Original Research

Long-term outcome and quality of life after initial and repeat resection of colorectal liver metastasis: A retrospective analysis

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ABSTRACT

Background: Repeat hepatectomy is a widely accepted treatment for patients with recurrent colorectal liver metastasis (CRLM). The aim of this study was to compare initial and repeat hepatic resection concerning overall survival, prognostic factors and postoperative quality of life.

Methods: Data on patients who underwent initial or repeat hepatic resection for CRLM between 2010 and 2016 were prospectively collected and retrospectively evaluated. Follow-up data, EORTC QLQ-C30 and QLQ-LMC21 questionnaire results for quality of life (QoL) evaluation were analyzed.

Results: 160 patients at a median age of 62.8 ± 11.8 years were analyzed. 122 were initially resected and 38 underwent a repeat hepatic resection. Disease-free survival (DSF) was superior in the initial resection group (p < 0.001), while there was no difference in overall survival (OS) (p = 0.288). BMI > 30 (p = 0.012), extrahepatic tumor manifestation (p = 0.037), > 1 CRLM manifestation (p = 0.009), and perioperative chemotherapy (p = 0.006) in the initial resection group and primary left colon tumor (p = 0.001) in the repeat resection group were identified as prognostic factors in multivariate Cox regression analysis. EORTC QLQ-LMC-21 module symptom score displayed an increased occurrence of a dry mouth in the initial hepatectomy group (p = 0.003). EORTC QLQ-C30 general functioning and symptom scores showed no difference.

Conclusion: Repeat hepatic resection for CRLM is as effective as primary surgical treatment in terms of OS and QoL. Patients should be selected carefully concerning prognostic factors as DFS is decreased after repeat hepatic resection.

1. Introduction

Colorectal cancer is the third most common cancer worldwide. At time of colorectal cancer diagnosis 15–25% of the patients already have liver metastasis, while an additional 40–50% will eventually develop colorectal liver metastasis (CRLM) [1–4]. Hepatic resection has been shown to prolong long-term survival and is widely accepted as a standard treatment for resectable CRLM [5,6].

However, the recurrence rate of CRLM post initial resection was estimated to be as high as 57% [7]. For selected patients with limited recurrence, a repeat hepatectomy has been found to be a feasible treatment option. Several studies evaluated the long term outcome of a repeated resection. 5-year survival rates of up to 54% were reported post repeat hepatectomy of recurrent CRLM [8–10].

However, only a few studies compare survival rates between initial and secondary hepatectomy. In particular, it remains unclear which

clinical factors are leading to a long term-survival post repeat hepatectomy [11,12]. Furthermore clinical aspects other than survival rate such as postoperative Quality of Life are coming into focus. Here we present, to our knowledge, the first Quality of Life (QoL) data obtained from patients with initial and repeat resection of CRLM. The aim of the current analysis was to assess and evaluate QoL in patients post primary and repeat hepatic resection for CRLM. A second goal was to compare both groups concerning overall- and disease-free survival and to identify independent prognostic factors.

2. Patients and methods

2.1. Inclusion criteria and endpoint

We retrospectively evaluated data on patients who underwent primary or repeat liver resection in curative intention for CRLM between

January 2010 and October 2016 at the Department of General, Visceral and Transplantation Surgery at our institute. Follow-up data was collected in a prospective manner. Exclusion criteria were a second primary carcinoma, grossly residual tumor after surgery (R2), more than one repeat liver resection for CRLM and patients with incomplete information. CRLM or recurrent CRLM was pathologically proven in all patients. Time to tumor recurrence and time to death were selected as study endpoints. The relevant Institutional Review Board approved the present study. The work has been reported in line with the STROCSS criteria [13].

2.2. Diagnosis of CRLM

After initial CRLM resection and/or resection of the primary tumor, patients were monitored according to the German S3 guidelines for colorectal carcinoma [14]. Postoperative surveillance including physical examination, chest x-ray and abdominal ultrasonography was performed every 3–6 months for 3 years and annually thereafter. Colonoscopy was conducted every 12 months. In case of suspect results abdominal helical-computed tomography (CT) or magnetic resonance imaging (MRI) was performed. After diagnosis of CRLM or recurrent CRLM all cases were presented in an interdisciplinary tumor board with hepatobiliary surgeons, radiologists, radiooncologists and medical oncologists. Perioperative chemotherapy includes neoadjuvant and adjuvant therapy regimen.

2.3. Operative details

The type of resection was based on the extent of disease and surgical margins. Major hepatectomy was defined as a resection of more than a hemi-liver. Parenchymal dissection was performed by applying an ultrasonic dissector (CUSA®, Integra LifeSciences, Plainsboro, New Jersey, USA), while hemostasis was achieved by saline-linked cautery. Intraoperative ultrasonography was performed routinely to define location of the metastasis and the relation to portal pedicles and hepatic veins. R1-resection was defined as a microscopic margin of less than 1 mm.

2.4. Postoperative period

All resection specimens were histologically evaluated and the surgical margins were examined for tumorinvasion. Major post-operative complications were defined as complications of higher than grade IIIb in the *Clavien-Dindo* classification [15]. After hepatectomy, the use of postoperative chemotherapy was considered again in the interdisciplinary tumor board. Follow-up was performed in our Department or by the patient's local oncologist according to the German S3-guidelines for colorectal carcinoma. Patients were monitored until October 31st, 2016 or until death. For evaluating variables concerning survival rate and QoL prospectively, patients had periodical outpatient clinic visits. Patients were then asked to fill in an evaluation form and two questionnaires to evaluate their quality of life by assessing several patient related outcomes. Disease-free survival and Overall survival was defined as the interval between the date of index liver resection and the date of documented recurrence or last follow-up in patients without recurrence.

2.5. Quality of life assessment

The study was conducted using the validated EORTC QLQ-C30 questionnaire and the validated EORTC QLQ-LMC21 module for colorectal liver metastasis to assess QoL in cancer patients [16]. The EORTC QLQ-C30 consists of 30 different items, divided into various scales. It contains items for emotional, social and physical functioning, cognitive and role functioning and further global health status.

The QLQ-LMC21, specific for colorectal liver metastases, contains four scales assessing nutritional problems, activity/vigor problems, pain, and emotional function and nine single symptom items. All responses were transformed into scores from 0 to 100 for statistical analysis according to EORTC recommendations [17]. High scores represent better quality of life (better function) in the functional scales, but worse symptoms in the symptom scales.

2.6. Statistical analysis

For univariate comparisons the Chi-square test or Fisher's exact test, where appropriate, were used for categorical variables and the independent-samples t-test for numerical variables. Survival analysis was done using the Kaplan-Meier method. The results were plotted in Kaplan-Meier curves and compared using the log-rank test. Cox regression analysis was applied to examine the impact of several variables on survival. Variables associated with survival with a p-value less than 0.15 in univariate proportional hazards model were subsequently entered into a Cox multivariate regression model. In case of lacking statistical significance in univariate proportional hazards model all variables were entered into a Cox multivariate regression model with subsequent backward elimination. Quality of Life analysis was performed using one-way ANOVA. Continuous data were initially tested for normality using normality plots and the Shapiro-Wilk test. Statistical analysis was performed using the statistical software package SPSS version 23.0 (SPSS Inc., Chicago, Il, USA).

3. Results

258 patients who underwent surgical treatment due to colorectal liver metastasis at our institution between January 2010 and May 2016 were analyzed. 160 patients were included in the study. 122 patients received their initial resection of CRLM while 38 patients underwent a second resection as a consequence of recurrent CRLM. Median age was 62.8 ± 11.8 years and median follow up was 21 months (0–72 months).

3.1. Patients characteristics

Analyzing patient's characteristics no significant differences between the two groups were found concerning gender, age, BMI and ASA Score. 66% of the patients in both groups had more than one CRLM. Maximum diameter exceeded 5 cm in 26% of the cases with a non-significant trend towards the primary hepatectomy group (30% vs. 13%; p = 0.055). Synchronous CRLM occurred in 70%, while 30% developed metachronous CRLM. T stage, lymphatic invasion, differentiation and primary tumorlocation showed no statistical difference. 91% of the patients obtained a R0 resection with negative surgical margins. 9% had microscopically focal tumor-infiltrated resection margins and were classified as R1. Additional localablative therapy was performed in 11% of the cases. 26% had extrahepatic tumormanifestation at the time of resection. In 22% of the cases a major hepatectomy of more than a hemiliver had to be performed. Major complications occurred in 5% of the patients without statistically significant difference between the two groups as shown in Table 1.

3.2. Predictors of outcome

Independent prognostic factors were evaluated using the Cox regression proportional hazard model. In the initial resection group BMI > 30 (HR = 2.39, 95% CI = 1.22–4.70, p = 0.012), presence of extrahepatic tumor manifestation (HR = 1.90, 95% CI = 1.04–3.45, p = 0.037), more than one manifestation of CRLM (HR = 2.51, 95% CI = 1.26–5.00, p = 0.009) were independently associated with worse disease-free survival, while undertaking perioperative chemotherapy (HR = 0.26, 95% CI = 0.10–0.68, p = 0.006) was an independent factor for an increased disease-free survival (Table 2). In the repeat