# Molecular mechanisms of liver damage during neoadjuvant treatment for hepatic metastases of colorectal cancer

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BACKGROUND: *The main drawbacks of neoadjuvant chemotherapy of colorectal liver cancer metastases are related to the toxic liver damage. To determine the degree of biochemical and morphologic liver damage after therapeutic protocol treatment with "bevacizumab plus FOLFOX IV", as well as the correlation between the sex, age, the existence of metabolic syndrome, the length of neoadjuvant therapy treatment and the degree of liver damage.*
METHODS: *The study includes the total of 60 colorectal cancer metastases operated patients, divided into two groups of 30 patients: the group of patients who were treated with "bevacizumab plus FOLFOX IV" protocol as a neoadjuvant therapy - prior to liver metastases surgery and the control group, patients with the liver resection done without previous neoadjuvant chemotherapy. The following parameters were examined: biochemical liver function parameters, the presence of metabolic syndrome, pathohistological assessment of the degree of steatosis and SOS syndrome.*
RESULTS: *The increase in AF was observed in the experimental group (Z = 2.566, p = 0.010), Dbilirubin (Z = 1.970, p = 0.037), LDH (Z = 2.951, p = 0.003) and decrease in albumin values (t = 5.100, p <0.001). The pathohistological examination in only 3.3% showed moderate liver steatosis, while SOS syndrome was recorded in as many as two-thirds (66.66%) of patients in the study group. In 14 patients (46.7%) a mild degree was registered, and in 6 (20.0%) moderate levels of this type of liver damage. Pole (p = 0.13), age (p = 0.09) and length of administration of chemotherapy (p = 0.35), as well as the presence of metabolic syndrome ($\chi^2$ = 0.390, p = 0.830), did not have any statistically significant effect on the liver damage degree.*
CONCLUSION: *In our study, after the administration of the "bevacizumab plus FOLFOX IV" protocol, a statistically significant increase in AF, Dbilirubin and LDH, as well as a decrease in albumin values, were found. Dominant liver damage was by type of SOS syndrome (66.7%), while steatosis of the liver was recorded in only 3.3% of patients. Gender, age, the presence of metabolic syndrome and the number of chemotherapy cycles did not have any statistic significance on the biochemical parameters and morphological degree of liver damage.*

KEY WORDS: Colorectal cancer metastases, Liver surgery, Oncology, Neoadjuvant chemotherapy, Liver damage

## Background

The treatment of metastatic colorectal cancer nowadays is based on the multidisciplinary approach, which applies achievements of the modern liver surgery, interventional radiology and oncology, which enable creation of the individual treatment plan for each patient, taking into account numerous factors that influence the choice of the therapy modality.

Resection (surgical) therapy shows the best results (five-year-survival from 21-58% with the average life span from 40 months and the period of 30 months without recidive) but it is possible only in 20-25% patients [1-3]. The patients treated only with chemotherapy, beside the application of the newest anticancer medications

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(FOLFOX, FOLFIRI protocols) have the average survival span of maximum 20 months, with the five-year-survival rate of 10-15% [4] Biologic monoclonal antibody therapy against the growth factor /anti-EGF/-Cetuximab and anti–vascular endothelial growth factor antibody /anti-vEGF/-Bevacizumab, added to the already existing chemotherapeutic protocols at the beginning of XXI century, proonged the overal survival span to 25 months [5,6].

The combined therapy, which involves the application of neoadjuvent chemotherapy with the biologic agents prior to the liver surgery, has changed the views on the location, time and the scope of liver resection during the liver metastases treatment KRK [7-9].

Although the neoadjuvant treatment has a lot of advantages (the increase of the resectability rate, the chemosensitivity test, the elimination of micto-metastases, the prolonged recurrence period, the decrease of the exploratory laparotomy rate, making more conservative liver surgery possible and the decrease of operative mortality), the neoadjuvant therapy has some drawbacks, the most important being: the postponement of the operation, toxic liver damage, the increase of the surgical complications rate and the increase of the treatment costs [9,10].

Since the very beginning of cytostatics application in medicine (1940), many drugs have shown a hepato-toxic effect. Toxic liver damage with chemotherapy agents (citotoxic associated liver injury -CALI) is most commonly associated with two categories of pathological changes in the liver: non-alcocholic fatty liver disease (NAFLD), which leads to so-called "yellow liver" and occurs in 43% to 65% of patients [11], and the sinusoidal obstruction syndrome -SOS, so-called"Blue liver", which has been recorded in up to 51% of patients [12]. These negative effects are of particular significance in patients who shortly after chemotherapy undergo extensive liver resection, which increases the percentage of postoperative complications up to 54% 13 and mortality rates up to 14.7% [14].

The objectives of the study are set, based on the significance and existing dilemmas about the degree of the liver damage after neoadjuvant chemotherapy of the liver metastases KRK:

– To determine the degree of biochemical liver damage after the administration of therapeutic protocol "bevacizumab plus FOLFOX IV";
– To determine the morphological type of liver damage;
– To determine how the liver damage relates to the existence of metabolic syndrome;
– To determine the correlation between the length of neoadjuvant therapy administration (number of cycles) and the degree of the liver damage.

## Methods

The study includes a total of 60 colorectal carcinoma liver metastases patients, divided into two groups: in the examined group there are 30 patients who received "bevacizumab plus" FOLFOX IV" protokol / Oxaliplatin 85 mg/m², Leucovorin 200 mg/m² and 5-FU 400 mg/m² every 2 weeks one cycle/as a neoadjuvant therapy - before the liver metastases surgery and after the primary colorectal cancer surgery and after the liver metastases has been diagnosed.

In the control group, there are 30 patients who have undergone the liver resection due to the colorectal carcinoma metastases (synchronous or metachronic) without previous neoadjuvant chemotherapy administration.

All patients underwent the following preoperative and postoperative assessments:

– Liver function, (alkaline phosphatase, AST, ALT, γGT, bilirubin, LDH, 5-nucleotidase, albumin, alpha-oprotein, PT (PV));
– Presence of metabolic syndrome (defined if: glucose> / = 6.1 mmol / L; serum triglycerides> / = 1.7 mmol / L; serum HDL cholesterol <1.04 mmol / L; blood pressure> / = 130/85 mm Hg); BMI = kg / m² (20-25 ideal weight);
– Pathohistological assessment of steatosis degree (0-none; 1-mild steatosis (<30% of hepatocyte); 2-moderate steatosis (30-60% steatotic hepatocytes), 3-severe (steatosis in> 60% of hepatocyte);
– Pathohistological assessment of SOS syndrome (according to Deleeve, the following three parameters are considered): central vein endothelial damage, coagulation necrosis of hepatocyte and sinusoidal bleeding. Each parameter is estimated on a scale up to 4: 0 = absent, 1 = mild, 2 = moderate, 3 = serious. To classify SOS, the overall score is determined by adding points from <2 (none), 2 and 3 (mild), 4-6 (moderate) and 7-9 points (severe pathohistological change).

From the basic descriptive statistical parameters, standard statistical methods for qualitative and quantitative evaluation of the obtained results were used: absolute numbers, relative numbers (%), arithmetic mean, standard deviation (SD), minimum and maximum values. The regularity of the distribution of individual values was examined by Kolomogorov Smirnov's test. The comparison of the arithmetic means of two samples was done with a t-test, while nonparametric Mann-Whitney U test was used in cases of non-normal data distribution. The $\chi^2$ test was used to test the statistical significance of the absolute frequency differences among the samples. The interdependence between continuous variables is shown by Pirson's linear correlation coefficient, and in the case of categorical variables by the Spirman rank correlation coefficient.

To determine the predictor of liver damage, a univariate regression analysis and subsequent multivariate multiple regression were used for parameters that indicated statistical significance. The statistical hypothesis was tested at the level of risk significance from $\alpha = 0.05$, i.e. the difference between the samples is considered significant if $p < 0.05$.

## Results

The biochemical parameters of liver damage in the group of patients who received the "bevacizumab plus FOLFOX IV" protocol, showed a statistically significant difference in the following parameters compared to the control group: an increase in AF (Z = 2.566, p = 0.010), Dbilirubin = 1.970, p = 0.037), LDH (Z = 2.951, p = 0.003) and decrease in albumin values (t = 5.100, p <0.001).
None of the liver damage parameters (AF, AST, ALT, GGT, Dbilirubin, Tbilirubin, LDH, CK, albumin, and PT) showed statistically significant correlation with the administration length, or the number of neoadjuvant treatment "bevacizumab plus FOLFOX IV" cycles.
The pathohistological examination of the samples showed that steatosis was the only type of liver damage in the control group. It was registered in a total percentage of 30%, of which 7 (23.3%) patients were in mild form, and 2 (6.7%) patients were in the moderate one. In only one patient in the examined group (3.3%), the moderate hepatic steatosis was observed.
Patients who received the "bevacizumab plus FOLFOX IV" protocol had liver damage SOS syndrome type in as much as two-thirds (66.66%). In 14 patients (46.7%) there was a mild degree, and in 6 (20.0%) moderate levels of this type of liver damage was registred.
The demographic characteristics (sex and age) and the number of the "bevacizumab plus FOLFOX IV" protocol cycles by univariate multiple regression on the degree of SOS syndrome damage, showed no statistically significant predictive value among the tested variables.

TABLE I - *The incidence of metabolic syndrome in the examined and the control group.*

| | | Bevacizumab plus FOLFOX IV group n(%) | Control group n(%) | $\chi^2$ | P |
|---|---|---|---|---|---|
| Metabolic Syndrome | No | 22(73,3) | 21(70,0) | | |
| | Yes | 8(26,7) | 9(30,0) | 0,082 | 0,774 |

TABLE II - *Biochemical parameters of liver damage.*

| | Bevacizumab plus FOLFOX IV group $\bar{x}$ ± SD | Control Group $\bar{x}$ ± SD | Z/t* | P |
|---|---|---|---|---|
| AF | 133,90±47,03 | 133,40±144,77 | 2,566 | 0,010 |
| AST | 81,50±120,74 | 43,73±45,06 | 1,346 | 0,178 |
| ALT | 75,35±93,38 | 35,53±330,69 | 1,546 | 0,122 |
| GGT | 85,54±100,24 | 118,67±25,91 | 1,235 | 0,217 |
| Dbilirubin | 15,10±25,24 | 16,74±50,51 | 2,072 | 0,038 |
| Tbilirubin | 33,59±45,33 | 37,13±81,15 | 0,976 | 0,329 |
| LDH | 622,73±590,33 | 432,67±393,08 | 2,951 | 0,003 |
| CK | 141,74±102,99 | 197,17±280,03 | 0,703 | 0,482 |
| Albumini | 32,97±5,50 | 40,96±6,59 | 5,100 | <0,001 |
| PT (%) | 74,46±10,24 | 78,03±17,47 | 0,963 | 0,340 |

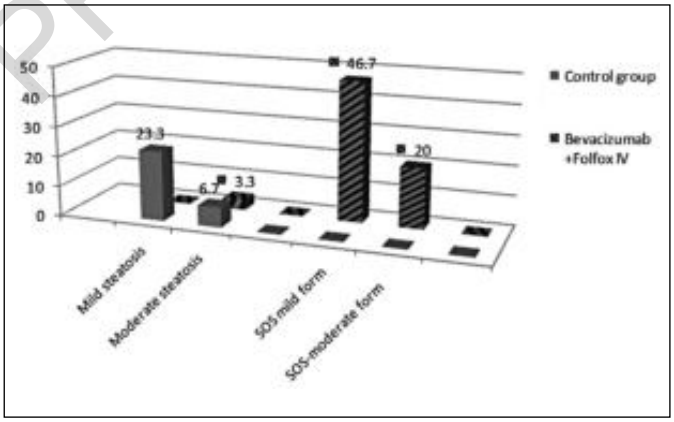
TABLE III - *The effect of the administration length of chemotherapy on the degree of the liver damage*

| | r | p |
|---|---|---|
| AF | 0,022 | 0,908 |
| AST | -0,178 | 0,347 |
| ALT | 0,134 | 0,479 |
| GGT | 0,110 | 0,563 |
| Dbilirubin | 0,174 | 0,359 |
| Tbilirubin | 0,130 | 0,495 |
| LDH | 0,005 | 0,980 |
| CK | 0,243 | 0,195 |
| Albumins | 0,161 | 0,395 |
| PT (%) | -0,238 | 0,205 |

r: Pirsons coefficient

TABLE IV - *Univariant multiple regression analysis of demographic characteristics and number of cycles in relation to the SOS syndrome developement in the examined group.*

| | Unstandardised coefficient | Standardised coefficient | Confidence 95% interval limits | | |
|---|---|---|---|---|---|
| | B | SG | Beta | Lower | Upper | p |
| Sex | 0,167 | 0,338 | 0,093 | -0,209 | 1,542 | 0,130 |
| Age | -0,026 | 0,015 | -0,315 | -0,057 | 0,004 | 0,090 |
| Cycles No | 0,060 | 0,064 | 0,176 | -0,070 | 0,191 | 0,353 |




Graphic 1. Morphological types of liver damage in the examined and control group.

Univariate multiple regression showed that the increase in D bilirubin is a risk factor for liver damage in the form of SOS syndrome (Beta = 0.499, p = 0.005),the same as the increase in T bilirubin (Beta = 0.548, p = 0.002) -0.516, p = 0.004), the decrease in albumine values, as well as the decrease in PT (Beta = -0.456, p = 0.011), which was confirmed by the multivariate multiple regression. The entire model, with all predictors, was statistically significant $\chi^2$ (df = 4, N = 30) = 5,431, p = 0.003, indicating that the model distinguishes

TABLE V - *Multivariate multiple regression analysis of biochemical parameters of liver damage in relation to the degree of SOS syndrome in the examined group.*

| | Unstandardised coefficient | | Standardised coefficient | Confidence 95% interval limits | | |
|---|---|---|---|---|---|---|
| | B | SG | Beta | Lower | Upper | p |
| Dbilirubin | -0,006 | 0,011 | -0,086 | -0,026 | 0,021 | 0,621 |
| Tbilirubin | 0,008 | 0,006 | 0,465 | -0,006 | 0,032 | 0,206 |
| Albumins | -0,038 | 0,023 | -0,324 | -0,092 | 0,006 | 0,109 |
| PT | -0,022 | 0,011 | -0,310 | -0,045 | 0,001 | 0,057 |

TABLE VI - *Distribution of SOS syndrome patients in relation to the metabolic syndrome presence.*

| | | Metabolic syndrome | | | |
|---|---|---|---|---|---|
| | | NO | YES | $\chi^2$ | p |
| SOS Syndrome | Absent | 8(36,4) | 2(25,0) | | |
| | Mild | 10(45,5) | 4(50,0) | | |
| | Moderate | 4(18,2) | 2(25,0) | 0,390 | 0,830 |

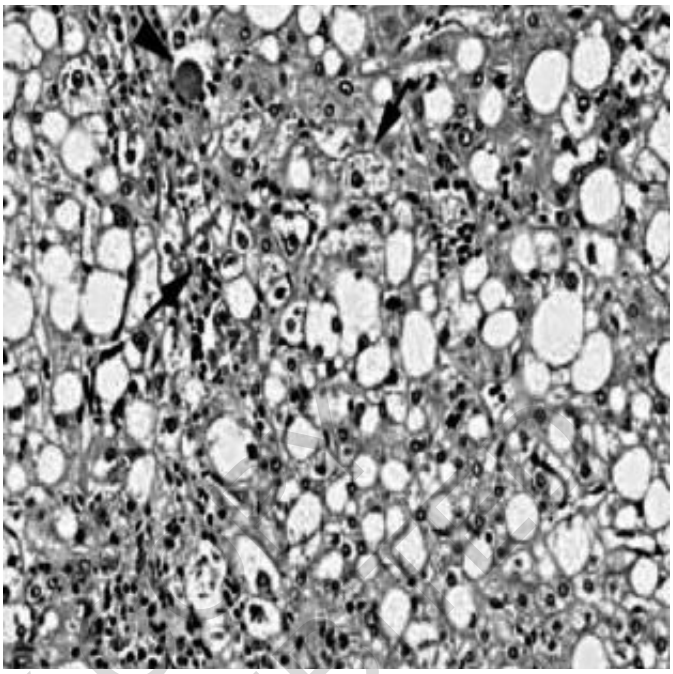


Fig. 1: liver steatosis (HEx150).

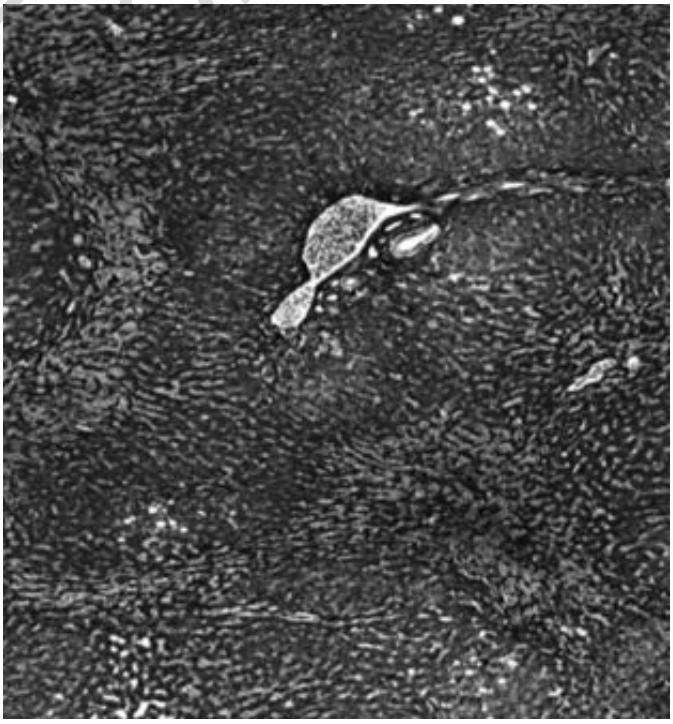


Fig. 2: SOS syndrome (HEx150).

subjects who developed SOS syndrome from those who did not.
No statistical significance has been determined in relation to the liver damage and the presence of metabolic syndrome ($\chi^2$= 0,390, p=0,830).

## Discussion

Making a decision about the optimal time for the colorectal cancer liver metastases surgery becomes very complex after new possibilities in the treatment of primary tumor / stent application in the resolution of malignant occlusion have been introduced, which may postpone the primary colon and especially rectum cancer surgery; preoperative chemoradiation and neoadjuvant chemotherapy [5-9]. Combined therapy, which involves, first of all, the use of neoadjuvant chemotherapy (FOLFOX, FOLFIRI) prior to liver surgery in order to reduce the size and stage of the primary tumor and the metastases themselves, has significantly changed the views on the location, time and the extent of the surgical liver resection in the treatment of liver metastatic KRK [9,10]. The addition of monoclonal antibodies against the epidermal growth factor (anti-EGF-Cetuximab) and vascular endothelial growth factor (anti-vEGF-Bevacoubub) by existing chemiotherapeutic protocols significantly increases the degree and intensity of the therapeutic response in terms of reducing the number and size of the liver metastases 78%) and almost doubles the rate of patients who can be subjected to resection interventions, moving patients from the group of primarily unresectable to resectable of 33% (secondary resectability) [6].
However, despite the high percentage of favorable therapeutic responses, neoadjuvant chemotherapy of the liver

metastases is associated with the risk of toxic liver damage by chemotherapy agents (citotoxic associated liver injury -CALI) [11]. These negative effects are of a particular significance in patients who undergo chemotherapy shortly after chemotherapy with the extensive liver resection. There is an increase in the percentage of postoperative complications of up to 54%, to the operative procedures on previously damaged liver as opposed to a maximum of 25% of complications after liver resection undamaged by previous chemiotherapy [13]. The mortality rate in modern liver resection surgery is up to 3%, while in the case of cytotoxic damage, this percentage rises up to as much as 14.7% [14].

The duration of neoadjuvant chemotherapy administration, or the number of administered cycles, significantly increases the rate of postoperative complications from 19% to 54%, with a critical cycle duration of 6 cycles (13). Neoadjuvant HT also prolongs the ospitalization (from 11 to 15 days) and the percentage of reintervention (from 0 to 11%) with a critical therapy duration of 12 cycles [15,16].

However, in our study, in which patients received an average of 5.73 ± 2.13 cycles of "bevacizumab plus FOLFOX IV" protocol (3-10 cycles), sex, age and the number of chemotherapy cycles, did not have any statistically significant influence - as well on biochemical parameters - as on the morphological degree of the liver damage.

Toxic liver damage is most often associated with two categories of pathological changes in the liver: the development of non-alcocholic fatty liver disease (NAFLD), which leads to so-called "yellow liver" or sinusoidal obstruction syndrome syndrome (SOS) syndrome, so-called "blue liver".

NAFLD occurs in the categories from simple fat accumulation (steatosis) in the liver, through inflammatory changes (steathepatitis) to fibrosis and cirrhosis of the liver in the most severe cases. It is associated with diabetes, obesity, alcohol abuse and metabolic syndrome. It is present in 20-30% of adult Americans [17]. The occurrence of NAFLD after neoadjuvant chemotherapy has been described from the application of the first, fluoropyrimidine protocols (5-Fluorouracil and Leukovorin), which still represent the basis of complex chemotherapeutic protocols in the treatment of metastatic colorectal cancer [14,17]. NAFLD, as a rule, occurs after the application of protocols containing irinotecan (FOLFIRI, FOLFOXIRI, FOLFIRINOX). The mild form of NAFLD, liver steatosis, is recorded in 43% to 65% of themoterapy treated patients andit is more common in patients with high BMI and metabolic syndrome [12,14,16]. More severe cases of steatohepatitis forms are recorded in 20.2% of patients treated with Irinotecan, compared to 4.4% in the group of patients without HT [14].

Irinotecan-based protocols are more commonly used as the first line of chemotherapy in the United States, while in Europe the first line is based on Oxaliplatin protocols [17,18]. On the other hand, the occurrence of NAFLD is rare after Oxaliplatin chemotherapy protocols have been administrated. After this protocol administration, only 3.8% of steatosis and 6.3% steatohepatitis [14] are recorded. In our material, moderate liver steatosis was also registered in only 3.3% of patients, which is far less than in the control group of patients without chemotherapy (30%).

Sinusoid obstruction syndrome (SOS syndrome) is a common chemotherapy complication [14,19]. Rubbia-Brandt and associates were the first to describe the sinusoidal dilatation development after chemotherapy and proposed the following hypothesis: in the beginning of the damaged endothelial cells cause activation of stellate cells, which leads to fibrosis and erythrocyte and cytoplasmic balance aggregation in the perisinusoidal space, which brings about the sinusoidal and the centrilobular venules obstruction [20,21].

SOS syndrome is registered from 18.9% [14] to 49% [13] or even 51% [21]. In our material, liver damage according to the type of SOS syndrome was registered in a high percentage (even two thirds of patients (66.66%). In 14 patients (46.7%), a mild degree was registered, and 6 (20.0% moderate degree of this type of liver damage. The strongest correlation for liver damage in the form of SOS syndrome was shown by the increase in D levels of bilirubin, T bilirubin and a decrease in albumin values, prolonging PT.

According to the results of most authors, there is a clear correlation between the appearance of this type of liver damage and the metabolic syndrome or isolated high BMI values [13,14,22]. In contrast, our study did not find the existence of statistical significance in relation to the degree of the liver damage by the type of SOS and the presence of metabolic syndrome ($\chi^2 = 0.390$, $p = 0.830$). From the practical aspect of surgery, the question arises: is so high liver damage degree of damage responsible for the increase in postoperative morbidity and mortality in resectional liver surgery, which follows the Oxaliplatin Chemotherapy Protocols? Although the increase in the morbidity rate from 13% to 38% was registered in the study of Karoui and associates [13], according to the conclusion of most studies, SOS syndrome does not lead to a significant increase in postoperative morbidity and mortality, as opposed to steatohepatitis induced by chemotherapy agents, based on Irinotecan [14,22].

## Conclusion

Despite many advantages, the neoadjuvant chemotherapy of colorectal cancer liver metastases also has certain disadvantages, the most important of which are related to toxic liver damage.

In our study, after an average of 5.3 administered cycles according to the "bevacizumab plus FOLFOX IV" protocol, a statistically significant increase in AF, Dbilirubin

and LDH values, as well as a decrease in albumin values, have been found. The dominant liver damage was according to the type of SOS syndrome. It has been registered in a high percentage, in two-thirds of patients, mostly in a mild degree, while the moderate liver steatosis has been recorded in an extremely small percentage (3.3% of patients). Sex, age, the presence of metabolic syndrome as well as the number of chemotherapy cycles have not had any statistically significant influence either on biochemical parameters or on the morphological level of liver damage.


## Riassunto

I principali aspetti negativi della chemioterapia neoadiuvante delle metastasi epatiche da carcinoma del colon-retto sono relativi ad un danno tossico del fegato. Questo studio è finalizzato a determinare il grado di danno epatico biochimico e morfologico dopo il trattamento con il protocollo terapeutico di bevacizumab più FOLFOX IV, nonché la correlazione tra sesso, età, esistenza della sindrome metabolica, durata del trattamento neoadiuvante e grado di danno al fegato.

Lo studio si è svolto su un totale di 60 pazienti operati per metastasi dal cancro del colon-retto, divisi in due gruppi di 30 pazienti ciascuno: un gruppo di studio, cioè di quelli pretrattati con terapia neoadiuvante secondo il protocollo "bevacizumab più FOLFOX IV", ed un gruppo di controllo di pazienti trattati direttamente con resezione epatica senza chemioterapia neoadiuvante. Sono stati esaminati i seguenti elementi: parametri biochimici della funzionalità epatica, presenza di sindrome metabolica, valutazione isto-patologica del grado di steatosi e sindrome di SOS.

Risultati: L'aumento di AF è stato osservato nel gruppo sperimentale (Z = 2.566, p = 0,010), Dbilirubin (Z = 1.970, p = 0,037), LDH (Z = 2.951, p = 0.003) con diminuzione dei valori di albumina (t = 5.100, p <0,001). L'esame isto-patologico solo nel 3,3% ha mostrato steatosi epatica moderata, mentre la sindrome della ostruzione sinusoidale (SOS) è stata registrata in ben due terzi (66,66%) dei pazienti nel gruppo di studio. In 14 pazienti (46,7%) è stato registrato un grado lieve e in 6 (20,0%) livelli moderati di questo tipo di danno epatico. Genere (p = 0,13), età (p = 0,09) e durata della somministrazione della chemioterapia (p = 0,35), nonché la presenza della sindrome metabolica ($\chi^2$ = 0,390, p = 0,830), non hanno avuto alcun effetto statisticamente significativo sul grado di danno epatico.

Conclusione: Nel nostro studio, dopo la somministrazione del protocollo "bevacizumab plus FOLFOX IV", è stato riscontrato un aumento statisticamente significativo di AF, Dbilirubin e LDH, nonché una diminuzione dei valori di albumina. Il danno epatico dominante era del tipo di sindrome SOS (66,7%), mentre la steatosi epatica è stata registrata solo nel 3,3% dei pazienti. Genere, età, presenza di sindrome metabolica e numero di cicli di chemioterapia non hanno avuto alcun significato statistico sui parametri biochimici e sul grado morfologico di danno epatico.


## References


1. A Tsoulfas G, Pramateftakis MG: *Management of rectal cancer and liver metastatic disease: Which comes first?* International Journal of Surgical Oncology, 2012.

2. Adam R: *Colorectal cancer with synchronous liver metastases*. British Journal of Surgery, 2007; 94: 129.

3. Morris EJA, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, Cottier B, Poston G: *Surgical management and outcomes of colorectal cancer liver metastases.* Brit Journ Surg, 2010; 97: 1110-118.

4. Tournigand C, Andre T, Achille E, et al.: *FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study*. J Clin Oncol, 2004; 22:229-37.

5. Stathopoulos GP, Batziou C, Trafalis D, Koutantos J, Batzios S, Stathopoulos J, Legakis J, Armakolas A: *Treatment of colorectal cancer with and without bevacizumab: a phase III study.* Oncology, 2010; 78:376-81.

6. Hurwitz HI, Tebbutt NC, Kabbinavar F, Giantonio BJ, Guan ZZ, Mitchell L, Waterkamp D, Tabernero J: *Efficacy and safety of bevacizumab in metastatic colorectal cancer: Pooled analysis from seven randomized controlled trials.* Oncologist, 2013; 18:1004-12.

7. Benoist S, Nordlinger B: *The Role of Preoperative chemotherapy in patients with resectable colorectal liver metastases.* Ann Surg Oncol, 2009; 16:2385-390.

8. Chua T, et al.: *Systematic Review of Randomized and Nonrandomized Trials of the Clinical Response and Outcomes of Neoadjuvant Systaemic Chemotherapy for Resectable Colorectal Liver Metastases*. Ann Surg, Oncol, 2010; 17:492-501.

9. Nordlinger B, et al.: *Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial*. Lancet, 2008; 371(9617): 1007-16.

10. Jang HJ, Kim BJ, Kim JH, Kim HS: *The addition of bevacizumab in the first-line treatment for metastatic colorectal cancer: an updated meta-analysis of randomized trials*. Oncotarget, 2017; 8, (42):73009-16.

11. Parikh AA, Gentner B, Wu TT, et al.: *Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy*. J Gastrointest Surg, 2003, 7:1082-88.

12. Shen Z, Ye Y, Bin L, Yin M, Yang X, Jiang K, Wang S: *Metabolic syndrome is an important factor for the evolution of prognosis of colorectal cancer: Survivel, recurence, and liver metastasis*. Am J Surg, 2010; 200(1):59-63.

13. Karoui M, Penna C, Amin-Hashem M, et al.: *Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases*. Ann Surg, 2006, 243:1-7.

14. Vauthey JN, Pawlik TM, Ribero D, et al.: *Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after*

*surgery for hepatic colorectal metastases*. J Clin Oncol, 2006, 24:2065–72.

15. Aloia T, Sebagh M, Plasse M, et al.*: Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer livermetastases*. J Clin Oncol, 2006, 24:4983-990.

16. Colangelo LA, Gapstur SM, Gann PH, et al.: *Colorectal cancer mortality and factors related to the insulin resistance syndrome*. Cancer Epidemiol Biomarkers Prev, 2002; 11:385-91.

17. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, Primrose JN, Parks RW: *Guidelines for resection of colorectal cancer liver metastases*. Gut, 2006; 55(Suppl III).

18. Pawlik TM, Scoggins CR, Zorzi D, et al.: *Effect of surgical margin statuson survival and site of recurrence after hepatic resection for colorectal metastases*. Ann Surg, 2005; 241(5)715-22, discussion 722–24.

19. Hemly A: *Review article: updates in the pathogenesis and therapy of hepatic sinusoidal obstruction syndrome*. AP&T, 2006; 23:11-25.

20. Rubbia-Brandt L, Audard V, Sartoretti P, et al.: *Severe hepatic sinusoidal obstruction associated with oxaliplatinbased chemotherapy in patients with metastatic colorectal cancer*. Ann Oncol 2004, 15:460-66.

21. Rubbia-Brandt L, Lauwers GY, Huamin H, at al: *Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis.* Histopathology, 2010; 56(4):430-39.

22. Nordlinger B, Sorbye M, Debois M, et al.: *Feasibility and risks of pre-operative chemotherapy (CT) with Folfox 4 and surgery for resectable colorectal cancer liver metastases (LM): Interim results of the EORTC Intergroup randomized phase III study* 40983. J Clin Oncol; 23:253s, 2005 (suppl, abstr 3528).

23. Klinger M, Eipeldauer S, Hacker S, et al.: *Bevacizumab protects against sinusoidal obstruktion syndrome and does not incrise response rate in neoadjuvant XELOX/FOLFOX IV therapy of colorectal cancer liver metastasi*s. EJSO; 2009; 35(5):515-20.

24. Zorzi D, Chun YC, Madoff DC, et al.: *Chemotherapy With Bebacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastasis*. Annals of Surgical Oncology, 2008; 15(10):27652772.

25. Ribero D, Wang H, Donadon M, et al.: *Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases.* Cancer, 2007, 110:2761-767.

26. Fakih MG: 5-*Fluorouracil Leucovorin i Oxaliplatin (FOLFOX IV) in the Treatment of Metastatic Colon Cancer with Severe Liver Dysfunction*. Oncology, 2004; 67:222-24.