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RESEARCH

# Bevacizumab Treatment Before Resection of Colorectal Liver Metastases: Safety, Recovery of Liver Function, Pathologic Assesment

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**Abstract** Patients with metastatic colorectal cancer receive chemotherapy prior liver resection more and more frequently. This preoperative treatment has many effects which have to be analysed, like the safety of liver resection, toxicity, tissue regeneration, radiological and pathological response and survival data. The aim of the study was to evaluate the safety of bevacizumab containing preoperative chemotherapy and functional recovery of the liver after resection for colorectal liver metastases (CLM) and to analyse radiological and pathological data. Data of three groups of 120 consecutive patients —(1) CTX+BV: cytotoxic chemotherapy + bevacizumab, (2) CTX: cytotoxic chemotherapy, (3) NC: no treatment before liver resection—were analysed. Postoperative liver function and complications were compared, clinical, radiological and pathological data were evaluated. Between 01.12.2006 and 31.12.2010 41 resections was performed after chemotherapy + bevacizumab (CTX+BV) and 27 resections was performed after preoperative chemotherapy without bevacizumab (CTX). There were 60 hepatic resections in this period without neoadjuvant treatment (NC). 8 patients had repeated resections. The postoperative complication rate was 40 % but there was no statistical difference between the groups ($P$=0.72). Only the type of resection was associated with a significantly higher complication rate ($p$=0.03). The subgroup of patients, who received irinotecan had a higher complication rate in the CTX group than in the BV+CTX group (55 % vs 41 %). Preoperative administration of bevacizumab was associated with higher peak postoperative AST, ALT levels but did not affect functional recovery of the liver. The RECIST system was not able to predict the outcome after chemotherapy in every patient and in many cases this system overestimated the effect of chemotherapy. On histopathological examination the presence of necrosis was not associated with chemotherapy or pathological response. Use of chemotherapy before hepatic resection of CLM was not associated with a significant increase in complication rates. The functional recovery of the liver was not affected by the preoperative administration of chemotherapy. The use of combined neoadjuvant chemotherapy is safe before hepatic resection.

**Keywords** Colorectal liver metastases · Preoperative chemotherapy · Bevacizumab · Complications · Functional liver recovery

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## Introduction

Liver resection is still the only potentially curative therapy for colorectal liver metastases (CLM) but only 25 % of patients are potentially suitable for operation due to the extent of the tumor. For patients, who are no candidate for

surgery, there are two preoperative treatment options to achieve resecability. Preoperative portal vein embolisation by increasing the volume of the remnant liver and/or neoadjuvant chemotherapy to decrease tumor volume, to asses tumor response to therapy and to potentially treat micrometastases [1, 2].

With preoperative chemotherapy there is the possibility of downsizing metastatic tumors, thus, rendering the disease resectable in another 10–22 % of patients. Following chemotherapy, hepatic resection may result in 5-year-survivalrate of up to 40 % or more compared with 2 % in patients without resection [3–6].

Bevacizumab (BV), a monoclonal antibody to vascular endothelial growth factor (VEGF), is commonly used in combination with other cytotoxic chemotherapies in patients with CLM even before surgical resection. However, all chemotherapeutic drugs are hepatotoxic what can impact patients' outcome and liver recovery after hepatectomy. Irinotecan can cause chemotherapy associated steatohepatitis (CASH), and oxaliplatin causes sinusoideal obstruction (SOS) with the risk of bleeding or the reduction of hepatic reserve [7]. It has been reported that bevacizumab may reduce the hepatotoxicity of irinotecan and oxaliplatin, but associated with an increased risk of thrombosis, bleeding and gastrointestinal perforation [3, 8, 9]. There are previous studies that confirmed that preoperative bevacizumab treatment did not significantly increase postoperative complications, others found more complications [2, 3, 10–13]. Most authors compare patients receiving bevacizumab with groups receiving other neoadjuvant chemotherapies.

This single institution study compares two groups of patients with preoperative administered combined chemotherapy and a group of patients receiving no chemotherapy prior liver resection. Safety, functional recovery of the liver and clinical response was analyzed.

## Patients and Methods

Patients undergoing liver resection with curative intent for colorectal liver metastases (CLM) between 1 December 2006 and 31 December 2010 were identified retrospectively from a prospectively collected database.

Three groups of patients were characterised. In the first group patients received preoperative chemotherapy with bevacizumab (CTX+BV). In the second group cytotoxic chemotherapy (FOLFIRI: folinic acid-fluorouracil-irinotecan or FOLFOX: folinic acid-fluorouracil-oxaliplatin) was administered without bevacizumab before hepatic resection (CTX) and in the third group patients received no preoperative chemotherapy (NC).

The administration of preoperative chemotherapy was decided mostly only by a medical oncologist. Our surgical department is a tercier centrum for hepatic surgery, operating patients from the whole country. Most of the patients received the preoperative chemotherapy before the first visit in our institution. In cases where liver surgeon was a member of the oncoteam as well, the indication for the preoperative chemotherapy were: (1) borderline cases where resecability was not evident, (2) synchronous resectable liver metastases were seen in young patiens, and in the waiting period before major hepatic surgery, the completion of chemotherapy administration was decided, (3) a higly positive effect of the preoperative chemotherapy (indicated only by a medical oncologist) was seen by the oncoteam and the continuitiy of the administration was decided till the resection (last dose before 6 weeks of surgery). If progression was observed during chemotherapy, and the metastasis/es were resectable, the resection was decided by the liver surgeon and performed in 6–8 weeks. Therefore there were patients who received chemotherapy as a neoadjuvant setting and there were much less patients who received preoperative chemotherapy to reach resecability. This study was a retrospective study, we used the collected data, and in most cases we couldn't influence the preoperative treatment.

The radiological response rate to chemotherapy was evaulated according to the RECIST (Response Evaluation Criteria in Solid Tumours) [14]. Patients in the bevacizumab group received bevacizumab by intravenous infusion at a dose of 5 mg/kg every 2 weeks. Chemotherapy was discontinued at least 5 weeks before surgery.

Hepatic resections were classified as anatomical or non-anatomical resections according to the segmental anatomy of the liver. Major hepatic resections were defined as removal of three or more liver segments. Preoperative chest, abdomen and pelvis CT were obtained to determine the size and number of liver metastases and to identify extrahepatic disease. Hepatoduodenal lymph node involvement was not a contraindication for curative resection but there was no patient with other extrahepatic disease known at the time of surgery. We performed hepatoduodenal lymph node dissection if the preoperative examinations showed the involvment of the nodes or if intraoperatively the involvement of the nodes was suspected. The number of lesions was not determinant for resecability. The Pringle maneuver was used mainly for all procedures, parenchymal division was performed with clamp-crushing technique. Intraoperative ultrasound was used to control hepatic lesions and patients received standard prophylactic abdominal drain following resection.

Surgical complications and mortality rates were stratified according to the Clavien classification [15]. All surgical specimens were reviewed by a surgical pathologist and tumor number, maximum size and margin status, degree of necrosis were determined. When multiple metastases were detected, all foci were examined and the degree of necrosis

was calculated [16]. In the CTX+BV group the degree of fibrosis, necrosis, the ratio of residual tumor cells and tumor regression grade (TRG) were also calculated. Recorded functional parameters included serum total bilirubin level, International Normalized Ratio values (INR), serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alcalic phosphatase.

The *t*-test and ANOVA were performed to assess differences between continuous variables and the Chi-square- and the Spearman-test was applied to assess the association between categoric variables. ANOVA was used to compare recovery of liver function over time between the groups. Logistic regression analysis was used to compare complication rates. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 17 software (SPSS, Chicago, IL, USA).

## Results

There were 120 consecutive patients treated for CLM between 1 December 2006 and 31 December 2010, a total of 128 curative resections were performed. 41 resections were performed after bevacizumab + cytotoxic chemotherapy (CTX+BV) and 27 resections after cytotoxic chemotherapy (CTX). There were 60 hepatic resections in this period without neoadjuvant treatment (NC). There were eight patients with repeated resections, and only one of these eight patients received cytotoxic chemotherapy before the second resection, the other seven patients had repeated resection without neoadjuvant treatment. The median age was 61 years (range 32–83), 68 % of patients were male (Table 1). There was no difference in the type of resection (major or minor) between the groups ($P$=0.44).

In patients who received bevacizumab the median duration of treatment was 8 cycles (3–12), in the CTX group it was 9 cycles (6–12). Bevacizumab administration was stopped at a median of 8 weeks before surgery. In the CTX+BV group 96 % of patients received irinotecan, in the CTX group 41 % of patients received irinotecan and 44 % received oxaliplatin based regiments (Table 1).

In the NC group 67 % of patients had solitary metastatic lesion, in the BV+CTX and CTX group it was 49 % and 41 %. Patients with multiple metastatic lesions received chemotherapy more often before liver surgery but there were patients with multifocal metastatic lesions in the NC group as well.

With statistical analysis there was no significant difference in the operative time, ischemic period, hospital stay or perioperative blood transfusion between the groups (Table 1). Overall, there were 51 (40 %) cases who developed postoperative complication. With uni- and multivariate analysis (variables including age, type of chemotherapy, type of resection, transfusion) only the type of resection was associated with significantly higher complication rate ($p$=0.03, OR 2,371; 95 % CI 1.105 to 5.086). There was no statistical difference in the complication rates between the three groups. ($P$=0.72) Altough the Clavien 2 or 3 complications were more common in the CTX+BV and in the CTX group compared to the NC group but it was not significant ($P$=0.44) (Table 2).

The subgroup of patients, who received irinotecan had a higher complication rate in the CTX group than in the BV+CTX group, but it was not significant (55 % vs 41 %, $P$=0.64) (Table 3). The complication rate was neither different between the FOLFIRI and FOLFOX subgroups in the CTX group ($P$=0.38). In the CTX+BV group, only one patient received FOLFOX regimen.

Mortality was 2 % in the CTX+BV group and in the NC group. One patient in the bevacizumab group died from mesenteric ischemia and one patient in the NC group from multisystem-organ failure after repeated hepatic resections. 5 patients developed wound infection but there was no correlation with preoperative chemotherapy.

The number and maximum size of the resected metastases were comparable in the groups. The type or the presence of pre-hepatectomy chemotherapy did not impact operative margin status. The majority of patients (91 %) had R0 resection (microscopically negative margins). The R1 or R2 (microscopically or macroscopically positive margin) resection was 9 % in the CTX+BV group, 7 % in the CTX group and 7 % in the NC group.

On histopathological examination, the presence and degree of necrosis in the tumor was higher in the bevacizumab group but 33 % of patients in the NC group had major necrosis as well ($p$=0.26) (Table 1.) Three different methods of calculating pathological response comared in the CTX+BV group. The incidence of major pathologic response, according to the degree of necrosis, residual tumor cell ratio and TRG scoring system showed different results using the three methods, which needs further analysis (data not shown). Less necrosis, but more fibosis with few residual tumor cells predicts better patologic response (Fig. 1).

Comparing clinical response based on the RECIST guidelines and on macroscopic pathological data, including tumor size and number of lesions, there was mild correlation between the two examinations. There was no difference between the patients with progressive disease, altough in patients with stable disease or partial response there was a difference when the clinical and pathological data were compared (Table 4). RECIST predicted quite accurately the progressive disease but overestimated the response.

No difference in serum liver function parameters was observed between the groups directly before surgery. There was no statistical difference in the peak postoperative serum bilirubin and INR levels between the groups. Peak

**Table 1** Baseline characteristics

| | | CTX+BV ($n$=41) | CTX ($n$=27) | NC ($n$=60) | $P$ |
|---|---|---|---|---|---|
| Age[a] | | 60 (32–75) | 61 (40–77) | 62 (44–83) | 0.41 |
| Sex | Male | 32 (78) | 19 (70) | 36 (60) | 0.16 |
| | Female | 9 (22) | 8 (30) | 24 (40) | |
| Ischaemia time (mins)[a] | | 20 (0–32) | 17 (0–30) | 17 (0–29) | 0.23 |
| Duration of surgery (mins)[a] | | 100 (60–200) | 100 (50–180) | 105 (60–180) | 0.73 |
| Hospital stay (days)[a] | | 10 (7–30) | 10 (7–28) | 10 (5–28) | 0.25 |
| Transfusion | | 7(17) | 1(4) | 8(13) | 0.26 |
| CRC stage | I. | – | – | 3 | 0.52 |
| | II. | 8(20) | 6(22) | 14(23) | |
| | III. | 12(29) | 10(37) | 14(23) | |
| | IV. | 21(51) | 11(41) | 29(49) | |
| Liver metastases | Metachronous | 20(49) | 16(59) | 31(51) | |
| | Synchronous | 21(51) | 11(41) | 29(49) | |
| Type of chemotherapy | FOLFIRI | 39(96) | 11(41) | | <0.01 |
| | FOLFOX | 1(2) | 12(44) | | |
| | Both | 1(2) | 3(11) | | |
| | Other | | 1(4) | | |
| Time from last BV dose to surgery (weeks)[a] | | 8 (5–15) | | | |
| Duration of chemotherapy (cycles)[a] | | 8 (3–12) | 9 (6–12) | | |
| Metastatic liver lesions | 1 | 20(49) | 11(41) | 40(67) | 0.21 |
| | 2 | 10(24) | 10(37) | 9(15) | |
| | 3 | 5(12) | 3(11) | 3(5) | |
| | ≥4 | 6(15) | 3(11) | 8(13) | |
| Max size of metastatic lesions (mm) | | 110 | 100 | 135 | 0.51 |
| Microscopically positive margin (R1) | | 3(7) | 2(7) | 4(7) | 0.71 |
| Macroscopically positive margin (R2) | | 1(2) | – | – | |
| Tumor necrosis | Major (>50 %) | 17(41) | 6(22) | 20(33) | 0.26 |
| | Minor (<50 %) | 24(59) | 21(78) | 40(67) | |

Values in parenthese are percentages

*CTX+BV* preoperative chemotherapy with bevacizumab, *CTX* preoperative chemotherapy without bevacizumab, *NC* no preoperative chemotherapy, *CRC* colorectal carcinoma, *BV* bevacizumab, *FOLFIRI* folinic acid-fluorouracil-irinotecan, *FOLFOX* folinic acid-fluorouracil-oxaliplatin

[a] Values are median (range)

postoperative AST, ALT and AP levels were higher in the CTX+BV and CTX group compared with the NC group but it was not significant. There was no difference in functional

**Table 2** Association between clinical variables and postoperative complications on univariate and multivariate logistic regression analyses

| Clinical variable | Univariate P | Multivariate P | Odds ratio | 95 % CI |
|---|---|---|---|---|
| Age | 0.12 | 0.14 | 1.03 | 0.99 to 1.08 |
| Preoperative chemotherapy | 0.46 | 0.72 | 1.08 | 0.71 to 1.64 |
| Type of resection | 0.02 | 0.03 | 2.37 | 1.11 to 5.09 |
| Transfusion | 0.73 | 0.65 | 0.77 | 0.25 to 2.37 |

**Table 3** Complications according to the type of the preoperative chemotherapy regiments

| | CTX+BV | | CTX | | P |
|---|---|---|---|---|---|
| | N | Complications | N | Complications | |
| FOLFIRI | 39 (96) | 16 (41) | 11 (41) | 6 (55) | 0.64 |
| FOLFOX | 1 | 0 | 12 (44) | 5 (42) | |
| Both | 1 | 1 | 3 (11) | 1 | |
| Other | | | 1 (4) | 1 | |
| All | 41 | 17 | 27 | 13 | |

Results are the number of resections

Values in parenthese are percentages

*CTX+BV* preoperative chemotherapy with bevacizumab, *CTX* preoperative chemotherapy without bevacizumab, *FOLFIRI* folinic acid-fluorouracil-irinotecan, *FOLFOX* folinic acid-fluorouracil-oxaliplatin

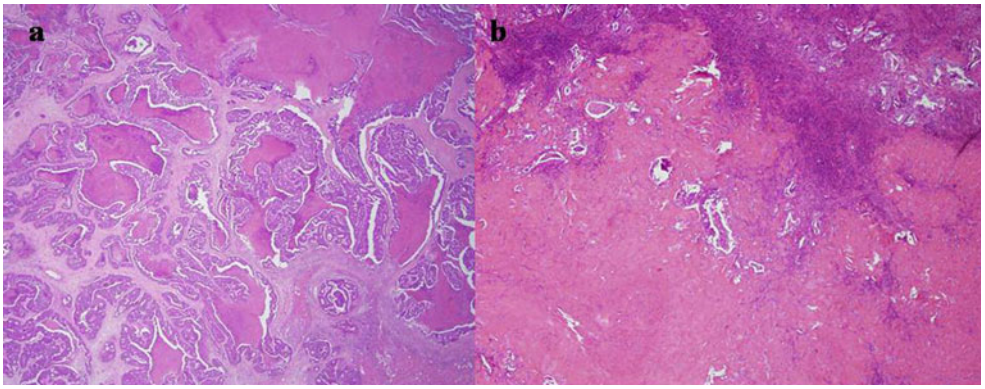


**Fig. 1** Histopathological examination (HE) a: tumor with more necrosis but more residual tumor cells b: tumor with more fibrosis, less necrosis but few residual tumor cells

recovery of liver parameters between the groups. Bevacizumab administration was associated with lower serum bilirubin levels and higher INR values (Fig. 2).

## Discussion

Hepatic resection is the standard of care for patients with hepatic metastases from colorectal cancer and there are a number of patients with primary irresectable metastases who are potential candidates for hepatic resection after preoperative treatment. Neoadjuvant bevacizumab treatment is being used even more frequently to increase the rate of patients with resectable metastatic colorectal disease.

**Table 4** Clinical response according to the RECIST and to the macroscopical pathologic data in patients with different preoperative chemotherapy

| | | Clinical response acording to RECIST | Clinical response according to the macroscopical pathologic data |
|---|---|---|---|
| BV+CTX | PR | 26 (63) | 14 (34) |
| | SD | 9 (22) | 19 (46) |
| | PD | 6 (15) | 8 (20) |
| CTX | PR | 6 (22) | 3 (10) |
| | SD | 9 (33) | 12 (45) |
| | PD | 12 (45) | 12 (45) |
| (BV+CTX)+CTX | PR | 32 (48) | 17 (25) |
| | SD | 18 (26) | 31 (46) |
| | PD | 18 (26) | 20 (29) |

Results are the number of cases

Values in parenthese are percentages

Sperman-test: value: 0.347, $p=0.005$

*RECIST* Response Evaluation Criteria in Solid Tumours, *CTX+BV* preoperative chemotherapy with bevacizumab, *CTX* preoperative chemotherapy without bevacizumab, *NC* no preoperative chemotherapy, *PR* partial response, *SD* stable disease, *PD* progressive disease

Preoperative/neoadjuvant chemotherapy potentially downsizes tumours and it also gives the opportunity to rule out the non-responders who are unlikely to benefit from extended surgical resection [17]. The response to chemotherapy is a part of the prognostic models for outcome following liver resection for colorectal cancer metastases [18].

In addition, there are reports about patients with initially resectable hepatic metastases from CRC origin who received preoperative chemotherapy. Altough some data in literature suggest that patients with potentially resectable CLM may be candidates for preoperative chemotherapy as well, for the majority of liver surgeons, the accepted treatment for a resectable hepatic metastases from CRC origin is firstly resection [19–23]. Obviously, the higher proportion of patients undergo hepatic resection after chemotherapy, the more important it is to find prognostic factors and to collect data about the safety of hepatic resection in these cases.

Scapaticci et al. reported increased wound healing complications [24]. D'Angelica et al. and Reddy et al. found no significant difference in postoperative complications between patients receiving preoperative chemotherapy with or without bevacizumab [10, 12]. Likewise, Kesmodel et al., Tamandl et al. and Mahfud et al. reported no difference in morbidity, mortality, wound healing or specific hepatic complications between patients receiving preoperative chemotherapy with or without BV [2, 13, 25].

In the present study there were no significant differences in the operative time, ischaemic period, hospital stay or perioperative blood transfusion between patients who have or have not received preoperative chemotherapy (with or without bevacizumab). The type of resection affected the blood transfusion rate, as expected, major resection increased blood loss.

In our series the postoperative morbidity was 40 % in accordance with other reports. There was no statistical difference in the overall complications rate between the three groups, although, especially the Clavien 2 or 3 complications were more common in the CTX+BV and the CTX group than in the NC group (39 % vs 34 % vs 26 %). One

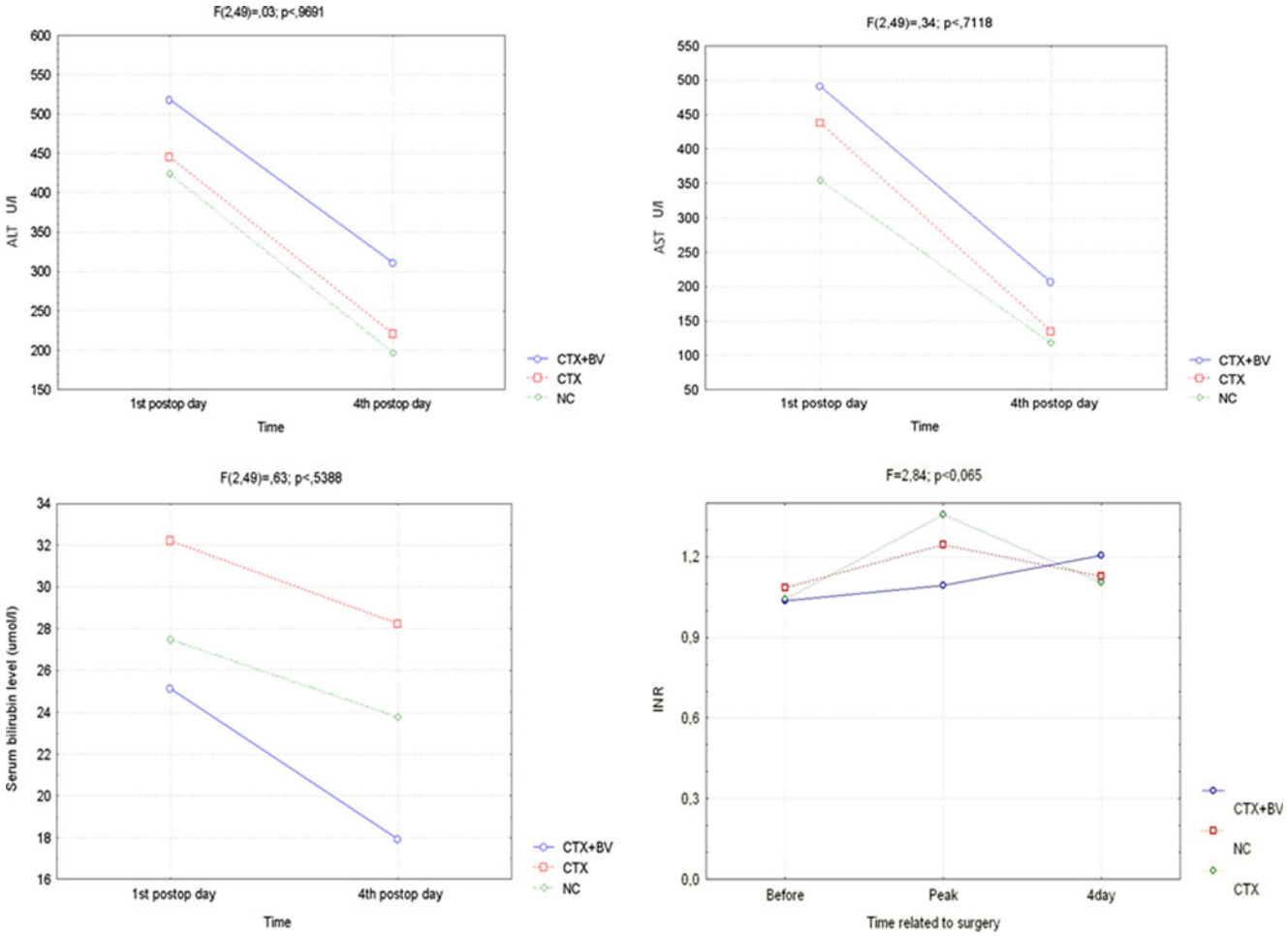


**Fig. 2** Postoperative changes in serum ALT, AST, bilirubin and INR levels in patients treated with or without preoperative chemotherapy (ANOVA)

reason for this increase in the BV+CTX group could be a slightly higher rate of major resections (49 % vs 37 %).

There are reports about increased and also about no difference in wound healing complications after bevacizumab treatment [10, 12, 24]. Likewise, we found no difference in wound healing complications between the groups.

There is likely a correlation between preoperative chemotherapy, liver recovery, liver histology, complications and patients' outcome. Specific chemotherapy can cause steatohepatitis, irinotecan can cause periportal inflammation while oxaliplatin is associated with sinusoidal obstruction. It is also reported, that preoperative chemotherapy diminishes the recovery and hypertrophy of the remnant liver. Vauthey et al. reported that the presence of steatohepatitis increases the complication rate and the duration of preoperative chemotherapy affects hepatotoxicity [7]. Kishi et al. found a significant increase in hepatotoxicity and hepatic insufficienty after 9 cycles of chemotherapy [26]. Mahfud et al. observed a significantly lower incidence of postoperative hepatic failure in patients receiving bevacizumab, and it is also reported that bevacizumab may reduce the hepatotoxicity of oxaliplatin [3, 8, 13].

On histopathologic analysis hepatotoxicity was more common in the CTX group than in the BV+CTX and in the NC group (89 % vs 61 % vs 68 %). Patients in the BV+CTX group received irinotecan-based chemotherapy, and hepatotoxicity rate in the BV+CTX group was less than in the subgroup of patients in the CTX group who received irinotecan and similar to the NC group. The number of patients in this subgroup was few for a correct statistical analysis, but this implies a potential protective effect of bevacizumab against irinotecan-associated hepatotoxicity. Although we found no correlation between hepatotoxicity and complication rate in the subgroup of patients, who received irinotecan as cytotoxic chemotherapy, the complication rate was less in the BV+CTX group than in the CTX group (41 % vs 55 %).

Higher peak postoperative AST and ALT levels were found in the CTX+BV group compared with the CTX and NC group. These data confirm the findigs of Wicherts et al.

who found that peak postoperative AST and ALT levels were higher in patients treated with bevacizumab. It is also confirmed that bevacizumab administration or the type of cytotoxic chemotherapy did not affect the postoperative changes in total bilirubin and INR values. Our data also confirmed that preoperative administration of bevacizumab did not affect the functional recovery of the liver, moreover, bevacizumab administration was associated with lower serum bilirubin levels compared with the observations in the non-treated population [3].

Bevacizumab has a relatively long half-life (~20 days) compared to other chemotherapeutic drugs, thus, it is recommended to wait at least 5 weeks after the last dose of bevacizumab before hepatic surgery. Kesmodel et al. reported a higher complication rate (55 % vs. 44 %) in patients receiving bevacizumab within 8 weeks of surgery but it did not reach statistical significance [2]. Mahfud et al. found no difference in the occurence of complications in patients who had received bevacizumab ≤6 weeks or in those who had taken bevacizumab ≥6 weeks before resection [13]. In our series bevacizumab treatment was discontinued at least 5 weeks prior surgery. In this period there are authors who administer chemotherapy without bevacizumab but mostly it is recommended to have a "drug holiday" to minimize the chemotherapy-associated side effects [3, 6, 10, 12, 13, 19, 27].

To predict the benefit of a chemotherapy RECIST system is used worldwide [14]. RECIST based on the diameter and on the number of lesions according to the CT or MRI scans which should be the same as the data of the final pathologic examination. Altough pathologic data are available only after a resection. In our series there was a difference in patients with partial response to chemotherapy or stable disease when clinical and pathologic data were compared concerning number and size of hepatic metastases. It suggests that RECIST system is not able to predict the outcome after chemotherapy in every patient and in many cases this system overestimates the effect of chemotherapy. For this reason, Chun et al. recommend to analise the morpholgic apperance of the tumor as well, when controlling the effect of chemotherapy [28].

Pathological response is a microscopically detectable effect on the tumor bearing tissue after chemotherapy, including several, not yet exactly defined factors. Several authors have reported an improved pathological response when bevacizumab was administered. Complete pathological response rate was observed in up to 9 % of patients treated with bevacizumab [12, 16]. Bevacizumab is an angiogenetic inhibitor, thus it is obvious to analyse the necrosis. In our series presence and degree of necrosis was higher in patients treated with bevacizumab similarly to other authors' reports but there was no complete pathologic response [3]. In the CTX+BV group the presence and grade of necrosis was much higher than in the CTX group, but 33 % of patients in the NC group had major necrosis at the pathological examination, which demonstrates that the presence of necrosis is not enough to predict pathological response. It supports the findings of Rubbia-Brandt et al. that it is more likely that necrosis is related to spontaneous phenomena [29]. The use of a more accurate pathologic staging system after preoperative chemotherapy is required. If "tumor regression grade (TRG) scoring system", "the ratio of residual tumor cells" or "tumor thickness at the tumor-normal interface (TNI)" can evaluate more accurately the response to chemotherapy is still a question [16, 29–31].

There were two limitations of our study. The first limitation is that this is a retrospective analysis. The second limitation is that in the first period of the analysed interval the administration of preoperative chemotherapy was decided only by the medical oncologist and not by an onco-team. Therefore there are patients who received chemotherapy as a neoadjuvant setting and there are patients who received preoperative chemotherapy to reach resecability. Consequently, it is not possible to calculate the effect of the preoperative chemotherapy on the resecability rate.

In conclusion, this study confirms that preoperative treatment and bevacizumab in combination with other preoperative chemotherapies does not increase significantly the complication rate of liver resections, and does not affect functional recovery of the liver. Moreover, bevacizumab may have a potential protective effect against irinotecan caused hepatotoxicity. There is a tendency that more and more patient with liver metastases irrespectively of primary resecability will receive combined preoperative treatment in the future and it is safe to perform a hepatic resection after neoadjuvant chemotherapy with bevacizumab. The adaptation of a more detailed pathologic staging system of the pretreated colorectal liver metastases is required.

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