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Steatosis is not associated with increased risk of chemotherapy-associated liver injury in metastatic colorectal cancer

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It is well characterised that chemotherapeutic agents cause hepatotoxicity, known as chemotherapy-associated liver injury (CALI).[1] This can take the form of transient elevations in liver function tests, drug-induced hepatitis, veno-occlusive disease and steatohepatitis, as well as chronic manifestations such as fibrosis and cirrhosis.[2] Three forms of CALI are recognised, including (1) chemotherapy-associated steatohepatitis (CASH) (eg, post 5-fluorouracil (5-FU) and irinotecan[3]); (2) nodular regenerative hyperplasia (NRH), for example, post bleomycin, cyclophosphamide and doxorubicin; however, recent literature has identified oxaliplatin as the foremost causative drug[4]; and (3) sinusoidal obstruction syndrome (SOS) found in over 50% of patients with CALI.[5] CALI has clinically significant consequences and is associated with increased morbidity and mortality, treatment disruption and reduced tolerance of chemotherapy.[6–9] Chronic sequelae can develop, and SOS and NRH are causes of non-cirrhotic portal hypertension.[4] In the neoadjuvant setting, the occurrence of CALI can adversely affect surgical outcomes. This is particularly evident in the case of metastatic colorectal cancer (MCRC), for which chemotherapy is increasingly used to optimise the resectability of liver metastases at hepatectomy. Chemotherapy regimens used combine several of the agents discussed above, namely, oxaliplatin, irinotecan and 5-FU.[5 10] In this setting, CALI confers impaired liver functional reserve preoperatively, with higher morbidity and increased length of hospital stay after hepatectomy.[11] An increase in overall postoperative mortality has also been observed, specifically resulting from postoperative liver failure.[12]

The metabolic syndrome and its associated insulin resistance and obesity are major risk factors for CALI.[13] This is likely in the context of pre-existing metabolic dysfunction-associated steatotic liver disease (MASLD),[14] which has also been demonstrated to affect the metabolism and pharmacokinetics of different medications, increasing the rate of adverse drug effects.[15] In inflammatory bowel disease, steatosis has been identified as a risk factor for hepatotoxicity in patients on immunosuppressive treatment, for example, via disordered hepatic metabolism of azathioprine.[16 17] The metabolic syndrome is also an established risk factor for colorectal cancer, and studies have highlighted an association between MASLD and colorectal cancer.[18] Optimal management of MCRC requires individualised decision-making and may include combination chemotherapy and/or hepatectomy.[10] Balancing the risk of CALI (and its implications for operative management) should be a part of this process.[13] Steatosis may be an important risk factor which can be detected on baseline imaging.[19]

We hypothesised that pre-existing steatosis increases the risk of CALI in patients with MCRC.

We performed a retrospective analysis of the medical records of all patients treated for MCRC with chemotherapy at a regional tertiary referral centre for MCRC, between January 2016 and December 2019. Figure 1 summarised the study selection process. Patients <18 years old were excluded, as well as those with a concurrent haematological or solid organ malignancy. We used liver magnetic resonance imaging (MRI) and positron emission tomography and computed tomography (PET-CT) as validated methods to evaluate for steatosis. Baseline demographic data, mutational status and drug exposure were collected from medical records.

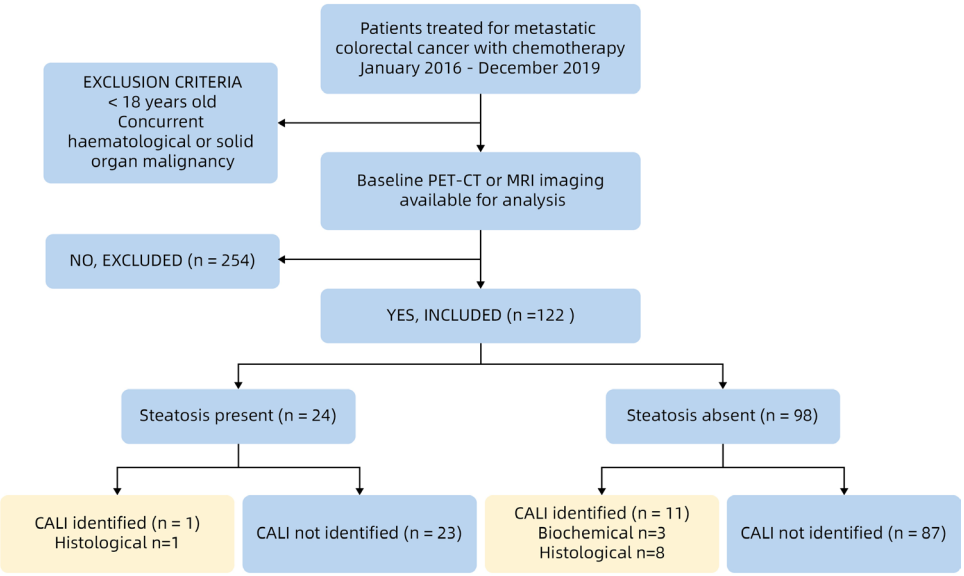

Figure 1 Inclusion and exclusion criteria and summary of findings. CALI, chemotherapy-associated liver injury; MRI, magnetic resonance imaging; PET-CT, positron emission tomography and computed tomography.

The exposure of interest in this study was whether a patient had radiological evidence of pre-existing hepatic steatosis. The primary outcome measure was evidence of CALI after first-line chemotherapy, given over a 3-month period. To increase the sensitivity of case detection, we used the following criteria to create a broad definition of suspected CALI:

i. Elevation in alanine transaminase (ALT) of ≥3 times the upper limit of normal (ULN) AND/OR
ii. Histological evidence of drug-induced liver injury (DILI, including SOS, steatohepatitis and NRH).

The secondary outcome was the number of changes to treatment regime, including dose reductions and delays to chemotherapy or cancellations of chemotherapy and/or surgery. Further details on study methods are provided in the online supplemental file 1.

RESULTS

A total of 376 patients were initially identified. Of these, 122 patients had sufficient imaging data to determine the presence of pre-existing steatosis. 19.6% (n=24) of patients were identified to have steatosis on baseline imaging (see figure 1).

The median age of all patients was 66 years (interquartile range (IQR) 57–74 years). 35.2% (n=43) of patients were female. 91% (n=111) of patients were of white ethnicity. The mean body mass index (BMI) was 27.2 kg/m^2, with a median of 25.6 kg/m^2 (IQR 23.0–30.5 kg/m^2). None of the patients had a formal diagnosis of liver disease. Five patients had hazardous or harmful alcohol consumption at the time of starting chemotherapy, which was defined as an alcohol use disorders identification test consumption (AUDIT-C) score >5 without evidence of dependency and alcohol use disorder, respectively.[20] 82.8% (n=101) of patients had liver metastases at the time of starting chemotherapy.

Table 1 displays the frequency of different chemotherapy regimens delivered. The most frequently used regimen was capecitabine and oxaliplatin (CAPOX) (54.1%; n=66), followed by folinic acid, 5-FU and irinotecan (FOLFIRI) (19%; n=23) and single agent capecitabine (13%; n=11).

Table 2 summarises the characteristics of the study population, stratified by the presence or absence of baseline steatosis. Mean BMI was 5.1 kg/m^2 greater in the

Table 1 Chemotherapy regimens received by the study population

Chemotherapy regimen	n	Percentage (%)
Capecitabine-oxaliplatin	66	54
Capecitabine	13	11
FOLFIRI	23	19
FOLFIRI-panitumumab	5	4
FOLFIRI-cetuximab	5	4
FOLFOX	3	2
FOLFOX-cetuximab	1	1
Cisplatin-etoposide	1	1
Carboplatin-etoposide	1	1
Cisplatin-5-FU	2	2
Irinotecan-panitumumab	1	1
Raltitrexed	1	1
Oxaliplatin-containing regime	70	57.3
Irinotecan-containing regime	34	27.9

FOLFIRI, 5-FU-irinotecan-folinic acid; FOLFOX, 5-FU-oxaliplatin-folinic acid; 5-FU, 5-fluorouracil.

Table 2 Characteristics of the study population, distinguished by the presence or absence of steatosis on baseline imaging (MRI and/or PET-CT)

	Steatosis present (n=24)	Steatosis absent (n=98)	P value	χ^2
Mean age (years)	66	64.3	0.58	_
Female sex (n; %)	6 (25%)	37 (38%)	0.24	_
Mean BMI (kg/m^2)	31.2	26.1	<0.001	_
↑ alcohol consumption (%)	1 (4.2%)	6 (6.1%)	0.71	_
Presence of liver metastases (n; %)	21 (87.5%)	81 (82.7%)	0.57	_
Previous Oxaliplatin use (n; %)	1 (4.2%)	1 (1.0%)	0.28	_
Number of cycles of chemotherapy received (median; IQR)	4 (4-8)	4 (2-8)	_	_
Considered for liver metastectomy (n; % of those with liver metastases)	11 (52.3%)	45 (55.6%)	_	_
Developed CALI (n; %)	1 (4.2%)	11 (11.2%)	0.3	1.08

BMI, body mass index; CALI, chemotherapy-associated liver injury; IQR, interquartile range; MRI, magnetic resonance imaging; PET-CT, positron emission tomography and computed tomography.

steatosis group (p<0.001). 25% (n=6) of the steatosis group were female. One patient in the steatosis group had received previous treatment with oxaliplatin. The proportion of patients considered for hepatectomy and the number of cycles of chemotherapy received were similar between both groups.

9.8% (n=12) of patients had evidence of CALI. Of these, three patients had biochemical evidence of CALI, and nine had histological evidence (four with SOS; three with NRH and two with CASH). Table 3 summarises the characteristics of the patient group who developed CALI. Of note, only one patient had steatosis at baseline (χ^2=1.08, p=0.30), and the mean BMI of the CALI group was 1.8 kg/m^2 lower than that of the total population (p=0.09). No patients had previously received oxaliplatin. A diagnosis of CALI was not associated with delays to subsequent surgery or chemotherapy, or reduction in the number of cycles of chemotherapy. 83.3% (n=10) of patients in this group received CAPOX chemotherapy.

A total of 39 patients (32%) had histological analysis of liver tissue performed after chemotherapy, in most cases performed after hepatectomy. Eight patients (21%) had histological evidence of new steatosis, with no adverse features. Seven of these patients received CAPOX and one received FOLFIRI and panitumumab.

DISCUSSION

Main findings

We performed a retrospective review of patients with MCRC who started on chemotherapy treatment over 4 years in a regional oncology referral centre. Our results did not support our hypothesis, with our main finding being that there is no obvious association between hepatic steatosis and the development of CALI. This study cannot comment on the relationship between pre-existing liver fibrosis and cirrhosis and CALI.

Table 3 Characteristics of the total study population and subgroup of patients who developed CALI

	Total study population (n=122)	Patients who developed CALI (n=12)	P value
Mean age (years)	64.6	66.3	0.65
Female sex (n; %)	43 (35.2%)	3 (25%)	_
Mean BMI (kg/m^2)	27.2	25.4	0.09
↑ alcohol consumption	7 (5.7%)	0	_
Presence of liver metastases	100 (82%)	12 (100%)	_
Previous oxaliplatin use	2 (1.63%)	0	_
Number of cycles of chemotherapy received (median; IQR)	4 (4–8)	4 (4–5)	_
Considered for liver metastectomy (of those with liver metastases)	56 (56%)	11 (91.7%)	_
Baseline steatosis	24 (19.6%)	1 (8.3%)	_

BMI, body mass index; CALI, chemotherapy-associated liver injury; IQR, interquartile range.

The incidence of CALI in our study (9.8%) was lower than previously reported in the literature. In a large study by Vauthey *et al*,[12] hepatic injury was identified in the histological samples of 37% of patients who received chemotherapy prior to resection of hepatic colorectal metastases. Steatohepatitis was identified in 13.7% of patients and was particularly associated with irinotecan with an OR of 5.4 compared with no chemotherapy (p<0.001; 95% CI 2.2 to 13.5). Sinusoidal dilatation as a hallmark of SOS was identified in 8.9% and was strongly associated with oxaliplatin compared with both no chemotherapy and irinotecan (OR 8.3; 95% CI 2.9 to 23.6 and OR 5.2; 95% CI 1.65 to 16.3, respectively). A study by Rubbia-Brandt *et al*[5] found that 54% of patients treated with oxaliplatin developed SOS. The rates of CASH and SOS in our study were 1.6% and 3.3%, respectively. Of the two patients who developed CASH, one received irinotecan, and of the four who developed SOS, all received oxaliplatin. It is surprising that the rate of SOS in our study was not higher, especially given that 57.3% of patients received oxaliplatin, compared with 31.8% in the Vauthey *et al* study.[12]

Importantly, our study identified no adverse consequences in those that developed CALI, in terms of delays to subsequent cycles of chemotherapy or hepatic resection. This is in contrast with the study by Vauthey *et al*,[12] which found that CASH was associated with an increased 90-day mortality rate compared with patients who did not have steatohepatitis (14.7% vs 1.6%, respectively; p=0.001; OR 10.5; 95% CI 2.0 to 36.4). Specifically, the risk of death from postoperative liver failure (5.8%) was higher in this group versus all other patients (0.8%; p=0.01; OR 7.7; 95% CI 1.24 to 47.7). The baseline characteristics of the study population in terms of median age, sex distribution and median BMI were comparable between the two studies.

Strengths and limitations

The findings of this study contrast with those of the previous work and suggest a lower risk of CALI, both in terms of incidence and its consequences, in patients with MCRC receiving chemotherapy. However, our study had important limitations. As a single-centre study, it had limited power to detect the outcome of interest. Moreover, the study design was retrospective, and data collection was limited to what was recorded in the medical records. It is therefore possible that some relevant details may have been omitted.

In our study, we included only patients who had baseline MRI liver or PET-CT imaging. This imaging is typically requested in patients with potentially resectable disease.[10] Patients who did not have this imaging performed (and who therefore were not considered for resection) were excluded from the study. There may be important differences between the excluded group and the study population—such as a dissimilar proportion of patients with lower fitness for treatment and/or high volume metastatic disease—which we have not detected and which may influence the risk of CALI.

It is important to note that in similar previous studies,[5 12] all patients had histological analysis of hepatic tissue performed after chemotherapy, compared with less than one-third of patients in our study, and this is likely to have significantly reduced the sensitivity in detecting cases of CALI. Of the nine patients who had a histological diagnosis of CALI made, only one also met the criteria for a biochemical diagnosis. Therefore, there may be a number of cases of CALI which went undetected in our study, introducing type 2 error.

Other evidence

Notably, the rate of pre-existing steatosis in our study population at 19.6% was lower than that of the general population. A recent systematic review estimated the global prevalence of MASLD to be 30% and 25% in Western Europe.[21] Prevalence increases with age and is highest in males aged 40–65 years, a group which reflects a significant proportion of our study population.[22] The lower than expected rates of steatosis in our study population may be reflective of the selection bias introduced by including only patients eligible for PET-CT and MRI. Such patients would, by association, be those considered fit enough for surgical management of liver metastases.

An area for further research concerns the impact of steatosis on the incidence of immunotherapy-mediated DILI. The use of immunotherapy drugs (such as the programmed cell death-1 (PD-1) inhibitors pembrolizumab and nivolumab, and the cytotoxic T-lymphocyte antigen 4 (CTLA4) inhibitor ipilimumab) in MCRC has expanded in recent years, and hepatotoxicity is common. The KEYNOTE 177 study found that 14–16% of patients with MCRC treated with pembrolizumab developed raised aminotransferases, and 3% developed hepatitis.[23] A retrospective analysis of 135 patients treated with anti-PD-1 agents found that non-alcoholic fatty liver disease was a potential risk factor for developing immunotherapy-mediated DILI (HR 29.34; 95% CI 3.169 to 271.6, p=0.003).[24] Further studies are needed to better characterise this relationship in order to aid clinicians' decision-making when considering the use of immunotherapy in patients with MASLD and cancer.

CONCLUSION

In this study, approximately 1 in 10 patients developed CALI following treatment for MCRC, but there was no association with baseline hepatic steatosis despite selecting a patient group exposed to particularly hepatotoxic chemotherapeutic agents. This finding is in contrast to previous studies. This has potential implications for decision-making in the management of MCRC, where chemotherapy regimens containing agents known to cause CALI are common. As increasing numbers of patients with MCRC are treated with immunotherapy in the future, further studies may elucidate the association of baseline steatosis with the incidence of immunotherapy-induced liver injury and the potential impact on cancer outcomes.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

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