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Influence of pre-surgical chemotherapy on liver parenchyma and post-surgical outcome of patients subjected to hepatectomy due to colorectal carcinoma metastases☆

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ABSTRACT

Introduction: The aim of the study was to evaluate the relationship between the pre-surgical administration of a chemotherapy regime based on irinotecan or oxaliplatin and the development of non-alcoholic fatty liver disease (NAFLD) or sinusoidal obstruction syndrome (SOS), and the influence of these histological changes on the outcome of patients after surgical intervention.

Patients and method: A prospective study which included 45 patients surgically intervened due to colorectal cancer liver metastases between May 2005 and July 2009. Demographic data and the variables before during and after the operation were collected. A specimen of the resection was obtained for histological analysis following the classification parameters of the NAFLD (NASH index) and SOS scale.

Results: Neoadjuvant chemotherapy was given before the resection in 22 cases (study group) and 23 patients made up the control group (no chemotherapy). Borderline or diagnostic steatohepatitis was observed in 4 of the 7 patients (57.2%) who were given preoperative irinotecan (P=.001). Seven of the 15 patients (46.7%) treated with oxaliplatin developed a moderate or severe SOS (P=.002). There were no differences in morbidity or mortality associated to the NAFLD grade, but there was a higher rate of liver complications and longer mean hospital stay in patients with moderate/severe SOS (*P*=.004 and *P*=.021, respectively).

Conclusions: Treatment with irinotecan was significantly associated with an increase in the incidence of steatohepatitis, but did not increase the morbidity or mortality. Patients treated with oxaliplatin had a higher incidence of SOS, an increase in liver complications and a longer mean hospital stay.

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Influencia de la quimioterapia preoperatoria en el parénquima hepático y en la evolución posquirúrgica de pacientes sometidos a hepatectomía por metástasis de carcinoma colorrectal

Palabras clave:
Quimioterapia
Esteatohepatitis
Obstrucción sinusoidal
Metástasis hepáticas

R E S U M E N

Introducción: El objetivo del estudio fue valorar la relación entre la administración preoperatoria de regímenes de quimioterapia basados en irinotecán u oxaliplatino con el desarrollo de enfermedad hepática grasa no alcohólica (EHGNA) o el síndrome de obstrucción sinusoidal (SOS) y la influencia de estas alteraciones histológicas sobre la evolución de los pacientes tras la intervención quirúrgica.

Pacientes y método: Estudio prospectivo en el que se incluyeron 45 pacientes sometidos a intervención quirúrgica por metástasis hepáticas de cáncer colorrectal entre mayo de 2005 y julio de 2009. Se recogieron variables demográficas, preoperatorias, de la intervención quirúrgica y de la evolución postoperatoria. Se obtuvo una muestra de la pieza de resección para su análisis histológico siguiendo los parámetros de clasificación de la EHGNA (índice NAS) y del SOS.

Resultados: En 22 casos se administró quimioterapia neoadyuvante previa a la resección (grupo de estudio) y 23 pacientes formaban parte del grupo control (no quimioterapia). En 4 de los 7 pacientes (57,2%) en los que se administró de forma preoperatoria irinotecán, se observó esteatohepatitis borderline o diagnóstica (p = 0,001). Siete de los 15 pacientes tratados con oxaliplatino (46,7%) desarrollaron un SOS moderado o grave (p = 0,002). No hubo diferencias en cuanto a la morbimortalidad en función del grado de EHGNA, pero sí hubo una mayor tasa de complicaciones hepáticas y mayor estancia media en los pacientes con SOS moderado/intenso (p = 0,004 y p = 0,021 respectivamente).

Conclusiones: La administración de irinotecán se relacionó de forma significativa con un aumento en la incidencia de esteatohepatitis, sin que esto aumentara la morbimortalidad. Los pacientes tratados con oxaliplatino tuvieron una mayor incidencia de SOS y existió un aumento de las complicaciones hepáticas y de la estancia media.

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Introduction

The liver is the most common site of colorectal carcinoma (CRC) metastases. Hepatic resection is the only treatment that currently offers the possibility of long-term survival in patients with hepatic metastases (HM) from CRC. However, although the disease is limited to the liver in approximately 30% of HM patients, hepatic resection has traditionally been used as a therapeutic option in only 10%-25% of cases.[1,2]

The appearance of new chemotherapy agents and their combinations offers patients with initially unresectable metastases the possibility for curative salvage surgery and it has substantially increased life expectancy in patients with metastatic CRC. Standard 5-FU chemotherapy regimens along with leucovorin combined with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) have yielded the possibility for curative salvage surgery in 9%-40% of initially, unresectable metastases.[3] Recently, a large number of studies have reported a negative effect on the hepatic parenchyma, mainly non-alcoholic fatty liver disease (NAFLD) and sinusoidal obstruction syndrome (SOS), due to different drugs used in the chemotherapy treatment of metastatic CRC, namely irinotecan and oxaliplatin.[4-11]

NAFLD is a process characterised by the accumulation of lipid substances in the liver. This disease includes simple hepatic steatosis, non-alcoholic steatohepatitis, and finally cirrhosis. Although the mechanism of NAFLD has not been completely elucidated, evidence points towards insulin resistance as the primary mechanism. In a second stage, and additional source of oxidative stress is capable of overcoming the cellular defence mechanisms, leading to inflammatory processes, degeneration, and fibrosis.[12] Although it is widely accepted that steatohepatitis is part of NAFLD, it can be difficult for pathologists to define and differentiate steatosis with inflammation of the hepatic parenchyma from steatohepatitis. For this reason, Kleiner et al[13] proposed a scoring system (NAS: Non-alcoholic Fatty Liver Disease Activity Score) in order to determine the severity of steatohepatitis based on these characteristics. This scoring system is based on the characteristics that are significantly associated with the diagnosis of steatohepatitis: the extent of steatosis, lobular inflammation, and hepatocellular ballooning. The purpose of this classification system was to provide a valid, semi-quantitative method for unifying the criteria used in different clinical studies. Each of these characteristics regarding steatohepatitis has been demonstrated to have an independent correlation with the diagnosis of this liver disease.

The depolymerisation of F-actin in endothelial cells of the sinusoids has been associated with the physiopathology

of SOS, along with activation of metalloproteases and the induction of oxidative stress. Cells lining the walls of the sinusoids become detached and enter circulation, embolising and obstructing sinusoidal blood flow. Rubbia-Brandt et al[7] were the first researchers to report the increased prevalence of SOS in the liver tissue of patients that had received treatment with oxaliplatin for HM from CRC.

The objective of this study is to evaluate the relationship between the preoperative chemotherapy regimens based on irinotecan and oxaliplatin and the development of NAFLD and SOS, and the influence of these histological alterations on the recovery of patients after surgery.

Patients and methods

Patient selection

Our prospective study included all patients that underwent surgical procedures for HM from CRC at the Hepatobiliopancreatic Surgery Unit of the General and Digestive Apparatus Surgery Department at La Princesa University Hospital, Madrid between May 2005 and July 2009. A multidisciplinary meeting of the Tumour Committee of the Hospital made the decision as to the type of surgical treatment and the resectability of the HM. All patients signed informed consents, accepting the procedure for liver biopsy before the surgical treatment, and the study was approved by the Hospital Ethics Committee.

The patients were divided into two groups: a study group and a control group. Inclusion criteria for the study group were: patients with CRC and HM that received preoperative chemotherapy in accordance with protocols at La Princesa University Hospital, with an interval between the end of chemotherapy treatment and surgery of 4-6 weeks; which were to undergo anatomical or non-anatomical hepatic resection, with or without vascular occlusion; and did not have chronic liver disease. Inclusion criteria for the control group were: patients with HM that had not received any chemotherapy in the 6 months prior to surgery, which were to undergo hepatic resection and did not have chronic liver disease. The study group was divided according to the chemotherapy regimen administered: patients that received therapies based on irinotecan (FOLFIRI) and those that received oxaliplatin-based therapies (FOLFOX).

Patients with unresectable HM, chronic liver disease, and those that had undergone preoperative portal venous embolisation were excluded from the study, since portal embolisation produces severe ischaemia with probable changes in the sinusoids.

In all cases, clinical information was collected prospectively for each patient, including demographical variables (sex, age, body mass index [BMI], patient background, including arterial hypertension, DM, dyslipidemia [total cholesterol >200 and/or TG>150]), HM preoperative characteristics (number, location [unilateral/bilateral], synchronous/metachronous, size of the largest lesion), CEA levels at the time of diagnosis, time transpired between the primary tumour surgery and resection of the metastases, type of chemotherapy (duration, number of cycles, and toxicity), surgery characteristics (duration of the procedure, intraoperative transfusion or not, type of hepatectomy, anatomical/non-anatomical resection, vascular clamping and duration, number of resected metastases), and postoperative characteristics (lab results: Prothrombin time, bilirubin, transaminase levels (GOT/AST, GPT/ALT), alkaline phosphatase, and GGT, on days 1, 3, 5, and 7; liver complications (biliary fistula, haemorrhage, abscesses, uninfected collections, and liver failure), and medical complications (pulmonary, cardiac, renal, and infectious), the need for reoperations or percutaneous drainage, duration of hospital stay, and postoperative mortality at 30 days. Liver failure was defined as altered mental state associated with a coagulopathy (INR>1.5) in patients without pre-existing cirrhosis.

Surgical treatment

All hepatic resections were performed as a curative measure. The peritoneal cavity was initially assessed in order to rule out any extrahepatic disease. We then proceeded with a complete examination of the liver through palpitation and ultrasound in order to determine the locations of the lesions and their relationship with vascular structures, and in order to rule out hidden lesions that were not revealed during the preoperative imaging tests. The hepatic transection was performed using an ultrasonic dissector CUSA® (Valleylab, Boulder, Colorado, USA). We also used the Tissuelink® (Tissuelink Medical Inc., Dover, NH, USA) to provide haemostasis during the procedure. When necessary, we used a vascular clamp for the portal triad (Pringle manoeuvre). The resection was considered anatomical when it followed the fissures that delineate the anatomical borders as defined by the Brisbane[14] classification. Non-anatomical or atypical resections were those that did not.

Histopathological study

From the surgical specimen extracted from the resection, we obtained a 1×1 cm sample of liver tissue distant from the tumour, and performed a histological analysis using Haematoxylin-Eosin and Masson trichrome. This sample was analysed following the NAFLD classification parameters (NASH index[13]) (steatosis, lobular inflammation, and hepatocellular ballooning) (Table 1, Figure 1). For the diagnosis of the steatohepatitis, we considered the following scores: 0-2: no diagnosis of steatohepatitis; 3-4: borderline, and 5-8: diagnosis of steatohepatitis.

The grade of sinusoidal dilation (SOS) was assessed according to the Rubbia-Brandt et al[7] classification system as 0: absent; 1: mild (centrilobular involvement, limited to 1/3 of the lobular surface); 2: moderate (centrilobular, extending to 2/3 of the lobular surface); 3: severe (involvement of the entire lobular surface). The level of fibrosis was classified as 0: no fibrosis; 1: perisinusoidal or periportal: 1A: mild, perisinusoidal, 1B: moderate, perisinusoidal, 1C: portal/periportal but not perisinusoidal; 2: perisinusoidal and periportal/portal; 3: fibrous bridges, and 4: cirrhosis (Figure 2). We also compared the type of chemotherapy administered, the effects on the hepatic parenchyma, and morbidity and mortality after surgery.

Table 1 – Patient background by treatment group

	Group											
	Control group (No.=23)			Irinotecan group (No.=7)			Oxaliplatin group (No.=15)			Total (No.=45)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Sex (P=.039)												
Male	15	65.2		5	71.4		4	26.7		24	53.3	
Female	8	34.8		2	28.6		11	73.3		21	46.7	
Age, years) (P=.17)			58.3 (11)			53.9 (11)			61.7 (6)			58.8 (10)
Height, m (P=.158)			1.65 (0.1)			1.66 (0.1)			1.59 (0.1)			1.63 (0.1)
Body mass index (P=.062)			26.2 (4)			29.3 (5)			25.0 (4)			26.3 (4)
Arterial hypertension (P=.67)												
Yes	9	39.1		3	42.9		4	26.7		16	35.6	
No	14	60.9		4	57.1		11	73.3		29	64.4	
DM (P=.55)												
Yes	1	4.3		1	14.3		2	13.3		4	8.9	
No	22	95.7		6	85.7		13	86.7		41	91.1	
Dyslipidemia (P=.15)												
Yes	2	8.7		1	16.7		5	33.3		8	18.2	
No	21	91.3		5	83.3		10	66.7		36	81.8	
No. metastases (P=.085)			1.4 (1)			2.5 (2)			1.5 (1)			1.6 (1)
Size of the largest, cm (P=.31)			2.1 (1)			2.5 (1)			3.4 (3)			2.6 (2)

DM indicates diabetes mellitus; SD, standard deviation.

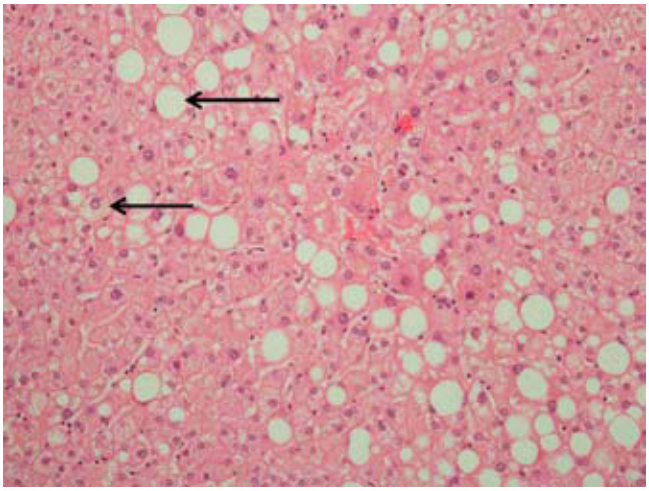

Figure 1 – Haematoxylin-eosin (20×): histological preparation of hepatic tissue with a visual microscope. Steatosis and hepatocellular ballooning (arrows) was observed in different areas of the hepatic parenchyma.

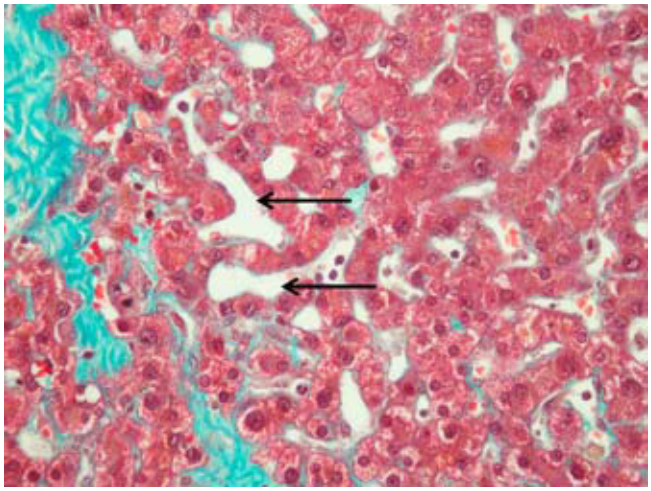

Figure 2 – Masson Trichrome (40×): histological preparation of hepatic tissue with a visual microscope. Different areas with severe sinusoidal dilation (arrows) are observed.

Statistical analysis

All data were introduced into a database and analysed using SPSS statistical software, 15th ed® (SPSS, Chicago, Illinois, USA). Those quantitative variables that followed a normal distribution were defined by their mean, standard deviation, and range of values. In those that did not follow a Gaussian distribution, we used the median instead of the mean as a measure for central

tendency. Qualitative variables were defined by the number of cases and percentages. Quantitative and qualitative variables were compared using the Student's t test for independent samples (comparing two means) and ANOVA (comparing more than two means) when the quantitative variables followed a normal distribution. When the quantitative variables did not follow a Gaussian distribution, we used the Mann-Whitney test for comparing two means or the Kruskal-Wallis test for comparing more than two means. In the case of comparing two discrete variables, we used the chi-square test. When the expected value was less than 5 in any of the boxes from the contingency table, we used Fisher's exact test. The analysis of two normal quantitative variables was performed using the Pearson's comparison method, whereas when at least one of the variables did not follow a Gaussian distribution, we used Spearman's test. Values were considered significant when $P<.05$.

Results

Demographic characteristics

During the study period, 45 patients (24 men and 21 women) complied with the inclusion criteria and formed part of the study. Twenty-two out of 45 patients were administered some neoadjuvant drug within the 4 to 6 weeks before the resection (study group), and 23 patients did not receive chemotherapy before the resection (control group). In the study group, 7 patients received chemotherapy treatment based on irinotecan (FOLFIRI, with cetuximab added in 2 cases, and bevacizumab in 1 case), and oxaliplatin-based therapy was used in 15 patients (FOLFOX, cetuximab was added in 4 patients, and bevacizumab in two).

The distribution of patient histories according to treatment group is displayed in Table 1.

Histological Evaluation

NAFLD

In our study, we tested for relationships between the existence of steatosis and lobular inflammation and irinotecan as the chemotherapeutic agent administered prior to surgery. 57.2% of patients treated with irinotecan had moderate or severe hepatic steatosis (>33%) ($P=.001$). Only one patient in the control group and none in the group treated with oxaliplatin developed the same level of hepatic steatosis. Additionally, irinotecan use was correlated with lobular inflammation, 71.4% ($P=.02$), compared to 13% in the control group and 26.7% in the oxaliplatin group.

When calculating the NASH index (Table 2), we observed a clear relationship between the existence of borderline or diagnostic steatohepatitis and the chemotherapeutic regimen used, observing this histological abnormality in 4 out of the 7 patients (57.2%) that received irinotecan before the surgical procedure ($P=.001$).

SOS

By analysing the level of sinusoidal dilation (Table 2), we observed a clear relationship between the use of oxaliplatin in neoadjuvant chemotherapy treatment and the presence of moderate or severe sinusoidal dilation in the liver tissue. Seven out of the 15 patients treated with oxaliplatin-based chemotherapy regimens (46.7%) developed moderate or severe SOS. In contrast, only one patient from the control group and no patients from the irinotecan group developed similar histological alterations ($P=.002$).

Morbidity and mortality according to the grade of NAFLD

The parameters measured during the surgical procedure were similar between groups in spite of the grade of NAFLD. Nor were there difference in the liver function tests immediately following the operation, rate of medical or hepatic complications, or the need for reoperations or percutaneous drains. Mortality in these patients was 0%, and the mean duration of hospital stay was similar to the control group (Table 3). The type of hepatectomy performed (major or minor) was similar, with no statistically significant differences between groups.

Morbidity and mortality according to the grade of SOS

The duration of surgery, the need for vascular clamps, and the units of blood transfused were not affected by the existence

Table 2 – NAFLD (NASH index) and SOS according to treatment group

	Group							
	Control group (No.=23)		Irinotecan group (No.=7)		Oxaliplatin group (No.=15)		Total (No.=45)	
	No.	%	No.	%	No.	%	No.	%
NASH ($P=.001$)								
No steatohepatitis (0-2)	23	100.0	3	42.9	14	93.3	40	88.9
Borderline (3-4)	0	–	2	28.6	1	6.7	3	6.7
Steatohepatitis (5-8)	0	–	2	28.6	0	–	2	4.4
SOS ($P=.002$)								
Absent/mild	22	95.7	7	100.0	8	53.3	37	82.2
Moderate/severe	1	4.3	0	–	7	46.7	8	17.8

SOS indicates sinusoidal obstruction syndrome.

Table 3 – Morbidity and mortality and mean duration of hospital stay according to grade of NAFLD (NASH index)

	Steatohepatitis (NASH INDEX)							
	No steatohepatitis (No.=40)		Borderline (No.=3)		Steatohepatitis (No.=2)		Total (No.=45)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Duration of surgery, minutes (P=.34)	288 (61)		270 (30)		350 (71)		290 (60)	
Units transfused	2		–		–		2	
Prothrombin time, % (5th day) (P=.68)	91 (15)		90 (15)		99 (6)		91 (15)	
Total bilirubin levels, mg/dl (5th day) (P=.89)	0.6 (0.3)		0.7 (0.4)		0.6 (0.1)		0.6 (0.3)	
GOT/AST levels, U/L (5th day) (P=.26)	78 (57)		59 (44)		121 (19)		79 (55)	
Liver complications (P=.26)		17.5% (No.=7)		33.3% (No.=1)		50% (No.=1)		20% (No.=9)
Medical complications (P=.9)		12.5% (No.=5)		0		50% (No.=1)		13.3% (No.=6)
Reoperations (P=.65)		7.5% (No.=3)		0		0		6.7% (No.=3)
Percutaneous drainage (P=.7)		7.5% (No.=3)		0		0		6.7% (No.=3)
Duration of hospital stay, days (P=.89)	10.4 (6)		9.7 (4)		10		10.3 (5)	

SD indicates standard deviation.

Table 4 – Morbidity and mortality and mean duration of hospital stay according to grade of SOS

	Sinusoidal dilation					
	Absent/mild (No.=37)		Moderate/severe (No.=8)		Total (No.=45)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Duration of surgery (P=.7)	284.9 (63)		312.5 (45)		289.8 (60)	
Units transfused (P=.19)	1		2		1.5 (1)	
Clamps used (P=.07)						
Yes		8 (21.6%)		0		8 (17.8%)
No		29 (78.4%)		8 (100%)		37 (82.2%)
Maximum size (according to PA) (P=.47)	2.5 (1)		4.2 (3)		2.8 (2)	
Prothrombin time, % (5th day) (P=.36)	93.2 (14)		86.0 (21)		91.7 (15)	
Total bilirubin levels, mg/dl (5th day) (P=.89)	0.6 (0.3)		0.8 (0.3)		0.6 (0.3)	
GOT/AST levels, U/l (5th day) (P=.08)	87 (58)		47 (24)		79 (55)	
Liver complications (P=.004)		10.8% (No.=4)		62.5% (No.=5)		20% (No.=9)
Medical complications (P=.59)		13.5% (No.=5)		12.5% (No.=1)		13.3% (No.=6)
Reoperations (P=.45)		5.4% (No.=2)		12.5% (No.=1)		6.7% (No.=3)
Percutaneous drainage (P=.77)		2.7% (No.=1)		25% (No.=2)		6.7% (No.=3)
Duration of hospital stay, days (P=.021)	9.4 (4)		14.4 (8)		10.3 (5)	

SD, standard deviation.

of moderate or severe sinusoidal dilation, or by the results from liver function tests. A greater rate of liver complications was observed in patients with moderate/severe sinusoidal damage (P=.004). In this group, 3 patients had uninfected collections, and in 2 of these, an abscess was discovered in the surgical area. Although there was no difference in the rate of medical complications, need for reoperations, or percutaneous drains, the mean duration of hospital stay

was significantly higher in these patients (14.4±8 days in the groups with severe sinusoidal damage, compared to 9.4±4 days in the group with no histological abnormalities, P=.021) (Table 4). Just as described in the previous paragraph, no significant differences were observed depending on the type of surgery performed.

Discussion

In recent years, the combined use of chemotherapy and surgery has proven to be the optimal strategy for improving the survival of patients with initially unresectable HM from CRC. Steatohepatitis as a complication following chemotherapy treatment was first described in a small study by Fernandez et al.[4] In their study, the authors observed a significant increase in steatohepatitis in patients that underwent surgery following treatment with irinotecan. The duration of treatment and total dosage was not correlated with the grade of steatohepatitis, but body mass index (BMI) was. Later, Vauthey et al[5] performed a multicentre retrospective study with 406 patients who underwent hepatectomy due to metastases, and found that 20% of patients treated with chemotherapy regimens based on irinotecan had steatohepatitis. The risk was greater in patients with a BMI greater than 25 kg/m^2.

When calculating the NASH index in our study, the development of borderline steatohepatitis (Kleiner 3-4) or steatohepatitis (Kleiner 5-8) was significantly associated with previous administration of irinotecan (P=.001). The duration of the pre-surgical treatment was similar in all groups. Furthermore, in our study, patients with severe steatohepatitis had a significantly higher BMI than those without altered hepatic parenchyma (P=.015). Although the differences between groups were not significant, it is important to point out that the patients that received irinotecan-based chemotherapy had a slightly higher BMI than the other groups (Table 1), and the percentages of diabetic and dyslipidemic patients were also slightly higher. Although this result did not have statistical relevance in our study, it deserves special mention and should be taken into account, since most studies report that these factors are involved in the development of NAFLD.

To date, few studies have analysed the impact of steatohepatitis on morbidity and mortality after hepatic resection. The previously mentioned study by Vauthey et al[5] was the only one that observed a greater rate of mortality 90 days after surgery in patients with steatohepatitis as compared to those without steatohepatitis (14.7% compared to 1.6%, P<.001). Furthermore, the presence of steatohepatitis was associated with a significantly higher risk of mortality due to liver failure compared to other patients (6% compared to 1%, P<.01). On the other hand, other studies involving small surgical series showed no differences in morbidity or mortality in patients preoperatively treated with chemotherapy regimens including irinotecan. Similarly, in a retrospective study with 212 patients, Pawlik et al[6] did not observe a greater number of postoperative complications when analysing groups by grade of NAFLD, although they could not evaluate results using statistical methods because of the small number of patients with steatohepatitis (No.=3).

Our results support the fact that NAFLD, even in advanced stages, does not affect perioperative morbidity or mortality, although the small number of cases observed in our study (only two cases of steatohepatitis and three cases of borderline disease) impedes a conclusive analysis of these data.

With regard to the effects of oxaliplatin, as we have already mentioned, the Rubbia-Brandt et al[7] study was the first to associate the administration of oxaliplatin as a cytotoxic agent for the HM from CRC with the development of sinusoidal obstruction and dilation syndrome in liver tissues. In a retrospective study, they observed that 79% of patients treated with oxaliplatin developed perisinusoidal lesions that included dilation and congestion with fibrosis and venous occlusion. This relationship was independent of the dosage administered, and persisted at least 4 months after the final cycle. Other studies performed afterwards have confirmed this relationship.[5,6,8-11,15,16]

A clear tendency exists in all of these studies that relates the use of oxaliplatin with sinusoidal damage. Our results continue this trend. Of the 15 patients treated with oxaliplatin-based therapies before surgery, we observed a moderate or severe grade of sinusoidal dilation in 7 cases (47%), following the criteria set forth by Rubbia-Brandt et al[7] (P=.002). Only one patient from the control group and none from the irinotecan group developed similar histological alterations.

The majority of studies published in the literature relate the use of oxaliplatin-based chemotherapy with the development of SOS or with an increase in morbidity and mortality, but few relate these two variables with each other.

In our study, the duration of surgery, the need for vascular clamps, transfusion units and the liver function tests were not affected by the presence of moderate or severe sinusoidal dilation. However, there was a higher incidence of liver complications in patients with moderate/severe sinusoidal damage (P=.004). Furthermore, the mean duration of hospital stay was significantly higher in these patients (14.4±8 compared to 9.4±4 days in the group without histological alterations, P=.021).

In a study with 90 patients treated with preoperative chemotherapy by Nakano et al,[9] the mean duration of hospital stay was longer in patients with sinusoidal damage (14.7 days compared to 11.7 days, P=.02), as in our study. By analysing the subgroup of 36 patients who underwent major hepatectomy, they found a higher rate of liver complications in the group with sinusoidal damage (40% compared to 6.3%, P=.026). In this study, the authors pointed out the usefulness of preoperative liver biopsies in at-risk patients that received previous chemotherapy treatment.

In contrast, several studies have observed no increase in complications in patients with SOS. Vauthey et al[5] observed that the sinusoidal damage was not associated with greater rates of morbidity or mortality following the hepatectomy. Furthermore, a pathological analysis of 57 patients in the EORTC 40983 study[17] that compared hepatic parenchyma in patients randomly assigned either preoperative chemotherapy treatment or just surgery, found

no increases in the rate of morbidity in patients with sinusoidal damage. Kandutsch et al[10] related the existence of SOS with patient evolution following surgery, finding no evidence that sinusoidal damage acted as a risk factor in the recovery of these patients. Nor did the study by Hubert et al[18] find that the presence of severe hepatic lesions had any clinical impact on patient evolution.

An interesting finding from several recent studies[19,20] has been the potentially protective effect against sinusoidal damage of adding bevacizumab to oxaliplatin as a neoadjuvant treatment. This protective effect of bevacizumab was observed for the first time by Ribero et al,[19] and later was also described by Klinger et al.[20] However, it remains unknown whether or not the severe parenchymal lesions associated with oxaliplatin, such as nodular regenerative hyperplasia and SOS, are reversible with bevacizumab, and these results must be confirmed by other studies, since this protective effect of bevacizumab has not been observed in other publications.[5]

In our study, only two patients were treated with oxaliplatin-based therapies and bevacizumab (one of these had mild sinusoidal dilation and the other moderate/severe), and so we cannot evaluate this relationship.

One of the problems that arises when reviewing the information regarding the correlation between chemotherapy, the potential hepatic lesions it causes, and the impacts on patient evolution, is that differences exist in terms of the definitions of specific pathologies and postoperative results. On occasion, pathologists are in disagreement with the distinction between steatosis and steatohepatitis. At the same time, some studies include all cases of sinusoidal dilation, whereas others only publish severe cases. Furthermore, the definition of postoperative mortality also differs by study, since some authors refer only to mortality within 30 days, whereas others present mortality rates for longer intervals. These differences probably cause the heterogeneous results and different conclusions.

As Chun et al[21] put forth in a recently published review, we believe that cytotoxic treatments should be evaluated and individualised for each patient by a multidisciplinary committee, since certain agents, in particular oxaliplatin, have shown to affect patient recovery after surgery. However, as demonstrated in the multi-centre EORTC-40983 study,[22] the benefits of this therapy (in the right patients and with due precautions) are far superior to the possible inconveniences and complications.

Conflict of interest

The authors affirm that they have no conflict of interest.

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