Chemotherapy and Hepatic Steatosis: Impact on Postoperative Morbidity and Survival after Liver Resection for Colorectal Liver Metastases

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Keywords

Colorectal cancer · Liver metastases · Liver resection · Chemotherapy · Steatosis

Abstract

Background: Hepatic steatosis and chemotherapy in the treatment of colorectal liver metastases (CLM) are often linked to increased mortality and morbidity after liver resection. This study evaluates the influence of macrovesicular hepatic steatosis and chemotherapeutic regimes on graded morbidity and mortality after liver resection for CLM. **Methods:** A total of 323 cases of liver resection for CLM were retrospectively analysed using univariable and multivariable linear, ordinal and Cox regression analyses. The resected liver tissue was re-evaluated by a single observer to determine the grade and type of hepatic steatosis. **Results:** Macrovesicular steatosis did not influence postoperative morbidity and survival, as evidenced by risk-adjusted multivariable Cox regression analysis ($p = 0.521$). Conversion chemotherapy containing oxaliplatin was an independent and significant risk factor for mortality in risk-adjusted multivariable Cox regression analysis ($p = 0.005$). Identified independently, significant risk factors for postoperative morbidity were neoadjuvant treatment of metastases of the primary tumour with irinotecan ($p = 0.003$), the duration of surgery in minutes ($p = 0.001$) and the number of intraoperatively transfused packed red blood cells ($p \leq 0.001$). Surprisingly, macrovesicular hepatic steatosis was not a risk factor for postopera-

tive morbidity and was even associated with lower rates of complications ($p = 0.006$). **Conclusion:** The results emphasize the multifactorial influence of preoperative liver damage and chemotherapy on the severity of postoperative morbidity, as well as the significant impact of conversion chemotherapy containing oxaliplatin on survival.

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Introduction

Annually, 1.4 million patients are diagnosed with colorectal cancer worldwide; about 50% of these patients develop synchronous or metachronous liver metastases [1, 2]. Surgical resection of colorectal liver metastases (CLM) is the treatment of choice, with 5-year survival rates of up to 50% [3–6]. Independent risk factors for survival after liver resection for CLM include limited liver function and pre-existing hepatocellular damage, transfusion requirements, the size of the largest metastasis and its distance to the resection margin [6].

Although survival rates have significantly improved during the last decades, the rate of postoperative complications (morbidity) remains relatively high at up to 38% [7, 8]. Postoperative morbidity depends on common preoperative risk factors such as cardiovascular diseases, diabetes and ASA score, as well as surgery-specific risk factors such as the extent of surgery or the amount of transfused red blood cells [9]. Additionally, fatty liver de-

generation is expected to become a major concern in liver surgery [10]. Obesity, a risk factor for developing colorectal cancer, is also associated with the development of non-alcoholic fatty liver disease [11]. Non-alcoholic fatty liver disease occasionally advances to a non-alcoholic steatohepatitis, and in some cases to a non-alcoholic steatohepatitis-related liver cirrhosis with severe reduction of liver function. As a consequence, surgical options in the treatment of CLM might be limited, mainly due to higher demands on the size of the liver remnant and impaired hepatic regeneration after liver resection.

However, not only obesity is considered as a risk factor for hepatic steatosis and a potential challenge in the surgical treatment of CLM. Increasing numbers of patients are receiving various regimes of chemotherapy prior to the resection of CLM, either with adjuvant intent for treatment of the primary colorectal lesion or as conversion therapy in case of primarily irresectable hepatic lesions. In this context, various chemotherapeutic agents are known to cause drug-specific hepatic toxicity [12]. While oxaliplatin is known for its association with sinusoidal obstruction syndrome (SOS), irinotecan is linked to chemotherapy-associated steatohepatitis, causing an increase in morbidity and mortality [13, 14].

Only few studies have evaluated the impact of hepatic steatosis or associated chemotherapies on the postoperative outcome after liver resection for CLM. Kurmann et al. [15] associated hepatic steatosis with surgical site infections after hepatic and colorectal surgery. Vauthey et al. [16] reported that steatohepatitis caused by chemotherapy increases the risk of 90-day mortality after liver resection for CLM. Veteläinen et al. [17] concluded that hepatic steatosis is a major risk factor for surgical complications and 60-day mortality. The influence of the type of steatosis – that is, micro- or macrovesicular fat deposits – on morbidity and mortality after liver resection of CLM is mainly unclear. Data derived from orthotopic liver transplantations suggest that the degree of macrovesicular steatosis in the allograft is highly predictive of 90-day mortality [18].

The aim of this study was to investigate the influence of hepatic macrovesicular steatosis and chemotherapeutic regimes on patient survival and early morbidity, graded according to Dindo et al. [10], after liver resection for CLM.

Patients and Methods

Data Collection

This is a single-centre retrospective analysis with data from a German tertiary referral centre for hepatobiliary surgery and liver transplantation. The postoperative observational period ended on January 1st, 2017. Included were all cases of primary liver resection for CLM between January 1st, 2000, and October 31st, 2014, with available histological slides of the resection specimen. A descrip-

tive summary of the cohort is provided in online supplementary Figure 1 and Tables 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000510661).

Determination of Steatosis in Liver Resection Specimens

For the determination of hepatic steatosis, the same histological methodology was employed as described by Schrem et al. [18]. The extent of steatosis was assessed in the normal liver using histological slides from the liver resection specimen. The investigator was trained with pre-existing teaching slides by an expert in hepatic pathology. The first 20% were double-checked by that expert in a blinded fashion. Due to the fact that no mentionable differences occurred, the rest of the slides were assessed by a single observer with the pathologist in standby and ongoing random checks.

Determination of Data on Chemotherapy

Data on chemotherapy were gathered primarily from patients' medical charts. Additional information was collected on 313 patients using questionnaires sent to external oncologists and general practitioners who had treated the patients prior to liver resection. All data obtained were subjected to a series of automated plausibility checks as well as to scrutiny by an expert in gastroenterological oncology. Chemotherapies that had been applied for more than 6 months prior to CLM resection and resulted in resectable CLM that had initially been judged as irresectable were considered as conversion chemotherapy. The chemotherapeutic regimens were categorized according to the curative intent at the time of administration and according to the combinations of substances applied. Classified chemotherapeutic treatments that had been used in less than 8 cases prior to liver resection were subsumed under "other chemotherapeutic treatments" to enable meaningful statistical analysis.

Study Endpoints

The endpoints in this study were defined as patient survival in years, postoperative morbidity graded according to Dindo et al. [10] and the percentage of macrovesicular hepatic steatosis of normal liver tissue of the resection specimen.

Statistical Methods

Macrovesicular steatosis (%) and variables to describe categorized chemotherapeutic treatments prior to liver resection were investigated to determine their independent influence on patient survival in Cox regression analysis, risk adjusted for previously identified independent risk factors for survival [6]. Risk factors for the percentage of macrovesicular hepatic steatosis and graded postoperative morbidity according to Dindo et al. [10] were assessed using linear and ordinal regression analysis, respectively.

Continuous variables with multicollinearity in correlation analysis with a factor correlation $R > |0.500|$ were subjected to a clinically informed decision on the exclusion of one of them, to avoid multicollinearity effects in regression modelling.

All variables that demonstrated an independently significant influence ($p < 0.150$, the provided p values correspond to two-sided probabilities) were then submitted to multivariable regression analysis in order to avoid overfitting [19]. Stepwise backwards likelihood elimination of the least significant variables ($p > 0.050$) was repeated until only significant variables remained in the regression model. These models enabled the identification of significant explanatory variables for all defined endpoints, as well as the quantification of the effect of each variable, that is, the degree and trend of their regression.

The software package JMP Pro 13 (SAS Institute, USA) was used to perform statistical analysis, as well as the vast, community-driven and freely available infrastructure of the R-project to assess its usability as a cost-efficient alternative for upcoming studies.

Table 1. Significant variables with influence on survival in Cox regression analysis

Variables	Univariable regression			Multivariable regression		
	hazard ratio	95% CI	p value	hazard ratio	95% CI	p value
<i>Preoperative details</i>						
BMI	0.980	0.955–1.008	0.144			
Haemoglobin (g/dL)	0.851	0.774–0.935	0.001			
Platelets ($\times 10^3/\mu\text{L}$)	1.002	1.000–1.004	0.068			
Quick (%)	0.988	0.977–0.998	0.068	0.989	0.979–1.000	0.048
Resection severity index	1.102	1.015–1.196	0.037			
<i>Primary tumour characteristics</i>						
Location						
Caecum	Reference					
Colon ascendens	0.610	0.329–1.128				
Colon transversum	0.411	0.137–1.232				
Colon descendens	0.391	0.177–0.865	0.140			
Colon sigmoideum	0.464	0.269–0.780				
Rectum	0.497	0.291–0.849				
Neoadjuvant chemotherapy 5-FU	0.605	0.358–1.023	0.043			
Conversion chemotherapy 5-FU	2.254	1.310–3.878	0.009			
Conversion chemotherapy 5-FU + oxaliplatin	1.970	1.228–3.161	0.010	2.074	1.252–3.436	0.005
Conversion chemotherapy 5-FU + irinotecan	1.767	1.197–2.608	0.007			
Local relapse	1.547	0.930–2.574	0.114			
<i>Operative details</i>						
Operative duration (min)	1.003	1.001–1.004	0.011			
Intraoperative transfusion of pRBCs	1.850	1.408–2.432	<0.001	1.755	1.280–2.407	<0.001
Units of intraoperatively transfused pRBCs	1.103	1.056–1.1521	<0.001			
Distance to resection margin (mm)	0.984	0.970–0.999	0.018			
Size of largest metastases (mm)	1.008	1.004–1.012	<0.001	1.006	1.002–1.010	0.004

BMI, body mass index; 5-FU, 5-fluorouracil; pRBCs, packed red blood cells.

Results

Influence of the Categorized Chemotherapy Regimens on Survival

As shown in Table 1 and Figure 2, only conversion chemotherapy containing 5-fluorouracil (5-FU) and oxaliplatin had a statistically significant independent influence on patient survival (HR 2.074; 95% CI 1.252–3.436; $p = 0.005$).

Variables with an Influence on Graded Postoperative Morbidity

The results of ordinal regression analysis are summarized in Table 2. Significant independent risk factors for graded postoperative morbidity until hospital discharge were neoadjuvant chemotherapeutic treatments of metastases containing irinotecan (OR 4.315; 95% CI 1.751–10.633; $p = 0.003$), adjuvant chemotherapeutic treatments of the primary tumour containing irinotecan (OR 0.011; 95% CI 0– ∞ ; $p \leq 0.001$), the duration of surgery in minutes (OR 1.007; 95% CI 1.003–1.012; $p = 0.001$) and the number of intraoperatively transfused packed red blood cells (pRBCs; OR 1.198; 95% CI 1.077–1.332; $p \leq 0.001$). Surprisingly, macrovesicular hepatic steatosis showed a

significant independent protective influence on the occurrence of postoperative complications (OR 0.965; 95% CI 0.939–0.993; $p = 0.006$).

Risk Factors for Macrovesicular Steatosis

The results of the linear regression analysis are summarized in Table 3. Independent risk factors for macrovesicular steatosis were body mass index ($p \geq 0.001$), preoperative Quick ($p = 0.005$) and conversion chemotherapeutic treatment with 5-FU and oxaliplatin ($p = 0.003$), as well as local relapse ($p = 0.003$) of the primary tumour and the size of the largest metastasis ($p = 0.006$). To assess a pre-existing fibrosis, the FIB-4 score was included. An influence could not be shown in our cohort.

Influence of Macrovesicular Steatosis on Survival

The results of Cox regression analysis are summarized in Table 1. Separate multivariable Cox regression models revealed that macrovesicular steatosis (HR 0.997; 95% CI 0.987–1.007; $p = 0.521$) did not show a statistically significant independent influence on patient survival. This result was confirmed in Kaplan-Meier analysis (shown in Fig. 1) using the log-rank test ($p = 0.870$).

Table 2. Significant variables with influence on graded morbidity in ordinal regression analysis

Variables	Univariable			Multivariable		
	odds ratio	95% CI	p value	odds ratio	95% CI	p value
<i>Preoperative details</i>						
Haemoglobin (g/dL)	0.769	0.638–0.927	0.006			
Leucocytes ($\times 10^3/\mu\text{L}$)	1.218	1.065–1.393	0.005			
Platelets ($\times 10^3/\mu\text{L}$)	1.005	1.001–1.008	0.007			
Creatinine ($\mu\text{mol/L}$)	0.985	0.967–1.003	0.099			
Resection severity index	1.154	0.976–1.366	0.099			
<i>Primary tumour characteristics</i>						
Neoadjuvant chemotherapy 5-FU + irinotecan	3.999	1.762–9.076	0.002	4.315	1.751–10.634	0.003
Adjuvant chemotherapy 5-FU	0.488	0.252–0.945	0.026			
Adjuvant chemotherapy 5-FU + irinotecan	0.000	0.000– ∞	0.039	<0.001	0.000–0.000	0.011
<i>Operative details</i>						
1 point						
Left atypical LR	Reference					
Right atypical LR						
2 points						
Left segmental LR	1.867	0.822–4.241				
Right segmental LR						
Bilateral atypical LR						
3 points						
Left hemihepatectomy	0.413	0.051–3.371				
4 points			0.006			
Right hemihepatectomy	2.016	0.827–4.913				
5 points						
Extended left hepatectomy	6.197	2.404–15.976				
6 points						
Extended right hepatectomy	2.957	0.980–8.925				
Left hepatectomy + right atypical LR						
7 points						
Right hepatectomy + left atypical LR	2.050	0.588–7.146				
Operative duration (min)	1.010	1.006–1.013	<0.001	1.008	1.003–1.012	0.001
Intraoperative transfusion of pRBCs	4.213	2.369–7.491	<0.001			
Units of intraoperatively transfused pRBCs	1.286	1.168–1.417	<0.001	1.198	1.077–1.332	<0.001
Metastasis grade						
G1	<0.001	0.000–0.000				
G2	Reference		0.098			
G3	<0.001	0.000–0.000				
R status						
R0	Reference					
R1	3.532	1.324–9.423	0.050			
R2	2.578	0.229–29.015				
Macrovesicular steatosis (%)	0.973	0.948–0.999	0.023	0.965	0.939–0.993	0.006
Size of largest metastases (mm)	1.016	1.009–1.024	<0.001			

LR, liver resection; pRBCs, packed red blood cells.

Figure 2 visualizes the most important findings. The full regression analyses are shown in online supplementary Tables 3, 4 and 5.

Discussion

This study was motivated by the increasing evidence for an impact of fatty liver disease on postoperative morbidity and survival after liver resection of CLM, especially in the context of preoperatively administered chemotherapies. The primary aim was to analyse the frequency and grade of macrovesicular steatosis in patients under-

going liver resection for CLM and the chemotherapeutic regimes applied prior to surgery. Secondly, the potential influence of hepatic steatosis and associated chemotherapies on morbidity and survival after liver resection for CLM was explored.

Hepatic steatosis is mostly associated with secondary disorders such as the metabolic syndrome or other cardiovascular risk factors. Surprisingly, hepatic fat was not associated with a higher risk of postoperative morbidity in our study, and the body mass index showed no significant influence either in multivariable Cox regression analysis or in multivariable ordinal regression analysis. Patients with increasing degrees of liver fat deposits ap-

Fig. 1. Kaplan-Meier curves for macrovesicular steatosis and conversion chemotherapy with 5-fluorouracil (5-FU) plus oxaliplatin (Oxa.). The p values demonstrate the results of the log-rank test. The analyses were truncated when the numbers at risk were smaller than one-third of the starting number.

Table 3. Significant variables with influence on macrovesicular steatosis in linear regression analysis

Variables	Univariable		Multivariable <i>p</i> value
	<i>R</i> ²	<i>p</i> value	
<i>Preoperative details</i>			
Age at resection of metastases (years)	0.009	0.092	
Body mass index	0.203	<0.001	<0.001
Haemoglobin (g/dL)	0.043	<0.001	
Quick (%)	0.028	0.003	0.005
Fibrosis-4 score	0.013	0.077	
<i>Primary tumour characteristics</i>			
Neoadjuvant chemotherapy 5-FU + irinotecan	0.009	0.095	
Adjuvant chemotherapy 5-FU + oxaliplatin	0.008	0.105	
Conversion chemotherapy 5-FU	0.012	0.049	
Conversion chemotherapy 5-FU + oxaliplatin	0.018	0.016	0.003
Conversion chemotherapy 5-FU + irinotecan	0.008	0.111	
Local relapse	0.018	0.016	0.003
<i>Operative details</i>			
Intraoperative transfusion of pRBCs	0.024	0.005	
Units of intraoperatively transfused pRBCs	0.013	0.042	
Size of largest metastases (mm)	0.031	0.002	0.006
pRBCs, packed red blood cells.			

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pear to have a lower risk of developing postoperative complications than patients without hepatic steatosis. This result contradicts previously published studies that reported increased morbidity in case of fatty liver disease [20, 21]. Speculatively, the patients with hepatic steatosis in our cohort had undetected positive confounders explaining the lower rates of postoperative morbidity. Nev-

ertheless, some other studies have suggested only a mild impact of steatosis on patient mortality and morbidity [17].

As determined by a one-tailed z test, in order to quantitatively validate hepatic fat as a risk factor, a sample size of 10,000–100,000 patients would be needed. Of course, this exceeds the size of our study cohort, but in compari-

Fig. 2. The figure visualizes the influence of relevant variables in multivariable regression analysis on morbidity and mortality. 5-FU, 5-fluorouracil; pRBCs, packed red blood cells.

son to many recent studies, it appears of a reasonable size, especially when the additional information regarding chemotherapies is considered. Prospective studies are desirable to better understand the impact of steatosis on postoperative complications after liver resection for CLM, including cardiovascular risk factors or other secondary diseases. Moreover, as evidenced in our study, hepatic fat also had no influence on overall survival after

resection of CLM. Hence, no negative effects of macrovesicular hepatic steatosis on survival (as reported for fatty liver allografts in the context of liver transplantations) could be confirmed in our analysis of liver resections for CLM [18].

For the first time, we demonstrated an independent influence of irinotecan on graded postoperative morbidity after liver resection for CLM (OR 4.315; 95% CI 1.751–

10.633; $p = 0.003$). This effect appears not to be related to drug-induced hepatic steatosis, since no influence of irinotecan on macrovesicular steatosis was observed in our cohort, and, as pointed out, steatosis did not influence morbidity. Nevertheless, irinotecan has been reported to cause chemotherapy-associated steatohepatitis [13, 14]. Possibly, in the case of irinotecan, inflammatory “second hits” are required to drive any increased morbidity of fatty livers after hepatic surgery. In fact, our study emphasizes the influence of oxaliplatin- and 5-FU-based chemotherapies on macrovesicular hepatic steatosis to highlight the hepatotoxicity of the substance and the association of oxaliplatin with SOS, as reported previously by Pessaux et al. [13].

Collectively, our findings underline that chemotherapeutic treatments prior to liver resection imply the possibility of chemotherapy-associated liver injury, resulting in increased postoperative morbidity [22]. In case of conversion chemotherapy containing 5-FU and oxaliplatin, an independent and statistically significant negative influence on patient survival was detectable. That effect might also be explained by possible oxaliplatin-based side effects such as polyneuropathy or decreased liver function caused by SOS. Even more importantly, conversion chemotherapy is probably only administered in case of an initially extensive and irresectable hepatic tumour burden, likely related to impaired overall survival. Hence, the liver resections were only possible after successful chemotherapeutic treatment, and our findings do not disprove the use of chemotherapy to achieve secondary resectability of CLM. Instead, surgeons must be aware of higher postoperative risks and possibly an impaired overall outcome, which is to be considered when counselling patients prior to surgical treatment. However, in case of a primary resectable CLM, the results emphasize that surgery should be considered whenever possible to avoid chemotherapy-induced liver injury.

In addition to the negative effects of chemotherapeutic agents on morbidity, the duration of surgery and the amount of transfusion requirements also appear to significantly increase the risk of postoperative complications. The time demand of the surgical procedure is mainly influenced by the experience of the surgeon and the extent of liver resection, but also by anatomical variables including the presence or absence of obesity. Therefore, the duration of resection might serve as a surrogate parameter for other factors that increase the risk of complications. Compatible with the higher rate of complications observed in case of longer surgical procedures, another recently published study reported that prolonged operative times caused higher rates of infection-related complications [23]. Furthermore, according to Grutta-dauria et al. [24], the surgical time demand also correlates with intraoperative blood loss. In that study, intraopera-

tive transfusion of pRBCs also increased the risk of complications of Clavien-Dindo grade III or higher. Our present study emphasizes that transfused pRBCs are an independently significant risk factor for higher grades of postoperative morbidity (OR 1.198; 95% CI 1.077–1.332; $p \leq 0.001$), although the correlation of operating time demand with pRBC requirements was low ($R = 0.342$). As reported previously, transfusion requirements depend on the extent of liver resection, the proportional frequency of anatomical resections and the prolonged use of portal triad clamping [23]. Additionally, several studies have demonstrated blood loss to be an independent risk factor for compromised short-term and long-term outcome after liver resection [23, 25–28]. A correlation between extent of steatosis and extent of resection, possibly acting as a selection bias, could not be detected.

The sample size of our cohort might be considered as a limitation of the study. Nevertheless, other studies suggest a mild impact of hepatic steatosis on patient mortality and morbidity [17]. As determined by a one-tailed z -test, in order to quantitatively validate hepatic steatosis as an individual risk factor, a sample size of 10,000–100,000 patients would be needed. Such sample sizes exceed the cohorts of all trials considered and the possibilities of single-centre analyses.

Conclusions

An increased risk of the development of postoperative complications or impaired overall survival caused by hepatic steatosis could not be evidenced. We highlight the association of irinotecan with higher rates of postoperative complications. A conversion chemotherapy containing oxaliplatin and 5-FU was associated with limited overall survival, most likely referring to more extensive hepatic tumour disease. It must be marked that the clinical usefulness in preoperative patient counselling is limited, since most of the variables that appear to influence postoperative morbidity are only available after the performance of surgery, that is, duration and pRBC demand. Preoperative imaging occasionally indicates signs of hepatic steatosis, and even the duration of surgery and expectable blood loss can be anticipated based on the extent of hepatic segments affected by CLM. Hence, an approximate identification of potential patients at risk is still reasonable, eventually allowing for more profound patient counselling and intensified postoperative surveillance.

Statement of Ethics

The institution's Ethics Committee approved this retrospective study (Ethikkommission, Hannover Medical School; approval decision No. 3079-2016). All patients provided informed consent. Patient data were anonymized and de-identified prior to analysis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.C.M.: data collection and interpretation, statistical analysis, histological assessment of steatosis and preparation of the manuscript; T.C.W.: evaluation of chemotherapies and revision of the manuscript; B.H.: teaching of assessment of steatosis and double-checking of results, and revision of the manuscript; H.S. and J.F.M.: statistical analysis, interpretation of data and revision of the manuscript; A.K.: study design, statistical analysis, interpretation of data and revision of the manuscript; J.K.: study design and revision of the manuscript; U.K.: study design, statistical analysis, interpretation of data and preparation of the manuscript.