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INFLUENCE OF PRE-OPERATIVE CHEMOTHERAPY ON HEPATIC MORPHO-PATHOLOGY

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ABSTRACT Pre-surgical chemotherapy in colorectal liver metastases may determine histological changes in tumour-free liver, potentially impacting operative outcomes. Our study involved 92 patients with liver resection, undergoing treatment for liver metastases of colorectal origin; they were assigned into two groups, A and B, after random selection. Group A had 68 patients with pre-operative chemotherapy (standard FOLFOX/FOLFIRI) and Group B consisted of 24 patients considered chemotherapy naive. Pre-surgery FOLFOX/FOLFIRI chemotherapy induced hepatic lesions, the most important of which is not steatosis but vascular lesion. In-depth pathologic analysis showed that most serious vascular lesions may be traced back to enhanced intra-surgery transfusion. The risk for post-surgical complications is associated with length of pre-surgery chemotherapy.
Keywords: colorectal cancer, liver metastases, chemotherapy, liver resection

INTRODUCTION

Hepatic resection is the only approach considered successful in patients with colorectal liver metastases, due to recently reported percentage of 5-year post-hepatectomy survival rates coming as high as 58% (Abdalla et al., 2004; Choti et al., 2002; Fernandez et al., 2004; Pawlik et al., 2005).

Unfortunately, though, because of either presence of concurrent extra-hepatic disease or distribution of metastases inside the liver, it is only 10% - 15% of patients diagnosed as such who may undergo curative resection (Fong et al., 1999; Nordlinger et al., 1996; Auer et al., 2010). The solution for patients evaluated at the outset with unresectable disease remains systemic, biologic agents-free chemotherapy (Alberts et al., 2005; Grothey et al., 2004; Reddy et al., 2005; Masi et al., 2006), yielding 12 to 20 months median survival time and less than 5% in 5-year survival rate (Topham et al., 2002).

However, changes have occurred in the number of patients with colorectal liver metastases initially considered unresectable, who become eligible for curative hepatic resection. This opportunity has been due to development of more effective systemic therapy, on one hand, and further discovery of advanced surgical techniques, on the other hand (Topham et al., 2002; Belghiti et al., 2000; Imamura et al., 2002; Sauer et al., 2004; Gabrilovich et al., 2009; Mazzaferro et al., 2003). More effective systemic chemotherapy leading to subsequent potentially curative hepatectomy (reported

30% to 35%, of 5-year survival rate) has significantly enhanced the efforts aiming at achievement of resectability levels, resulting in increased intensity of chemotherapy administered to patients in this category (Vauthey et al., 2004; Adam et al., 2004; Troester et al., 2009; Karakousis et al., 2009).

Notwithstanding the relatively superficial knowledge concerning the actual effects that pre-surgery chemotherapy exerts on the tumour-free liver,it has been possible to associate chemotherapy with occurrence of alterations in poor parenchymal hemostasis, gross liver appearance (Fig. 1) and faulty liver regeneration, all potentially leading to enhanced post-surgery morbidity and mortality (Troester et al., 2009; Karakousis et al., 2009).

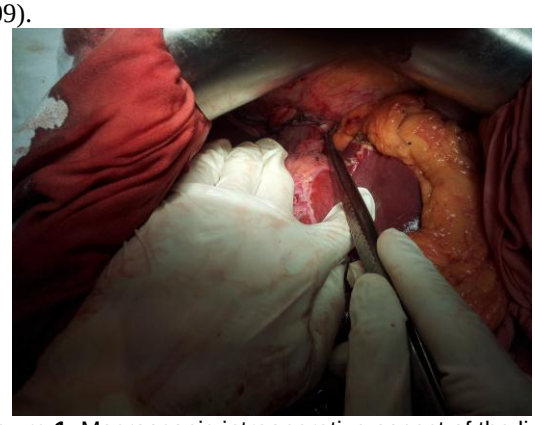

Figure 1. Macroscopic intraoperative aspect of the liver, postchemotherapy

Initial reports had attributed occurrence of phenotypic changes in the tumour-free liver after regional or systemic chemotherapy to the development of hepatic steatosis (Vauthey et al., 2006; Fernandez et al., 2005; Nordlinger et al., 2005; Elias et al., 1995; Behrns et al., 1998; Pocard et al., 2001; Parikh et al., 2003).

More recent studies however have reported it more likely that vascular lesions were more closely related to administration of pre-surgical hepatectomy than to steatosis, particularly concerning oxaliplatin-containing regimens (Vauthey et al., 2006; Rubbia-Brandt et al., 2004; Karoui et al., 2006).

The aim of this study has been to ascertain and assess potential relationships between noted hepatotoxicity and hepatectomy outcomes, on one hand, and systemic chemotherapy, on the other hand.

This has been achieved by comparing study variables in chemotherapy-naïve patients as well as in pre-hepatic surgery FOLFOX/FOLFIRI treated patients.

METHODS AND MATERIALS

The study was performed between January 2011 - April 2014, on a study lot consisting of 92 patients who had undergone hepatic resection for colorectal liver metastases. The lot was divided into two groups, according to patients' having received pre-hepatectomy systemic chemotherapy or not; therefore, Group A was set up of 68 patients (73,91%), who had received prehepatectomy systemic chemotherapy, whereas Group B included 24 patients (26,09%), who had not been given chemotherapy within 6 months before hepatic resection.

For patients in both groups, decisions concerning treatment sequence involved a multidisciplinary team for treatment planning; at the same time, decisions were based on intra-hepatic tumours size, number, and distribution.

Of the 68 patients included in Group A (patients with pre-hepatectomy systemic chemotherapy), 26 (38.24%) had been originally considered unresectable. In this group, surgery was performed as soon as the tumour had decreased in size enough to allow margin-negative resection. The remaining 42 patients (61.76%), irrespective of assignment to groups, had been initially considered resectable, and received pre-hepatectomy chemotherapy as neo-adjuvant treatment.

Furthermore, to allow assessment of the impact of preoperative chemotherapy duration on study outcomes, patients were also subgrouped based on the number of preoperative chemotherapy cycles (< 12 cycles, n=52; and >12 cycles, n=16).

Detailed pathologic analysis has been applied to all patients treated, with FOLFOX/FOLFIRI regimens. At the same time, patients who had not been given pre-surgical chemotherapy were selected for detailed pathologic analysis, therefore serving as control.

Most of the FOLFOX/FOLFIRI patients had received chrono-modulated chemotherapy by means of a time/dose programmed pump.

No patient received erythropoietin-stimulating agents.

Further on, data were collected from our hepatic surgery database regarding each patient's intraoperative course (e.g. fresh frozen plasma and RBC transfusion rates). Later steps have been taken, consisting of a classification of post-surgical complications into general or local, recording of the length of patient post-surgery stay in hospital as well as of measurement of post-surgery mortality rates at 2 and 6 months as of hepatectomy. Follow-up data have been set up for all patients, available at 6 months.

An in-depth microscopic assessment of hepatic tissue outside the tumour in specimens resected from each study patient has been performed by a hepato-biliary pathologist, who also conducted analysis of the tumour-free liver independently from tumour lesion analysis, with no previous knowledge on patient's pre-resection chemotherapy status or perioperative outcomes.

For identification of such histological entities as vascular lesions, fibrosis, surgical necrosis and macro-vacuolar steatosis, tumour-free liver tissues were analysed in line with a predetermined format.

Analysis of the histological entities lead to establishment of categories, as follows:

Categories of vascular lesions depended on the degree of severity, in ascending order, and therefore sinusoidal vasodilatation and congestion (Fig. 2), peliosis (Fig. 3), hemorrhagic centrilobular necrosis (Fig. 4) and regenerative nodular hyperplasia (Fig. 5) have been established.

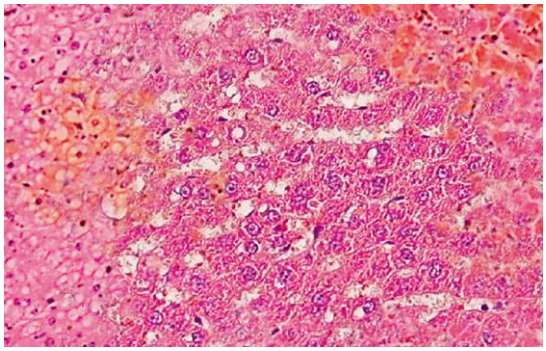

Figure 2. Vasodilatation and congestion in tumor-free liver, postchemotherapy

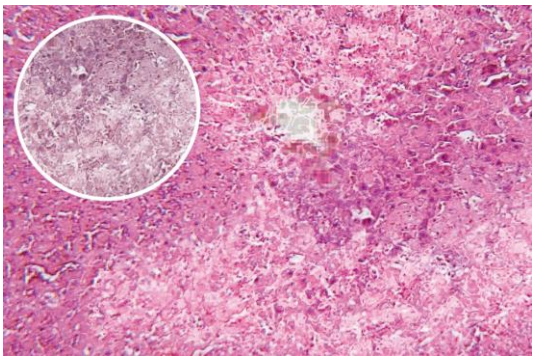

Figure 3. Peliosis in tum or-free liver, postchemotherapy

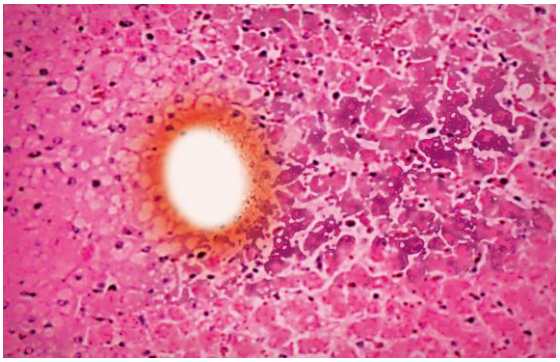

Figure 4. Hemorragic centrilobular necrosis in tumor-free liver, postchemotherapy

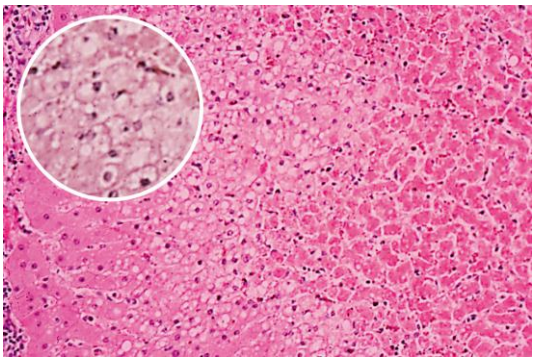

Figure 5. Nodular regenerative hyperplasia in tumor-free liver, postchemotherapy

In the same respect, presence of veno-occlusive lesions was also observed.

With regard to fibrosis, categories of portal fibrosis, porto-portal fibrosis, septal fibrosis, and cirrhosis have been established.

Finding of hepatocyte necrosis related to neutrophil pervasive dissemination within the centrilobular or periportal areas has suggested absence or presence of surgical handling-induced necrotic lesions of the liver, known as surgical hepatitis or surgical necrosis.

Categories of macro-vacuolar steatosis depended on their intensity and were accordingly classified as severe (over 60% hepatocytes), moderate (30% - 60% hepatocytes) or mild (less than 30% hepatocytes); these have been subjected to analysis when clinically significant involvement was assumed (moderate or severe steatosis).

Analysis of variance or Student's T tests were used to compare quantitative variables, whereas χ^2 tests were the analysis of choice for qualitative variables comparison. Significance of differences depended on p value (<0.05). Binomial logistic regression was applied to establish study factors related to unfavourable perioperative outcome (i.e., increased intra-surgery transfusion rates). SPSS software was used for all statistical calculations.

RESULTS

Demographic characteristics of study group participants included 58.7 years mean age (range, 40 to 85 years) and a 53:39 male to female ratio.

Further features were charted and similar in both goups, such as patient gender distributions, age, and maximum diameter of the largest metastasis Group A (45±32 mm) and Group B (41±14 mm). A difference was recorded however as regards the mean number of tumours resected in both groups (i.e. 3.2±2.9 tumours for Group A, vs. 1.9±1.3 tumours in Group B ($p<0.05$)).

The mean number of resected liver segments was similar in both groups (3.4±1.1 vs. 3.2±1 segments, respectively; $p=0.62$), as was use of hepatic pedicle clamping.

However, Group A patients showed four times higher mean packed red blood cell transfusion rate (2.1±2.4 units) in comparison with Group B patients (0.4±1.0 units; $p<0.05$).

Two additional features were also similar in groups A and B, i.e. mean length of stay and rates of fresh frozen plasma transfusion.

As shown in the study, Group A displayed more frequent liver vascular lesions than Group B (54% vs. 16%, respectively; $p<0.05$). At the same time, every type of vascular lesion was more common in Group A than in Group B, as well as higher incidence in Group A as compared to Group B of sinusoidal vaso-congestion and dilatation (24% vs. 11%, respectively), hemorrhagic centrilobular necrosis (23% vs 4%, respectively), regenerative nodular hyperplasia (6% vs. 1%, respectively) and peliosis (34% vs. 4%, respectively).

In addition, veno-occlusive disease has never been noted.

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On the other hand, the two study groups were characterised by similar levels of steatosis incidence. In that respect, 17.65% patients in Group A and 16.67% patients in Group B showed clinically significant levels (p=0.74) of steatosis. Thirty-two percent of Group A patients and 8% of Group B patients developed surgical necrosis (also known as surgical hepatitis) (p>0.05) (Table 1.).

	Group A		Group B	
	Mean±SD	%	Mean±SD	%
Size of largest metastases				
Mean	45		41	
SD	32		14	
Number of metastases				
Mean	3.2		1.9	
SD	2.9		1.3	
Number of resected segments				
Mean	3.4		3.2	
SD	1.1		1	
Packed red blood cells				
Mean	2.1		0.4	
SD	2.4		1	
Fresh frozen plasma				
Mean	0.3		0	
SD	1.5		0	
Steatosis		17.65		16.67
Surgical necrosis		32		8
Vascular lessions		54		16
Sinusoidal disorders		24		11
Peliosis		34		4
Hemorrhagic centrilobular necrosis		23		4
Regenerative nodular hyperplasia		6		1

Table 1. Distribution of some study factors in patients treated with chemotherapy and naïve patients

A comparison concerning study factors in both patients with enhanced transfusion requirements (1 unit red blood cell transfusion intraoperatively, 41.3%) and patients with diminished transfusion requirements (1 unit red blood cell transfusion intraoperatively, 58.7%) showed similar mean values of largest metastasis size, of number of metastases resected, of major resection rate as well as of number of segments resected.

It was further noted that the mean value of post-surgery length of stay for patients administered more than 1 unit of packed red blood cell transfusion was higher (14.8±4.8 days) in comparison with patients for whom 1 unit of packed red blood cell transfusion (10.8±2.8 days) was needed intra-operatively (p<0.05). Histopathologic analysis showed, similar distribution of steatosis and fibrosis between the two transfusion groups.

It was further noted that the low transfusion requirement group less commonly displayed vascular lesions (26%) than the enhanced transfusion requirement group (62%). Such differences became especially obvious on analysis of more serious vascular changes.

Rates of regenerative nodular hyperplasia and of hemorrhagic centrilobular necrosis were higher in the high transfusion requirement group (i. e. 4% vs. 1%, respectively, for regenerative nodular hyperplasia; p=0.07 and 41% vs. 12%, respectively; p=0.12, for hemorrhagic centrilobular necrosis).

On combining the incidence of the two serious vascular changes, the difference in serious vascular lesions incidence between low and high transfusion groups (i.e. 14% vs. 38%, respectively) reached statistical significance (p<0.05)

The various groups of patients received under 12 cycles and over 12 chemotherapy cycles and study variables were similarly distributed between them.

Pathologic analysis noted occurrence of hemorrhagic centrilobular necrosis more frequently in patients receiving over 12 chemotherapy sessions than patients

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receiving less than 12 sessions (52% vs. 38%, respectively; $p<0.05$).

DISCUSSION

Enhanced fragility of the liver parenchyma and heterogeneous aspect of the liver frequently observed during hepatic surgery in patients who have undergone pre-surgery chemotherapy have suggested the risk for the liver parenchyma to be adversely affected by systemic chemotherapy administered prior to hepatic resection.

All such observations however do not provide more knowledge concerning the relationship between action of systemic chemotherapy and resulting post-chemotherapy histologic changes in the tumour-free liver.

An additional element yet to be established is the congruence between administration of pre-surgery FOLFOX/FOLFIRI chemotherapy, liver toxicity as well as poor surgery outcomes.

Of all previous studies conducted in that respect, none reported specific post-surgery outcomes of FOLFOX/FOLFIRI chemotherapy-induced histologic changes, which is why our study has had a three-fold aim, seeking identification of specific liver lesions induced by chemotherapy, seen in relationship with chemotherapy duration and type as well as impact of such lesions on peri-surgery outcomes.

The method of choice has been thorough histo-pathologic analysis of the tumour-free liver and it mainly revealed a more frequent occurrence of vascular lesions of the liver in patients undergoing preoperative chemotherapy, which has been confirmed by results published recently by other groups (Vauthey et al., 2006; Rubbia-Brandt et al., 2004; Karoui et al., 2006).

Thus, a wider range of vascular changes have been examined, which traced the occurrence of the two most serious forms of vascular lesions back to intra-surgery erythrocyte transfusion requirements.

The finding indicating the tendency of overall morbidity rates in post-surgery progress to increase in Group A is consistent with initial results (Nordlinger et al., 2005) obtained by the European Organisation for Research and Treatment of Cancer.

This apparent increase in post-surgery chemotherapy-induced complication rates however has not resulted in detectable differences in post-surgery length-of-stay, which is consistent with results of previous studies, which also showed no such difference for patients both treated and non-treated with chemotherapy (Vauthey et al., 2006; Rubbia-Brandt et al., 2004; Karoui et al., 2006).

A further observation in the study has concerned the even distribution between the two groups of the number of segments subject to resection, metastases size and percentage of patients requiring major hepatectomy.

Last but not least, using multivariate analysis, we have established that administration of chemotherapy pre-operatively was the sole autonomous factor connected with intra-surgery red blood cells transfusions. This allows us to conclude that chemotherapy administered pre-operatively explained differences revealed by histo-pathologic analysis and noted in perioperative outcomes.

Findings related to the possibility of poorer short-term outcomes for patients with the most serious forms of vascular lesions are of practical importance however for patients considering to receive chemotherapy prior to hepatectomy. In patients whose disease was originally considered not suitable for resection, data found reveal that liver surgery should be performed as soon as chemotherapy has induced tumour decrease, allowing for margin-negative resection.

CONCLUSIONS

In light of the above data, in patients with liver metastases from colorectal cancer considered not fit for resection at the outset, administration of FOLFOX/FOLFIRI regimens preoperatively may give rise to the risk of histologic alterations induction in the tumour-free liver. However, this seems not reason enough for change of the decision concerning either combination of such regimens with liver resection or administration of chemotherapy.

On the other hand, before confirmation by the outcome from the European Organisation for Research and Treatment of Cancer, it may be appropriate for patients with similar conditions originally considered suitable to undergo resection to receive short-term chemotherapy sessions. It has become evident however that, because of possible development of serious vascular lesions induced by chemotherapy, longer-term sessions should be avoided in this specific indication.

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We attest to the fact that all Authors listed on the title

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page have the same contribution to the work.

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