here, this hypothesis is tested in patients undergoing resection for CLM following pre-operative chemotherapy.

Methods: We assessed the effects of background liver pathology, categorized as 'normal', 'steatosis' and 'other', on perioperative mortality, overall survival (OS) and cancer-specific survival (CSS) in LiverMetSurvey patients. Survival analyses included log-rank tests and multivariate Cox models, incorporating well-established prognosticators. In secondary analyses, re-populating the model with non-chemotherapy patients, the effect modification of chemotherapy on the impact of steatosis on survival was tested.

Results: Of 4329 patients undergoing first-time liver resection following pre-operative chemotherapy, histologies were normal in 1913 (44%), steatosis in 1675 (39%), and other abnormal pathologies in 741 (17%). For normal, steatosis and other, 90-day mortalities were 2.1%, 2.3%, and 3.5% ($P = 0.103$). For the three histo-pathological groups, 5-year OS rates were 39%, 42%, and 36% ($P_{logrank} = 0.363$); 5-year CSS rates were 43%, 45% and 41% ($P_{logrank} = 0.496$), respectively. The associations of steatosis with OS and CSS were materially unchanged in the multivariate models. Chemotherapy did not interact with the effect of steatosis on survival.

Conclusion: The findings of equivalent survivals challenge the common perception that steatosis in CLM patients after pre-operative chemotherapy is associated with increased peri-operative mortality and poorer long-term survival.

Keywords: Steatosis; Liver resection; Colorectal cancer; Chemotherapy; Survival

Introduction

Hepatic steatosis is the pathological accumulation of intra-hepatic triglycerides,[1] and is estimated to occur in one third of the Western adult population.[2,3] The diagnosis is conventionally made, at the time of histological examination, when ≥5 per cent of liver tissue contains fat.[4] The presence of steatosis mirrors the presence of excess body adiposity, and in turn, the latter is a risk factor for incident

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colorectal cancer.[5,6] Therefore, it is reasonable to speculate that steatosis might be an adverse factor for outcome after resection of colorectal liver metastases (CLM).

In patients undergoing resection of CLM, background liver steatosis may additionally be caused by preoperative chemotherapy (notably but not exclusively irinotecan-containing regimens),[7,8] in which the histological appearance is indistinguishable from that observed in a state of excess body adiposity. Steatosis is a relatively common finding in liver resection specimens, with rates varying from 18 to 56 per cent, depending on the diagnostic criteria used.[9–11] Several reports have described an association between steatosis and increased risk for perioperative morbidity, particularly in patients undergoing a major liver resection[9,12–14] (removal of three or more segments according to the Brisbane 2000 Terminology of Liver Anatomy and Resections[15]). A meta-analysis[16] concluded that moderate/severe steatosis (≥30 per cent) was associated with an increased risk for perioperative mortality, but apart from the study by Behrns *et al.*[12] (published at a time when it was uncommon to administer pre-operative chemotherapy), the other studies in that analysis lumped together patients with steatosis regardless of whether they had or had not received preoperative chemotherapy.[16] For long-term survival, to-date four studies have evaluated the impact of steatosis or steatohepatitis – one included cancer types other than CLM[13]; two were small CLM cohorts, and compared with patients without steatosis, reporting non-significant reductions in median overall survival (OS) and recurrence-free survival in patients with steatosis[11] and severe grade steatohepatitis,[17] respectively; and one large study, using a propensity score matching process to reduce confounding, reported significant reductions in local recurrence-free survival, but no change in OS, associated with the presence of steatosis.[18] If the confounding effects of preoperative chemotherapy are not taken into account, it is unclear whether obesity-related steatosis *per se* or the factors that select for preoperative chemotherapy impact adversely on early and long-term outcomes.

We previously reported, from LiverMetSurvey, that the presence of steatosis did not adversely influence survival in patients undergoing resection for CLM without pre-operative chemotherapy. Here, this hypothesis is tested in patients undergoing resection for CLM following pre-operative chemotherapy.

Methods

Database

LiverMetSurvey (http://www.livermetsurvey.org) is a prospective international database of patients undergoing surgery for CLM that comprises data voluntarily registered by 483 centres across 69 countries.[19–24] Details about the primary tumour, number, size, and location of liver metastases, chemotherapy history, hepatic resection, postoperative complications and survival are entered using a standardized online questionnaire. Data quality control is assessed by online queries and a bi-annual review by the survey data manager.

Histological categorization

The local clinical team uses the online questionnaire to document whether background non-tumour liver histology was normal or abnormal. If abnormal, a tick-box list is completed to indicate whether this reflected 'congestion', 'fibrosis', 'nodular regenerative hyperplasia', 'steatosis' or 'other'. More than one box may be ticked and free text used.

For the purpose of the primary analysis and to facilitate comparison with results for non-chemotherapy patients in the same LiverMetSurvey cohort,[22] background (non-tumour parenchymal) liver histology was categorized into three: "normal"; "steatosis"; and "other" (other hepatic pathologies apart from steatosis e.g. 'congestion', 'fibrosis', 'nodular regenerative hyperplasia'). Combinations of more than one category were re-allocated such that steatosis entries were given hierarchical preference to the steatosis category. For example, 'steatosis & fibrosis' or free-text documentation of 'steatohepatitis' were placed in the "steatosis" category; free-text phrases such as 'sinusoidal obstruction syndrome' and 'vascular congestion' were re-coded as congestion and placed in the "other" category.

As a secondary analysis, background liver histology was reclassified (denoted by "R-" prefix) to explore other histological abnormalities of clinical relevance in CLM patients treated with pre-operative chemotherapy – namely pure steatosis (i.e. not in combination with any other histological abnormalities); steatosis with fibrosis (used here as a surrogate marker of steatohepatitis); and sinusoidal congestion (Fig. S1, supplemental material).

Inclusion criteria

We included patients undergoing first-time resection between 1990 and 2011 with information on background liver histology, treated with pre-operative chemotherapy. Patients with the following were excluded: (i) non-surgical interventions; (ii) repeat resections; and (iii) absent reporting of background liver histology. For the main analysis, all patients recorded in the registry as 'Chemotherapy pre-operative – *yes*' were included. Sensitivity analyses were subsequently performed to explore the effect of steatosis on survival stratified by the timing of pre-operative chemotherapy and the number of recorded cycles. Duration of pre-operative and number of cycles were dichotomized at cut-off points of six months and three cycles, respectively, based on definitions used in the New EPOC trial[25] and previous LiverMetSurvey studies.[19,23]

Follow-up and outcome measures

Data recorded on the 'latest news' survey page were extracted to ascertain follow-up and vital status; recorded as alive, dead, and whether the death was cancer-related.