Original Paper

Lower Incidence of Hepatic Metastases of Colorectal Cancer in Patients with Chronic Liver Diseases: Meta-analysis

Goran Augustin[1], Tomislav Bruketa[1], Dragan Korolija[1] and Milan Milosevic[2]

[1]Department of Surgery, University Hospital Center Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia
[2]Depatment of Environmental and Occupational Health, Andrija Stampar School of Public Health, School of Medicine, University of Zagreb, Zagreb, Croatia

Corresponding author: Goran Augustin, M.D., Ph.D., Department of Surgery, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia; E-mail: augustin.goran@gmail.com

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ABSTRACT

Background/Aims: The rarity of metastatic malignancy in injured liver has been noticed. This meta-analysis evaluates the difference in occurrence of metastatic colorectal cancer in healthy and chronically injured liver. **Methodology:** Literature search of occurrence of metastatic colorectal cancer in chronically injured liver opposed to healthy liver was conducted. Chronically injured/damaged liver included cirrhosis, steatosis or fatty liver and infection with Hepatitis virus B or C. **Results:** A total of 7 retrospective studies between 1992 and 2010 matched the selection criteria with total of 4049 patients. Results suggest significantly lower incidence of colorectal metastasis in chronically injured liver (Pooled odds ratio = 0.260 (95% CI = 0.18 to 0.38); χ^2 (test odds ratio differs from 1) = 45.90 (df = 1); p <0.0001). **Conclusions**: Patients with chronic liver injury have significantly lower occurrence of hepatic metastasis of primary colorectal cancer than the patients with healthy liver.

INTRODUCTION

The data show that in up to 30% of patients with colorectal cancer, liver metastases were observed during first laparotomy (1-4). Also, the most common indication for non curative surgery is liver metastases. Thus, liver metastases are the most relevant prognostic factor for patients with colorectal carcinoma (5). On the other hand, there are indices that chronic liver injury, such as cirrhosis, steatosis and hepatitis B or C infection, could reduce the incidence of hepatic metastases of primary colorectal cancer.

The rarity of the occurrence of metastatic malignancy in injured liver has been noticed and described by several authors for almost seventy years (5-9). In 1942, Lisa et al. suggested that the cirrhotic liver is not a favorable soil for metastatic tumor cells (7). Since then there have been many theories about this phenomenon but the exact reason is still unknown.

During last twenty years only few articles have been published about colorectal metastases to injured liver and there is no meta-analysis or systematic review on the subject. We collected all relevant articles and performed a meta-analysis. This meta-analysis evaluates the difference in occurrence of metastatic colorectal cancer in healthy and chronically injured liver.

METHODOLOGY

Searching, selection and data abstraction

Two independent reviewers (G.A. and B.T.) conducted a comprehensive literature search by using predetermined collections of proformas. All non-English articles were translated in English and than analyzed. Data sources were Ovid, Medline, Embase, Cochrane library and Google Scholar. Inclusion criteria were all retrospective analyses assessing occurrence of metastatic colorectal cancer in chronically injured liver opposed to healthy liver. Chronically injured/damaged liver included cirrhosis, steatosis or fatty liver and infection with Hepatitis virus B or C. All this factors was clinically diagnosed according to the results of serum chemistry, serology and hepatic imaging (ultrasonography, MR). Exclusion criteria were trials with no control group, patients with hepatocellular carcinoma and retrospective analyses of patients that underwent chemotherapy. Measured outcome was occurrence of metastatic malignancy in injured and in healthy liver.

All studies were level of evidence 2b (10). Acquired studies with usable data were Hayashi et al. (5), Uetsuji et al. (8), Song et al. (11), Utsunomiya et al. (12), Iascone et al. (13,14), and Qian et al. (15). Two studies that had to be excluded were Gervaz et al. (no control group) (16) and Utsunomiya et al. (not adequate data) (9).

Data synthesis and statistics

Meta-analysis was performed using the software MedCalc (version 8.2.0.2). The effect sizes as odds ratio (OR) with 95% confidence interval (CI) were calculated. Both random-effects model and fixed-effect model were used, but interpretation was based on level of heterogeneity of the studies. In fixed-effect model, it is assumed that there is no heterogeneity in treatment effect between studies, whereas in random-effect model it is assumed that there is variation between studies and calculated odds ratio will be more conservative (17).

Funnel plot were assessed to provide a visual assessment of whether estimates were associated with study size and to detect publication biases. Bias was assessed visually by inspection of a bias assessment plot (**Figure 1**) and statistically by use of the *Horbold-Egger* test (bias = 0.5578 (92.5% CI = -2.487 to 3.602); p = 0.684).

RESULTS

Review of the data extraction showed 100% agreement between the two reviewers. A total of 7 retrospective studies published between 1992 and 2010 matched the selection criteria. Two studies by the

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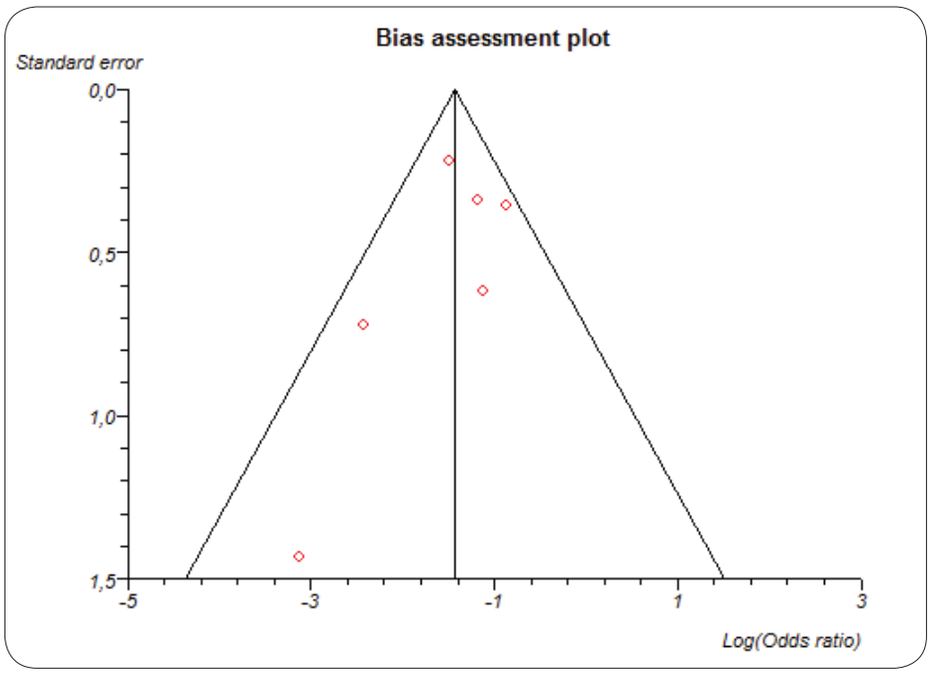

FIGURE 1. Bias assessment plot.

same author overlapped so the data from both were merged. Study selection process is shown in **Figure 2**. The results of studies are shown in **Table 1**. The studies assessed combined a total of 4049 patients. **Figure 3** is Forest plot that compares incidence of colorectal metastasis in chronically injured liver to incidence of colorectal metastasis in liver with no signs of injury. Since there was variations between studies random-effect model was used for interpretation of the data. Results suggest significantly lower incidence of colorectal metastasis in chronically injured liver (Pooled odds ratio = 0.260 (95% CI = 0.176 to 0.384); χ^2 (test odds ratio differs from 1) = 45.90 (df = 1); p <0.0001).

By this we infer with 95% confidence, assuming a random effects model, that the true size of the difference between incidence rates was somewhere between 0.17 and 0.38 for the chronically injured liver group compared with the control group; that is statistically significant, p <0.0001. Also, we can say with 95% confidence, assuming a random effects model that for those with chronically injured the true population risk of metastasis is at most 0.38 of the risk of those with healthy liver. Assuming a fixed effects model a stronger inference could be made about a relative risk of 0.32 (the upper confidence limit) but the high inter-study variation makes the fixed effects model less appropriate.

Results are comprehensively shown in **Table 2**.

DISCUSSION

Many decades ago it was noted on autopsy studies that patients with chronic liver injury had significantly lower incidence of hepatic metastases of different kinds of primary malignant tumors (18-20). Since rarity of the occurrence of metastatic disease of colorectal cancer origin in injured liver has been noticed and described by number of observers for almost seventy years it was our intention to analyze the results of all relevant studies published on the subject. This meta-analysis aimed to determine whether chronic liver injury, such as cirrhosis, steatosis and hepatitis B or C infection reduces incidence of hepatic metastasis of primary colorectal cancer.

All studies included in meta-analysis are level of evidence 2b (10). Accordingly, this meta-analysis is 2a level of evidence. Since there are only a few studies on this subject and it is impossible to conduct prospective study, level of evidence 2b is the highest possible.

This meta-analysis suggests that patients with chronic liver injury have significantly lower incidence of hepatic metastasis of colorectal cancer origin. The reason for this observation is still unknown. There are several theories and explanations. Lisa et al. suggested that cirrhotic liver is not favorable soil for transplanted tumor cells and the rarity of metastatic disease to the liver (7). The authors found only 5 case reports and described six patients of their own but not a single patient had primary colorectal cancer. Lieber et al. offered explanation that the fibrosis and subsequent distortion of small vessels in the liver constitute a mechanical impediment to the spread of cancerous tissue (6). Certain authors claim that activated immune cells residing in livers are effective in killing metastatic tumor cells. Others claim that patients with significant chronic liver injury, especially cirrhosis and primary malignant tumors have shorter life span thus lower possibility to develop metastases of any primary malignant tumor (21).

High metalloproteinase inhibitor contents and especially altered lectins or lectin binding sites in cirrhosis of the liver may help to explain the rare event "metastasis in cirrhosis" (22). Pathophysiological pathway of cirrhosis undergoes through the process of extracellular matrix remodeling leading to new collagen formation and deposition. The major role in matrix degradation is played by matrix metalloproteinases (MMPs), and their tissue inhibitors (TIMPs) (23). In progressive liver fibrosis, the overall MMP activity decreases, due to increased expression of TIMPs and other anti-proteases expressed by hepatic stellate cells and hepatocytes (24). Since fibrosis is the most significant pathological consequence of liver injury in fatty liver, process of extracellular matrix remodeling is also present in liver tissue. Process of remodeling is practically the same and it is done by MMPs and their TIMPs. Chronic hepatitis is accompanied with liver fibrosis and elevation of MMPs and TIMPs. Analysis of level of serum matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in chronic hepatitis

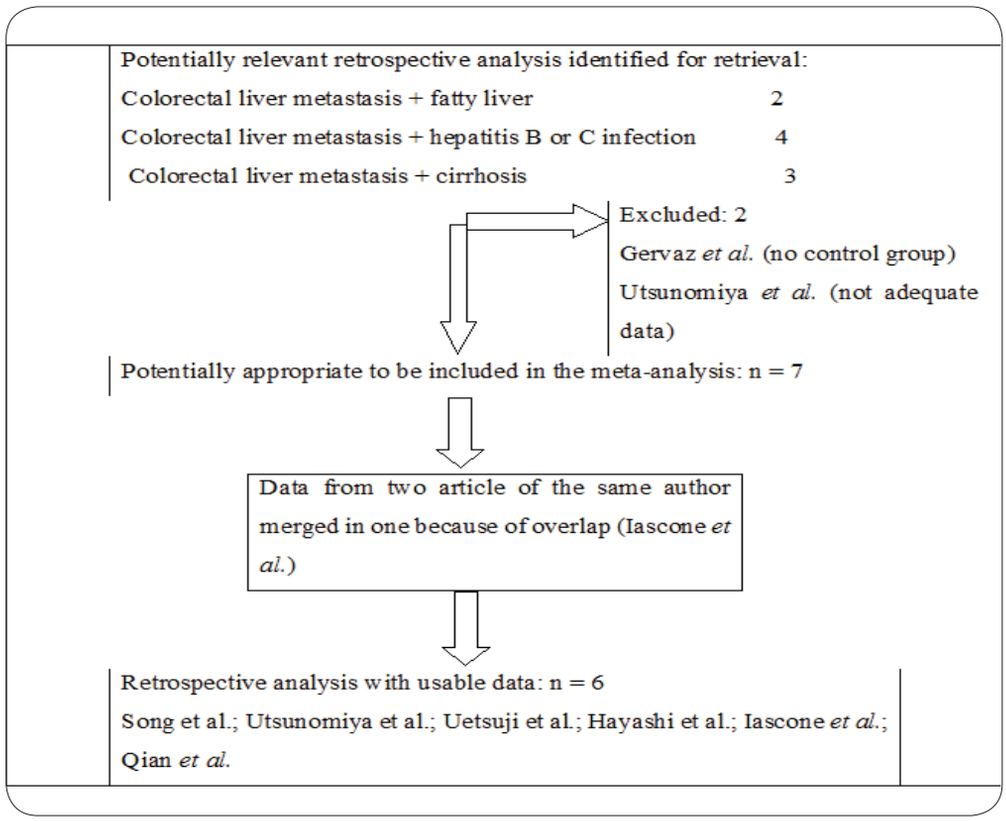

FIGURE 2. Flow diagram of retrospective analysis with adequate data (see text for details).

TABLE 1. The results of included studies with results of each study separately with number of patients.

Study	Injured liver	Injured liver with metastasis	Non-injured liver	Non-injured liver with metastasis
Song et al.	74	10	438	119
Utsomiya et al.	37	3	401	85
Uetsuji et al.	46	0	204	40
Hayashi et al.	121	2	718	115
Iascone et al.	291	28	543	174
Qian et al.	114	10	1062	254
Total	**683**	**53**	**3366**	**787**

C patients showed statistically significant increase of MMP-9 and TIMP-1 in hepatitis C patients compared with control group. Also there was a positive correlation between TIMP-1 and the degree of fibrosis (25). In progression of colorectal cancer MMPs also have great role. Namely, the balance between MMPs and their physiological TIMPs is crucial in tumor invasion and progression (26). Is seems that increased activity of MMPs stimulates tumor growth. Experimental use of selective MMP inhibitor resulted in a dose-dependent delay in the growth of tumors and reduced volume by 75% when treatment was begun five days after implantation (27). Due to these findings it is possible that increased expression of TIMPs have inhibitory role in the process of colonization and formation of colorectal metastasis in chronically injured liver.

Another possible proposed mechanism could lie in galectin-3. Galectin-3, member of the β-galactoside-binding proteins, is an intracellular and extracellular lectin which interacts with intracellular glycoproteins, cell surface molecules and extracellular matrix proteins. Galectin-3 is expressed widely in epithelial and immune cells and its expression is correlated with cancer aggressiveness and metastasis (28). When Galectin-3 is blocked with carbohydrate-based galectin-3 inhibitors, metastasis-associated tumor cell adhesion could be

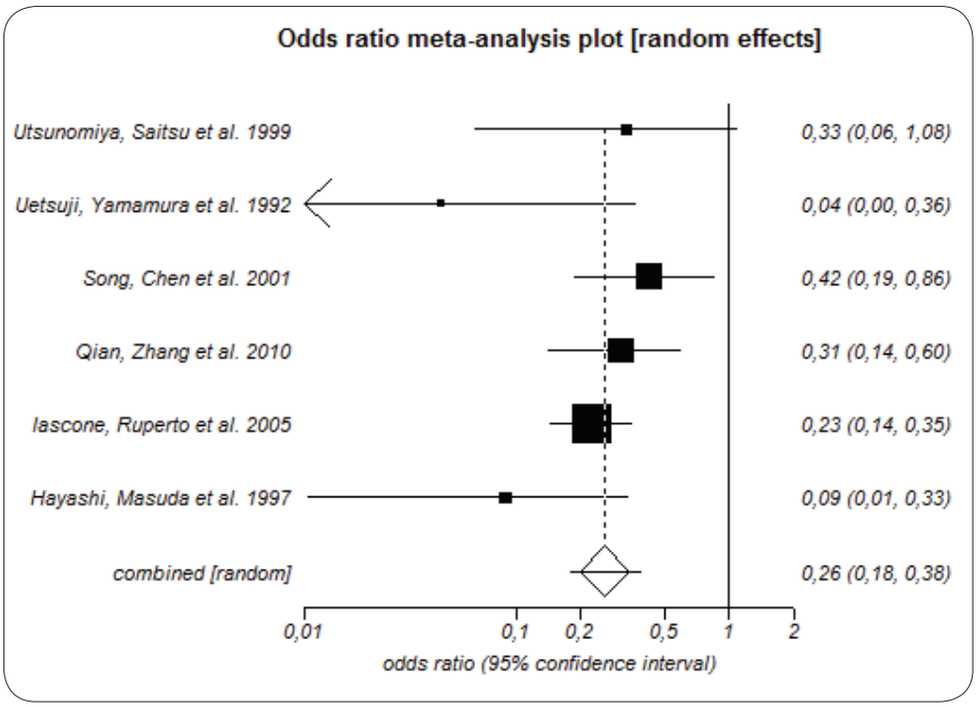

FIGURE 3. Forest plot that compares incidence of colorectal metastasis in chronically injured liver to incidence of colorectal metastasis in liver with no signs of injury.

TABLE 2. Results of the meta-analysis.

	Stratum			Table (xt, xc, nt, nc)	
1	3	85	34	316	Utsunomiya et al. 1999
2	0	40	46	164	Uetsuji et al. 1992
3	10	119	64	319	Song et al. 2001
4	10	254	104	808	Qian et al. 2010
5	28	174	263	369	Iascone et al. 2005
6	2	115	119	603	Hayashi et al. 1997

	Stratum	Odds ratio	95% CI (CML)		% Weights (fixed, random)	
1	0.328028	0.063065	1.084.864	5.382.285	9.095.765	Utsunomiya et al. 1999
2	0.043674	0	0.363354	6.096.076	18.743	Uetsuji et al. 1992
3	0.418855	0.185775	0.857467	12.133.887	2.147.105	Song et al. 2001
4	0.305875	0.140421	0.597477	18.323.258	23.017.847	Qian et al. 2010
5	0.225777	0.141563	0.35054	44.759.159	3.767.424	Iascone et al. 2005
6	0.088126	0.010419	0.334457	13.305.335	6.866.798	Hayashi et al. 1997

Fixed effects (Mantel-Haenszel, Robins-Breslow-Greenland)

Pooled odds ratio = 0.240 (95% CI = 0.178 to 0.324)

χ^2 (test odds ratio differs from 1) = 97.78; p <0.0001

Random effects (DerSimonian-Laird)

Pooled odds ratio = 0.260007 (95% CI = 0.176092 to 0.38391)

χ^2 (test odds ratio differs from 1) = 45.90 (df = 1); p <0.0001

inhibited efficiently (29). On the other hand, Galectin-3 is expressed in various tissues and organs but is significantly absent in normal hepatocytes. In chronic liver injuri such as cirrhosis and hepatitis C induces fibrosis expresion of Galectin-3 and Galectin-3-binding protein was increased (30,31). This could lead to conclusion that liver Galectin-3 receptors are being occupied thus not allowing metastatic tumor cell to adhere.

Yet another possible mechanism could lie in chemokines. It is said that chemokine involvement in cancer development and progression is divergent: while specific chemokines promote, others can inhibit such processes (32). On the other hand chemokines and their receptors are marked as key players i pathophysiology of hepatitis and cirrhosis (33,34). Here could lay yet not fully explained mechanism of lower incidence of hepatic metastases of colorectal cancer.

CONSLUSIONS

Colorectal cancer is a major health problem and hepatic metastases of colorectal cancer deteriorate prognosis. Rarity of the occurrence of metastatic disease of primary colorectal cancer in injured liver has been noticed and described for almost seventy years but was not so often explored and never completely explained. This meta-analysis proved that patients with chronic liver injury have significantly lower occurrence of hepatic metastasis of primary colorectal cancer than the patients with healthy liver and we reviewed possible theories for this observation. Studies included did not analyze if lower occurrence affect survival rate and also all studies do not distinguish different stages of liver injury. Previously, six independent determinants of survival in patients without intervention (natural history) were identified in the following order: percentage liver volume replaced by tumour, grade of malignancy of the primary tumour, presence of extrahepatic disease, mesenteric lymph-node involvement, serum carcino-embryonic antigen, and age (35). Observations and conclusion of this meta-analysis opens possibilities for exploration of how to induce or amplify mechanisms for elimination of metastatic cells that come in contact with the liver thus improving prognosis of patients with colorectal cancer without liver metastases.

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