Impact of chemotherapy-associated liver injury on tumour regression grade and survival in patients with colorectal liver metastases

ORIGINAL ARTICLE

Impact of chemotherapy-associated liver injury on tumour regression grade and survival in patients with colorectal liver metastases

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Abstract

Background: An inverse relation between chemotherapy-associated liver injury (CALI) and tumour response to chemotherapy has been reported. The aim was to validate these findings, and further investigate the impact of CALI on survival in patients who underwent partial hepatectomy for colorectal liver metastases (CRLM).

Methods: Patients who received neoadjuvant chemotherapy and underwent partial hepatectomy for CRLM between 2008 and 2014 were included. Liver and tumour specimens were histologically examined for CALI (steatosis, steatohepatitis, sinusoidal dilatation [SD], nodular regeneration) and tumour regression grade (TRG). TRG 1–2 was defined as complete tumour response.

Results: 166 consecutive patients were included with a median survival of 30 and 44 months for recurrence-free and overall survival, respectively. Grade 2–3 SD was found in 44 (27%) and TRG 1–2 was observed in 33 (20%) patients. Of studied CALI, only grade 2–3 SD was associated with increased TRG 3–5 (odds ratio 3.99, 95% CI 1.17–13.65, $p = 0.027$). CALI was not significantly related to survival. TRG 1–2 was associated with prolonged recurrence-free (hazard ratio 0.47, 95% CI 0.25–0.89, $p = 0.020$) and overall survival (hazard ratio 0.35, 95% CI 0.18–0.68, $p = 0.002$).

Conclusion: CALI was not directly related to survival. CALI was, however, associated with diminished complete tumour response, and diminished complete tumour response, in turn, was associated with decreased survival.

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Introduction

Neoadjuvant chemotherapy is used to downsize colorectal liver metastases (CRLM) with the aim of facilitating future hepatic resection.[1–3] Tumour downsizing relies on the tumour response to chemotherapy, as expressed by the tumour regression grade (TRG).[4] CRLM patients with complete tumour response have been shown to have better survival than those with poor response.[5]

Systemic chemotherapy may have beneficial effects, but frequently causes undesired liver parenchymal damage,

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collectively referred to as chemotherapy-associated liver injury (CALI). For instance, oxaliplatin-based treatment appears to be related to the development of sinusoidal obstruction syndrome[6–8] and nodular regeneration,[9] whereas irinotecan-based regimens are associated with increased occurrence of steatohepatitis.[10–12] The authors have recently demonstrated that chemotherapy-associated sinusoidal dilatation was related to increased major morbidity, and therefore advised adaptation of surgical management in case of its presence.[8] Moreover, the authors[13] and others[5] have previously shown that chemotherapy-associated sinusoidal dilatation is associated with poor tumour response to neoadjuvant chemotherapy.

Despite the significant inverse relation between CALI and tumour response, few studies have examined the effect of CALI on the long term survival of patients who undergo liver resection for CRLM. Although one study claimed that chemotherapy-associated sinusoidal dilatation was associated with shortened survival,[14] another study could not reproduce this.[5] Therefore, it remains unclear whether CALI influences survival. The first aim of the present study was to validate the relation between CALI and tumour response in an independent large cohort. The second aim was to explore whether sinusoidal dilatation, nodular regeneration, steatosis, and steatohepatitis were associated with survival in CRLM patients after partial hepatectomy.

Methods

Inclusion of patients

Consecutive patients who had undergone partial hepatectomy for CRLM at Maastricht University Medical Centre between January 2008 and December 2013 were considered for this study. Inclusion criteria were: (i) patients treated with neoadjuvant chemotherapy; (ii) availability of adequate histopathology assessment of non-tumour bearing liver tissue (i.e. presence of non-tumour-bearing liver at a distance of more than 2 cm from the tumour). Patients with cirrhosis were excluded from the study.

Definition and data collection

Comorbidity was defined as any disease affecting the patient apart from colorectal liver metastases (e.g. diabetes mellitus, and pulmonary, renal, cardiovascular, and other diseases). Overall morbidity was defined as any complication occurring within 30 days after surgery or during hospital stay and graded according to the classification of Dindo *et al.*[15] Major morbidity was defined as Dindo-Clavien score IIIa (requiring invasive intervention) or higher. The concept of a liver surgery-specific complication was in correspondence to the liver surgery-specific composite endpoint (CEP) developed in 2011, and included one or more of the following events: ascites, postoperative liver failure, bile leakage, intra-abdominal abscess, intra-abdominal haemorrhage, and operative mortality.[16] 90-day mortality rate was used as it has been shown to be an equivalently specific measure of surgery-related death and represents a legitimate measure of surgical quality.[17] Because postoperative infectious complications have been shown to be significant prognostic factors for long-term survival after hepatectomy for colorectal liver metastases,[18] they were included as confounders when studying factors related to survival in multivariable Cox regression models. Postoperative infectious complications were prospectively collected daily by an independent infection-control nurse based on the following definitions, and defined as a combination of surgical site infections,[19] remote site infections, and systemic sepsis. Radical resection was defined as resected tumour lesions with a surgical margin of more than 1 mm, and confirmed to have absent tumour cells on the margin from routine pathology reports. With respect to tumour recurrence, patients were followed up by monitoring blood levels of carcinoembryonic antigen (CEA) every three months together with liver radiologic imaging half-yearly in the first 2 years, and CEA half-yearly together with liver radiologic imaging annually up to 5 years after surgery. The date of last follow-up was November 2, 2016.

Pathology assessment of non-tumour-bearing liver and metastases

Sinusoidal dilatation, nodular regeneration, steatosis, and tumour regression grade were semi-quantitatively assessed by two experienced liver pathologists (AW and CV). Diagnosis of nodular regeneration was made only when confirming liver fibrosis was absent or minor. Assessment of steatohepatitis was performed by another experienced liver pathologist (JV) independently. All pathologists were blinded to clinical information concerning the patients.

The tissue was fixed in formalin, embedded in paraffin, and stained with haematoxylin & eosin and reticulin. Sinusoidal dilatation was graded according to Rubbia-Brandt *et al.*[20] Nodular regeneration was graded according to the Wanless scoring system.[21] Steatosis was graded according to Kleiner *et al.*[22] Grade 2–3 liver injuries (i.e. sinusoidal dilatation, steatosis, and nodular regeneration) were defined as severe lesions, respectively. Patients presenting with at least grade 1 of each of the three features (steatosis, hepatocellular ballooning, and lobular inflammation) were classified as having steatohepatitis according to the recently established SAF scoring system.[23] Tumour regression was graded as described by Mandard *et al.*,[4] for the assessment of tumour regression after preoperative chemoradiotherapy for esophageal carcinoma, and modified for liver metastases. Grade 1 is characterized by the absence of histologically identifiable residual tumour and extensive fibrosis; grade 2 shows the presence of rare residual tumour cells scattered through the fibrosis; grade 3 represents a substantial amount of residual tumour cells but fibrosis dominated; grade 4 reflects residual tumour cells outgrowing fibrosis; and grade 5 indicates the absence of any tumour regression. Tumour regression grade 1–2 was defined as complete tumour response, and grade 3–5 was defined as poor tumour response.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 20.0). The relationship between CALI and tumour regression grade was studied applying uni- and multivariable binary logistic regression models. Because portal venous embolization (PVE) is known to provoke tumour progression,[24,25] factors related to tumour regression grade were analysed within the whole population as well as within those patients that did not undergo PVE. Furthermore, the association between CALI, tumour regression grade, infectious complications, and survival was analysed using uni- and multivariable Cox regression models. Variables with p-value $\leq$ 0.10 in univariable analysis were included in the multivariable analysis. Odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI) were calculated. A p-value $\leq$ 0.05 was considered significant for all tests.

Results

A total of 166 consecutive patients were included (Table 1). Preoperative comorbidity was found in 106 (64%) patients, including 13 (8%) diabetes, 70 (42%) cardiovascular, 18 (11%) pulmonary, and 6 (4%) renal diseases. Ninety-nine (60%) patients had more than one liver metastasis. Capecitabine in combination with oxaliplatin (CAPOX) was the most commonly used regimen, which was administered to 152 (92%) patients. Postoperative surgical site infections were present in 41 (25%) patients, including 22 (13%) superficial wound, 6 (4%) deep wound, and 27 (16%) intraabdominal organ/space infectious. Remote site infections were found in 26 (16%) patients, including 12 (7%) urinary tract and 15 (9%) respiratory tract, and 6 (4%) central venous catheter-related infections.

Table 2 summarizes the pathology details of CALI. The impact of CALI and other potentially important factors on tumour regression grade is depicted in Fig. 1 (Detailed data are summarized in Supplemental Table 1). Given the fact that only one case of steatohepatitis was found, the relation between steatohepatitis and tumour regression grade could not be studied. Severe sinusoidal dilatation was associated with increased occurrence of diminished tumour response (OR 3.99, 95% CI 1.17–13.65, p = 0.027). An association between mild sinusoidal dilatation and diminished tumour response was statistically not significant (OR 2.38, 95% CI 0.83–6.85, p = 0.108). Addition of bevacizumab to the chemotherapy treatment tended to be associated with increased complete tumour response (OR 0.35, 95% CI 0.12–1.01, p = 0.052). Severe steatosis (OR 0.85, 95% CI 0.33–2.21, p = 0.741) and severe nodular regeneration (OR 1.88, 95% CI 0.39–9.12, p = 0.434) were not related to tumour regression grade. The association between CALI and tumour regression was also analysed in the subgroup of patients who did not undergo PVE, and similar results were found (Supplemental Table 1). In another subgroup analyses, an inverse relation between the addition of bevacizumab and occurrence of severe sinusoidal dilatation (OR 0.35, 95% CI 0.17–0.76, p = 0.008) was observed. Similarly, presence of severe steatosis was also inversely related to that of severe sinusoidal dilatation (OR 0.23, 95% CI 0.08–0.66, p = 0.006) (Supplemental Table 2).

The relation between potential prognostic factors and recurrence-free survival is summarized in Fig. 2 (Detailed data are summarized in Supplemental Table 3). Until the date of last

Table 1 Clinical characteristics

Factors	n = 166
General characteristics	
Gender (male)	103 (62%)
Age[a] (year)	65 (58–69)
Body mass index[a] (kg/m^2)	26 (24–28)
Comorbidity	106 (64%)
Portal venous embolization	9 (5%)
Primary colorectal tumour	
Rectal cancer	72 (43%)
Tumour stages 3–4 (n = 165[b])	144 (87%)
Lymph node with tumour cells (n = 162[b])	113 (70%)
Liver metastases	
Synchronous metastases (<12 months)	130 (78%)
Number of metastases[a]	2 (1–3)
Diameter of largest metastases[a]	3 (1–4)
CEA > 200 ng/ml at hepatectomy	5 (3%)
Chemotherapy details	
5-Fluorouracil	6 (4%)
Oxaliplatin	153 (92%)
Capecitabine	152 (92%)
Irinotecan	8 (5%)
Bevacizumab	105 (63%)
Surgical details	
Major hepatectomy (≥3 Couinaud segments)	78 (47%)
Pringle manoeuver	44 (27%)
Laparoscopic surgery	11 (7%)
Perioperative blood transfusion	32 (19%)
Radical resection	111 (67%)
Postoperative characteristics	
Overall morbidity	76 (46%)
Major morbidity (Dindo-Clavien III–V)	29 (17%)
Liver surgery-specific complications	32 (19%)
Infectious complications	51 (31%)
Surgical site infections	41 (25%)
Remote site infections	26 (16%)
Ninety-day mortality	5 (3%)
Length of hospital stay[a] (day)	8 (6–10)

CEA, carcinoembryonic antigen.
[a] Numeric variables are presented as median with inter quartile range.
[b] Due to missing data, indicated number of patients was below 166.

Table 2 Pathology characteristics

Pathology details	*n* = 166
Sinusoidal dilatation	
Absent	76 (46%)
Grade 1	46 (28%)
Grade 2	30 (18%)
Grade 3	14 (8%)
Nodular regeneration (*n* = 133[a])	
Absent	108 (65%)
Grade 1	11 (7%)
Grade 2	12 (7%)
Grade 3	2 (2%)
Steatosis	
Absent	62 (37%)
Grade 1	56 (34%)
Grade 2	29 (17%)
Grade 3	19 (11%)
Steatohepatitis	1 (1%)
Tumour regression grade	
Grade 1	20 (12%)
Grade 2	13 (8%)
Grade 3	47 (28%)
Grade 4	56 (34%)
Grade 5	30 (18%)

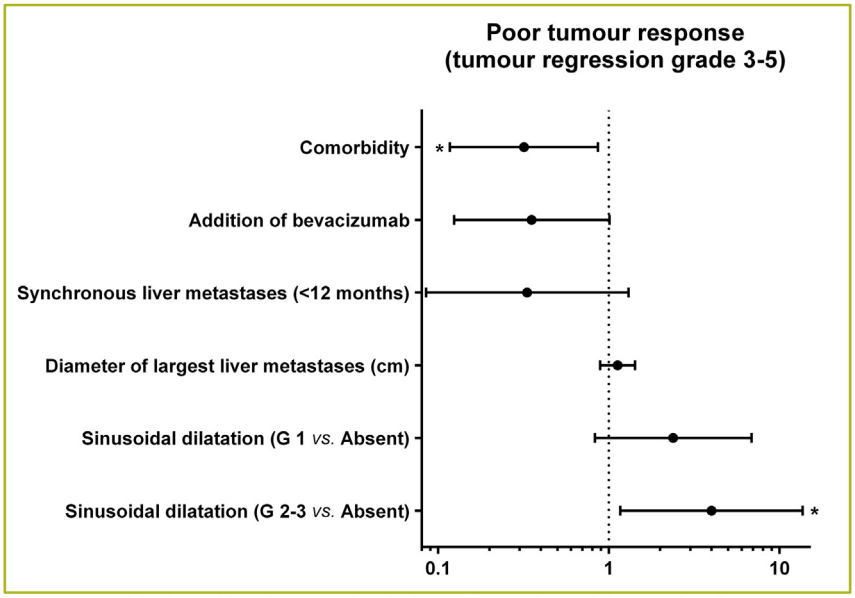
[a] Due to unavailable collagen staining, indicated number of patients was below 166.

follow-up, 97 (58%) patients developed recurrence. Median recurrence-free survival was 30 months (95% CI 23–38 months). Both complete tumour response (HR 0.47, 95% CI 0.25–0.89, $p = 0.020$) and radical resection (HR 0.58, 95% CI 0.38–0.88, $p = 0.011$) were associated with prolonged recurrence-free survival. The presence of remote site infections was the sole factor independently related to shortened recurrence-free survival (HR 1.87, 95% CI 1.06–3.30, $p = 0.030$).

Fig. 3 summarizes the association between potential prognostic factors and overall survival (Detailed data are summarized in Supplemental Table 4). Until the date of last follow-up, 65 (39%) patients were alive, and the rest deceased. Median overall survival was 44 months (95% CI 36–52 months). Complete tumour response (i.e. tumour regression grade 1–2, HR 0.35, 95% CI 0.18–0.68, $p = 0.002$) and radical resection (HR 0.52, 95% CI 0.34–0.80, $p = 0.003$) were associated with prolonged overall survival. Synchronous (<12 months) liver metastases (HR 1.98, 95% CI 1.14–3.47, $p = 0.016$) and remote site infections (HR 1.87, 95% CI 1.06–3.30, $p = 0.030$) were independently related to shortened overall survival.

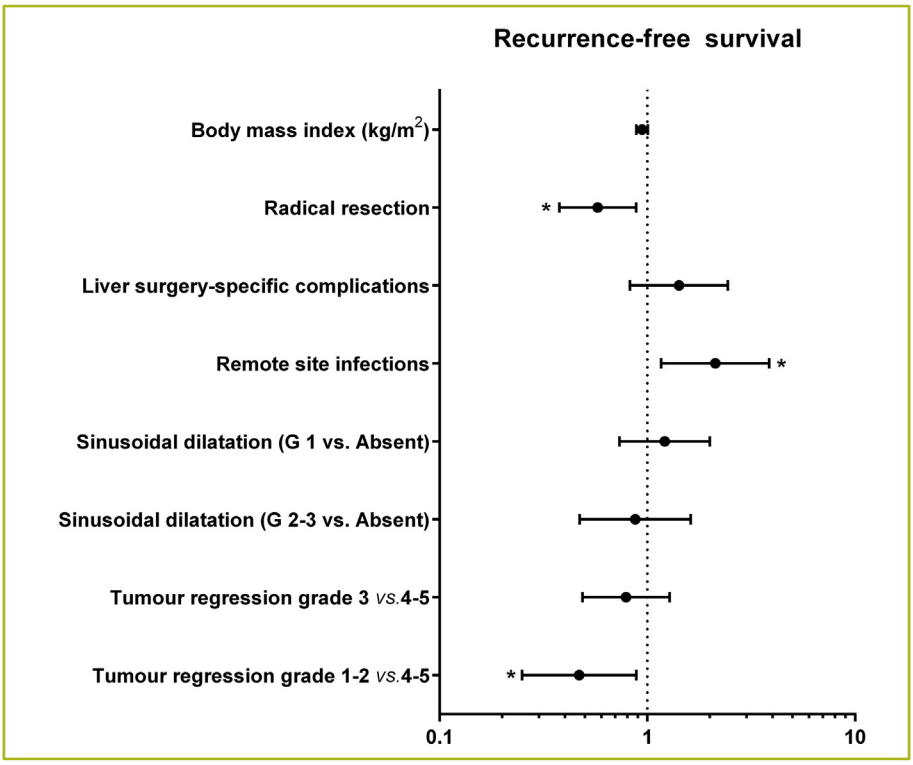
Discussion

The data of the present study demonstrate that poor tumour response after neoadjuvant chemotherapy occurred more often in patients with sinusoidal dilatation, whereas neither steatosis nor nodular regeneration was associated with tumour response. Complete tumour response, in turn, was a strong independent predictor of prolonged recurrence-free survival and overall survival. However, none of the studied background liver



Data are depicted as odds ratios (symbols) with 95% confidence intervals (bars) based on results of multivariable analysis; asterisks indicate p-value≤0.05

Figure 1 Factors related to tumour response



Data are depicted as hazard ratios (symbols) with 95% confidence intervals (bars) based on results of multivariable analysis; asterisks indicate p-value≤0.05

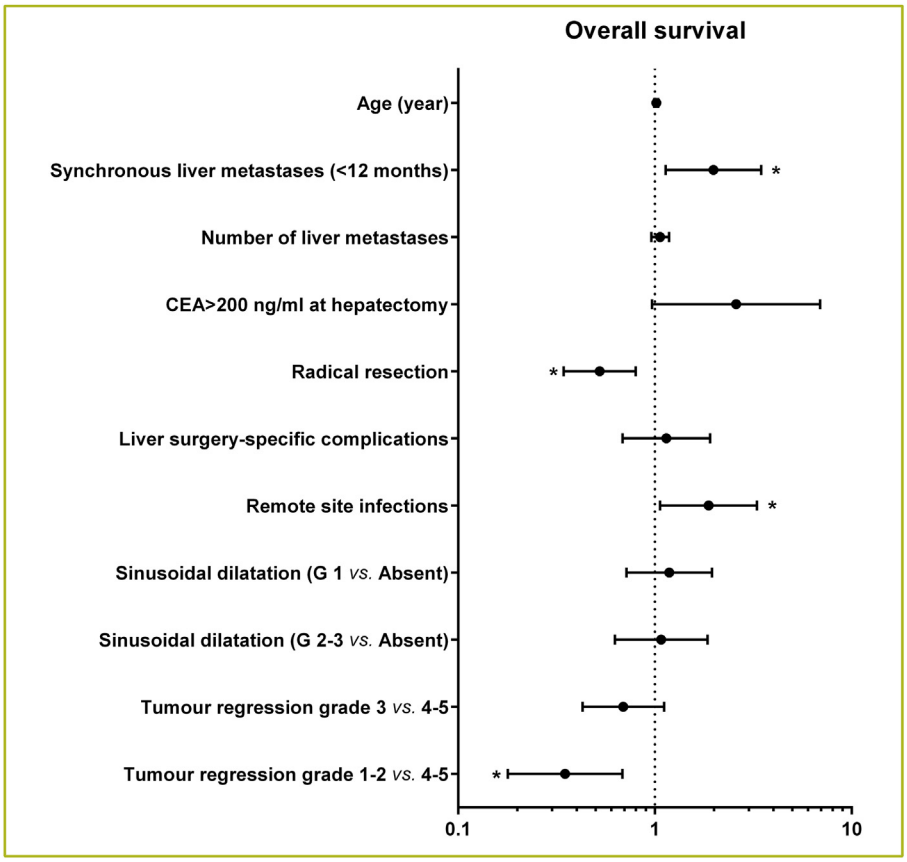
Figure 2 Prognostic factors related to recurrence-free survival

abnormalities was independently related to survival. Addition of bevacizumab to chemotherapy was associated with decreased occurrence of sinusoidal dilatation, and tended to be related to increased complete tumour response. Moreover, remote site infections were related to reduced recurrence-free survival and overall survival, whereas radical resection was associated with an increase for these outcome parameters.

Although sinusoidal dilatation was associated with diminished complete tumour response, which was associated with recurrence-free survival and overall survival, sinusoidal dilatation itself was not directly related to survival. As neoadjuvant chemotherapy provides increased complete tumour response,[26] and this is related to prolonged survival, this observation might indicate that the benefits of neoadjuvant chemotherapy in terms of prolonging survival outweigh the harm of chemotherapy-induced undesired parenchymal liver injury. It is also suggested that chemotherapy could be more beneficial if clinicians could reduce the negative impact of CALI on tumour response. Moreover, the absence of statistical significance of the relationship between sinusoidal dilatation and survival could also be due to a type II error. Therefore, future studies with larger sample size are encouraged. Since addition of bevacizumab to the chemotherapy treatment was associated with both a lower prevalence of sinusoidal dilatation and a tendency to increased tumour response, it seems beneficial to add bevacizumab to oxaliplatin-based chemotherapy.[27]

In the present study, the previously shown[5,13] inverse relation between chemotherapy-associated sinusoidal dilatation and tumour regression grade was confirmed. There may be several explanations for this finding. Loss of fenestrae in sinusoidal endothelial cells, which has been shown in an animal model of sinusoidal obstruction syndrome,[28] might inhibit the transport of compounds[29] such as oxaliplatin to the tumour, thereby limiting chemotherapy exposure. Oxaliplatin based chemotherapy is also known to lead to the detachment of sinusoidal endothelial cells from the space of Disse,[30] which may further weaken the hepatic microcirculation and limit transportation of drugs to the tumour.[30,31] Moreover, a compromised hepatic microcirculation will lead to hypoperfusion and may induce a state of hepatic hypoxia.[32] Tumour hypoxia will subsequently stimulate angiogenesis that may promote tumour cell invasion.[33] Taken together, loss of fenestrae from sinusoidal endothelial cells, a weakened hepatic microcirculation, and hepatic hypoxia related to sinusoidal dilatation are all potential contributors to a diminished tumour response.

In line with a previous report,[18] the present study shows a negative relation between the presence of remote site infections and recurrence-free survival as well as overall survival. Although



CEA, carcinoembryonic antigen; data are depicted as hazard ratios (symbols) with 95% confidence intervals (bars) based on results of multivariable analysis; asterisks indicate p-value≤0.05

Figure 3 Prognostic factors related to overall survival

the mechanisms underlying this observation remain unclear, and a specific cause–effect relationship cannot be proven, the innate or adaptive immunity may play an important role.

Some limitations of this study should be discussed. Although analysis of the effect of steatohepatitis on tumour regression grade and survival would have been of interest, this was not possible since only one patient was diagnosed with steatohepatitis. This very low incidence of steatohepatitis could be due to the fact that only a small number of patients were treated with irinotecan, a known risk factor for the development of steatohepatitis.[10–12] Next, data on the interval between cessation of neoadjuvant chemotherapy and partial hepatectomy, as well as the number of administered cycles, were not available for the majority of included patients, since chemotherapy was frequently administered at local referral hospitals. Therefore, the influence of these factors on tumour regression grade and survival could not be evaluated. Additionally, this study could not clarify whether patients with the lowest tumour responsiveness received continuous chemotherapy and therefore had an increased sinusoidal dilatation severity. Moreover, it could not identify whether patients who developed sinusoidal dilatation did not undergo partial hepatectomy at a later point, which could be associated with worse tumour pathologic evaluations. Because data on chemotherapy cycles and doses, as well as intervals between cessation of chemotherapy and surgery was lacking, we were not able to investigate whether patients with comorbidity and diminished tumour response received reduced cycles or doses of chemotherapy, which might underlie the observation that the presence of comorbidity was negatively related to tumour response. Despite this limitation, it must be highlighted that the majority of the studied population received the same regimen, which was capecitabine in combination with oxaliplatin. Therefore, the effect of treatment regimen related factors on tumour regression grade and survival was presumably minimal.

Conclusion

This study demonstrated that chemotherapy-associated sinusoidal dilatation is related to diminished complete tumour response after neoadjuvant chemotherapy. Complete tumour response was shown to be the strongest predictor of prolonged recurrence-free survival and overall survival. None of the background parenchymal chemotherapy-induced liver injuries were associated with survival. Addition of bevacizumab was associated

with decreased sinusoidal dilatation, and tended to be related to increased complete tumour response.

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Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2017.08.030.