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ORIGINAL ARTICLE

The impact of neoadjuvant chemotherapy on skeletal muscle depletion and preoperative sarcopenia in patients with resectable colorectal liver metastases

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Abstract

Background: Preoperative skeletal muscle depletion or sarcopenia has been suggested to predict worse outcome after resection of colorectal liver metastases. The aim of the present study was to investigate the impact of neoadjuvant chemotherapy on preoperative skeletal muscle mass prior to liver resection.

Methods: Patients operated with liver resection for colorectal liver metastases between 2010 and 2014 were retrospectively reviewed. Muscle mass was evaluated by measuring muscle area on a cross-sectional computed tomography image at the level of the third lumbar vertebra, and normalized for patient height, presenting a skeletal muscle index.

Results: Preoperative skeletal muscle mass was analysed in 225 patients, of whom 97 underwent neoadjuvant chemotherapy. In total 147 patients (65%) were categorized as sarcopenic preoperatively. Patients receiving neoadjuvant chemotherapy decreased in skeletal muscle mass (decrease by 5.5 (–1.1 to 11) % in skeletal muscle index, $p < 0.001$). Patients with muscle loss >5% during neoadjuvant chemotherapy were less likely to undergo adjuvant chemotherapy than others (68% vs 85%, $p = 0.048$). A >5% muscle loss did not result in worse overall ($p = 0.131$) or recurrence-free survival ($p = 0.105$).

Conclusion: Skeletal muscle mass decreases during neoadjuvant chemotherapy. Skeletal muscle loss during neoadjuvant chemotherapy impairs the conditions for adjuvant chemotherapy.

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Introduction

Colorectal cancer is one of the most common cancers worldwide and approximately 30% of the patients will develop liver metastases during the course of the disease.[1,2] For colorectal liver metastases (CRLM) surgery is, when feasible, the treatment of choice.[3,4] In addition, perioperative chemotherapy has been shown to prolong progression-free survival and is considered standard care.[5] Preoperative risk assessment is important to enhance surgical outcome. Poor patient performance status may predict worse surgical outcome.[6] However, there are currently no standardized assessment tools available.

Skeletal muscle depletion or sarcopenia is a known factor affecting patient performance status, causing functional impairment and increasing short-term postoperative morbidity in patients both with and without malignant diseases.[6,7] In recent years, sarcopenia has been shown to be a negative prognostic factor in malignant diseases of the lungs and the gastrointestinal tract.[8–10] In the context of hepatic resection for CRLM, preoperative sarcopenia has been suggested to be a predictor of worse recurrence-free and overall survival following resection.[11] In addition, a correlation between sarcopenia and major postoperative complications has been shown.[12]

Little is known about the impact of perioperative chemotherapy on skeletal muscle depletion. Reports of patients with pancreatic and oesophageal cancer who underwent neoadjuvant chemotherapy suggested post-therapy skeletal muscle losses.[13,14]

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Effects of chemotherapy have been investigated in patients with unresectable CRLM, suggesting post-therapy skeletal muscle loss shortens both progression-free and overall survival.[15] However, no previous studies of skeletal muscle depletion in the setting of neoadjuvant treatment of resectable CRLM have been made. The aim of the present study was to investigate the impact of neoadjuvant chemotherapy on skeletal muscle mass prior to hepatic resection in patients with CRLM, and also consider the effects on surgical outcome of preoperative sarcopenia.

Methods

Patient selection

All consecutive patients who underwent liver resection for CRLM at a single centre between January 2010 and December 2014 were retrospectively identified. Patients who underwent first-time resections and for whom preoperative computed tomography (CT) images were available were included in the study. Excluded from study analysis were patients with known extra-hepatic disease, including the primary tumor, that was eventually not resected, and patients receiving conversion chemotherapy. Patients' clinical and pathological data were retrospectively obtained from patient records. All patients were staged with a CT of the abdomen and chest. The treatment plan was decided in a multidisciplinary team conference. Indications for neoadjuvant chemotherapy were bilobar disease, more than three metastases and liver-first strategy. Postoperative complications were graded according to Clavien-Dindo.[16] The study protocol was approved by the regional ethics committee.

Skeletal muscle measurement

Patient skeletal muscle mass was retrospectively assessed using measurements of muscle area on existing diagnostic CT scans. The cross-sectional skeletal muscle area was manually traced and automatically calculated on a single transversal image of the abdomen at the level of the transverse processes of the third lumbar vertebra (L3).[17] Muscle attenuation was not taken into account. The calculated area was then normalized for body length, presenting a skeletal muscle index (cm^2/m^2) (SMI).[10] L3 skeletal muscle area has previously been shown to correlate with whole-body muscle mass.[17]

For patients who received neoadjuvant chemotherapy, measurements were made on the last scan prior to the first cycle of neoadjuvant chemotherapy and on the last scan prior to surgery. Pre- and post-chemotherapy measurements were then compared and the post-therapy skeletal muscle change could be calculated. For patients who did not undergo chemotherapy, only the last scan prior to surgery was used for measurement.

Sarcopenia was defined as an SMI less than 52.4 cm^2/m^2 for men and less than 38.5 cm^2/m^2 for women.[10] Patients receiving neoadjuvant chemotherapy were divided into two groups depending on whether or not they had lost muscle mass during therapy. Skeletal muscle loss was defined as a decrease in SMI of >5%, which has been found to predict decreased survival in patients with unresectable colorectal cancer undergoing palliative chemotherapy.[15]

Statistical analyses

All results are presented as median (interquartile range) if not stated otherwise. A Mann–Whitney *U*-test or the Wilcoxon test for paired samples was used to compare continuous data. A χ^2 test was used to compare categorical data. Overall and recurrence-free survival was estimated using the Kaplan–Meier method and risk factors were compared using the log rank test. Cox regression analysis was used to calculate hazard ratios and 95 per cent confidence intervals for risk factors on overall survival. Factors with a p-value < 0.1 on univariable analysis were included in a multivariable analysis. P-values < 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM, Armonk, NY, USA).

Results

Patients

Of 240 resected patients, eight underwent conversion chemotherapy and four had known extra-hepatic disease that was eventually not resected. These and three patients who died within 90 days of surgery were excluded from further analysis, leaving 225 patients included for study analysis. The median follow-up time was 32 (5–73) months.

Impact of neoadjuvant chemotherapy on skeletal muscle

Ninety-seven (43.1%) patients underwent neoadjuvant chemotherapy. The type of chemotherapy regimen was chosen by the medical oncologist after individual assessment, although oxaliplatin-based chemotherapy was normally considered as the first choice (Table 1). The median time from start of neoadjuvant chemotherapy to follow-up radiology was 54 (49–64) days. The median time from the last cycle of chemotherapy to operation was 35 (29–46) days. Neoadjuvant chemotherapy resulted in a decrease in skeletal muscle mass (decrease by 5.5 (−1.1 to 11) % in SMI, $p < 0.001$ as compared to pre-chemotherapy SMI). Patient characteristics for patients with and without skeletal muscle loss >5% are presented in Table 1. Muscle loss of more than 5% during neoadjuvant chemotherapy did not result in worse overall survival (40.3 vs 56.4 months; log rank $p = 0.131$) or recurrence-free survival (14.6 vs 17.5 months; log rank $p = 0.105$). Six patients who did not meet the criterion for sarcopenia at baseline turned sarcopenic after chemotherapy.

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