Metformin Intake Suppresses The Degree of Liver Metastasis From Colorectal Cancer In Diabetic Patients But Does Not Improve Their Prognosis

Akira Saito  
Jichi Medical University  
https://orcid.org/0000-0002-3247-7845

Joji Kitayama (✉ kitayama@jichi.ac.jp)  
Jichi Medical University

Hisanaga Horie  
Jichi Medical University

Koji Koinuma  
Jichi Medical University

Hideyuki Ohzawa  
Jichi Medical University

Hironori Yamaguchi  
Jichi Medical University

Hiroshi Kawahira  
Jichi Medical University

Toshiki Mimura  
Jichi Medical University

Alan Kawarai Lefor  
Jichi Medical University

Naohiro Sata  
Jichi Medical University

Research Article

Keywords: Metformin, Colorectal cancer, Liver metastasis, stage IV, Chenotherapy

Posted Date: November 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-951326/v1

License: ☒ This work is licensed under a Creative Commons Attribution 4.0 International License. 
Read Full License
Abstract

**Background:** Metformin reduces the risk of, and mortality from, colorectal cancer in patients with diabetes mellitus. However, the effect of metformin on patients with stage IV disease is unknown. In the present study we reviewed the clinical features and outcomes of patients with diabetes mellitus and stage IV colorectal cancer (M1, liver metastases) treated with or without metformin.

**Methods:** The 202 patients with colorectal cancer and macroscopic liver metastasis who were treated in the Department of Surgery or Department of Clinical Oncology at Jichi Medical University Hospital from January 2006 through June 2019 were surveyed treatment of diabetes, clinical and pathological factor and prognosis of these patients.

**Results:** We retrospectively examined the effect of metformin use on outcomes in 32 patients with liver metastases from colorectal cancer. Hepatic metastases were stage H1 in 8/8 patients taking metformin and stage H2-3 in 17/24 non-users. Of 22 patients who underwent colectomy, colorectal tumors were pT4 in 5 metformin users, and pT2-3 in 10/17 non-users. The mean survival of metformin users and non-users was equal (28.0 mo vs 29.3 mo, p>.05). No significant difference was detected when survival was compared between 6 metformin users and 19 non-users who received systemic chemotherapy.

**Conclusion:** These results suggest that metformin has less potent anti-tumor effects in patients with advanced stage disease. Metformin for the treatment of patients with metastatic colorectal cancer requires further study.

**Backgroud**

Type 2 diabetes mellitus (DM) is well known to increase the risk for development of various cancers, including colorectal cancer (CRC) [1–3]. Metformin, an oral anti-hyperglycemic agent, has been shown to reduce the incidence of cancer development among patients with type 2 DM, although the degree of reduction varies among different types of cancer [4–6]. Many epidemiologic studies have suggested that that metformin may also improve the outcome of patients with CRC [6–10], although a large population-based study did not support a significant association between metformin and cancer-specific mortality [11]. There is clear evidence that outcome of the diabetic patients who underwent curative surgery with stage II and III CRC is associated with better survival in metformin-users [9, 12–15]. However, survival benefit is less clear in patients with stage IV CRC. In fact, a retrospective study focused on the patients who received chemotherapy for stage IV CRC has shown that tumor response, change in target lesion size as well as patient outcome were not significantly different between the metformin treated and the non-treated patients [16]. In this study, therefore, we examined the clinical features and outcome of diabetic patients with stage IV CRC with liver metastases who were treated with or without metformin.

**Methods**
From January 2006 until June 2019, 202 CRC patients with liver macroscopic metastases were treated in the Department of Surgery or Department Clinical Oncology at Jichi Medical University Hospital. Among them, 32 patients (16 %) suffered type 2 DM and received medical treatment at diagnosis. In these patients, data for gender, age, medical history, treatment method, laboratory and pathological data and outcome were extracted from an electronic database. The stage of metastatic hepatic tumors was classified into the three categories with the number of liver nodules and the size of the largest metastasis: H1, \( \leq 4 \) lesions and \( \leq 5 \) cm; H2, \( \geq 5 \) lesions or \( >5 \) cm; and H3, \( \geq 5 \) lesions and \( >5 \) cm, according to criteria of the Japanese Society for Cancer of the Colon and Rectum [17]. This study was approved by the ethics committee of the Jichi University Hospital (approval no. clinic19-190) and was conducted in accordance with the guiding principles of the Declaration of Helsinki.

Statistical differences in clinical and pathological factors were evaluated with Fisher's exact test. Overall survival (OS) was calculated using the Kaplan-Meier method and differences were evaluated using the log-rank test. In all tests, the standard for a significant difference was set at \( p < 0.05 \).

**Results**

As shown in Table 1, 8 patients (25%) were treated with medications including metformin, 500mg~1000mg daily from 1 to 23 year (median=7 year), while other 24 patients were not exposed to metformin at diagnosis. No differences were detected in age, gender, tumor location and metastases in other sites between metformin-users and non-users. However, the degree of liver metastasis was all H1 stage in 8 metformin-users, while H2~3 stage in more than half (13/24) of non-users \( (p<0.018) \).

Surgery was performed in 22 patients (5 metformin-users and 17 metformin non-users). Curative surgery with colectomy including hepatectomy was performed in 2 metformin-users and 5 non-users, and other patients underwent only colectomy. Pathological examination revealed that the depths of invasion of resected colorectal tumors were pT4 in all the 5 metformin users while only 7 in 17 tumors (41%) were pT4 and others remained at pT2-3 stage in metformin non-users \( (p=0.024) \).

The overall survival (OS) of the patients was shown in Fig. 1. Mean survival time (MST) of the 8 metformin users and 24 non-users was equivalent (28.0 mo vs 29.3 mo, \( P=0.76 \)). Systemic chemotherapy was performed in 6/8 (75%) metformin users. FOLFOX and FOLFOX+bevasizumab (Bmab) was used for 4 and 2 pateins, respectively, with metformin continuation. In 24 metformin-non-usres, 19 patients (79%) received chemotherapy, 5 with FOLFOX, 6 with FOLFOX+Bmab, 1 with FOLFOX+Cetuximab (Cmab), 4 with FOLFIRI and 1 with SOX and 2 with capecitabibe. No significant difference was detected even when overall survival was evaluated in patients who received chemotherapy \( (\text{MST}:42.8 \text{ mo vs } 29.3 \text{ mo, } p=0.96) \).

**Discussion**


A growing body of evidence indicates that metformin have anti-tumor effects through various mechanisms including reduction of viability and proliferation of tumor cells, repression of epithelial-mesenchymal transition as well as modulation of tumor immune environment [18, 19]. In this study, we found that grade of liver metastasis in CRC patients was limited in H1 stage even though pT stage of primary tumor was more advanced in all metformin-users. This is consistent with the results of previous studies and supports the anti-metastatic effects of metformin. We previously reported that the number of nodal metastases was significantly lower in metformin-treated CRC patients with diabetes [15]. Taken together, these data suggest a possibility that metformin inhibits tumor metastasis not only at primary sites but also suppresses the growth of tumor cells in metastatic organs.

Epidemiological studies have suggested that metformin not only reduces the risk of developing CRC but also improve the outcome of diabetic patients, especially in those who underwent curative surgery with stage II and III CRC [6–10, 12–15]. Interestingly, however, the impact of metformin intake on the outcome of the stage IV patients has not been clearly documented in previous literatures and and therapeutic effect of metformin in metastatic CRC still remains unclarified. In this study, we could not found apparent survival benefit of metformin intake in CRC patients liver metastases, although H stage was less advanced in metformin-users. This is consistent with a previous Korean study [16], and suggest a possibility that anti-tumor effects of metformin is less prominent in advanced stage of CRC, although the sample sizes in both studies are not enough to draw a definite conclusion.

In fact, a number of basic studies have shown metformin can sensitize tumor responses to different chemotherapeutic drugs through various molecular mechanisms [20]. Many clinical trials are currently active to examine the synergistic effect of metformin on chemotherapeutic agents for various cancers [21]. In CRC, metformin has been shown to enhance the effects of adjuvant chemotherapy [22, 23]. In comparison, the effects of metformin on 5-Fu based chemotherapy for refractory CRC was reported to be modest [24]. Extensive randomized control trials will be necessary to confirm the real therapeutic potential of metformin for stage IV CRC.

Conclusions

These results suggest that metformin has less potent anti-tumor effects in patients with advanced stage disease. Metformin for the treatment of patients with metastatic colorectal cancer requires further study.

Abbreviations

DM: diabetes mellitus, CRC: colorectal cancer, OS: overall survival, MST: mean survival time

Declarations

Ethics approval and consent to participate
This study protocol was reviewed and approved by the Ethics Committee of the Jichi Medical University Hospital (approval no. clinicA20-110) and was conducted in accordance with the guiding principles of the Declaration of Helsinki.

**Consent for publication**

Not applicable

**Availability of data and materials**

All data generated or analysed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Author Contributions**

Joji Kitayama: Analyzed and interpreted the data.

Akira Saito: Analyzed and interpreted the data and wrote the paper.

Hideyuki Ohzawa: Contributed analysis tools or data.

Hironori Yamaguchi: Analyzed and interpreted the data.

Koji Koinuma, Hisanaga Horie, Hiroshi Kawahira, Toshiki Mimura, Alan Kawarai Lefor, Naohiro Sata: Contributed analysis tools or data.

**Acknowledgement**

We also thank Junko Shinohara, Hiromi Hatakeyama and Ikuko Nieda for technical and clerical work.

**References**

1. Orgel E, Mittelman SD. The links between insulin resistance, diabetes, and cancer. Curr Diab Rep. 2013;13:213–22.

2. Peeters PJ, Bazelier MT, Leufkens HG, de Vries F, De Bruin ML. The risk of colorectal cancer in patients with type 2 diabetes: associations with treatment stage and obesity. Diabetes Care. 2015;38:495–502.
3. Zhu B, Wu X, Wu B, Pei D, Zhang L, Wei L. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies. PLoS One. 2017;12:e0176068.

4. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, Gandini S. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2010;3:1451–61.

5. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One. 2012;7:e33411.

6. Dulskas A, Patasius A, Linkeviciute-Ulinskiene D, Zabuliene L, Urbonas V, Smailyte G. Metformin increases cancer specific survival in colorectal cancer patients-National cohort study. Cancer Epidemiol. 2019;62:101587.

7. Meng F, Song L, Wang W. Metformin Improves Overall Survival of Colorectal Cancer Patients with Diabetes: A Meta-Analysis. J Diabetes Res. 2017;2017:5063239.

8. Ki YJ, Kim HJ, Kim MS, Park CM, Ko MJ, Seo YS, Moon SM, Choi JA. Association between Metformin Use and Survival in Nonmetastatic Rectal Cancer Treated with a Curative Resection: A Nationwide Population Study. Cancer Res Treat. 2017;49:29–36.

9. Du L, Wang M, Kang Y, Li B, Guo M, Cheng Z, Bi C. Prognostic role of metformin intake in diabetic patients with colorectal cancer: An updated qualitative evidence of cohort studies. Oncotarget. 2017;8:26448–59.

10. Huang WK, Chang SH, Hsu HC, Chou WC, Yang TS, Chen JS, Chang JW, Lin YC, Kuo CF, See LC. Postdiagnostic metformin use and survival of patients with colorectal cancer: A Nationwide cohort study. Int J Cancer. 2020;147:1904–16.

11. Mc Menamin UC, Murray LJ, Hughes CM, Cardwell CR. Metformin use and survival after colorectal cancer: A population-based cohort study. Int J Cancer. 2016;138:369–79.

12. Garrett CR, Hassabo HM, Bhadkamkar NA, Wen S, Baladandayuthapani V, Kee BK, Eng C, Hassan MM. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012;106:1374–8.

13. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2012;131:752–9.

14. Fransgaard T, Thygesen LC, Gogenur I. Metformin Increases Overall Survival in Patients with Diabetes Undergoing Surgery for Colorectal Cancer. Ann Surg Oncol. 2016;23:1569–75.

15. Saito A, Kitayama J, Horie H, Koinuma K, Ohzawa H, Yamaguchi H, Kawahira H, Mimura T, Lefor AK, Sata N. Metformin changes the immune microenvironment of colorectal cancer in patients with type 2 diabetes mellitus. Cancer Sci. 2020;111:4012–20.

16. Lee DJ, Kim B, Lee JH, Park SJ, Hong SP, Cheon JH, Kim TI, Kim WH. [The effect of metformin on responses to chemotherapy and survival in stage IV colorectal cancer with diabetes]. Korean J Gastroenterol. 2012;60:355–61.

17. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishihara S, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito
Y, Sakai Y, Ueno H, Yoshino T, Boku N, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K. C. Japanese Society for Cancer of the Rectum, Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol. 2015;20:207–39.

18. Kamarudin MNA, Sarker MMR, Zhou JR, Parhar I. Metformin in colorectal cancer: molecular mechanism, preclinical and clinical aspects. J Exp Clin Cancer Res. 2019;38:491.

19. Bahrambeigi S, Shafiei-Irannejad V. Immune-mediated anti-tumor effects of metformin; targeting metabolic reprogramming of T cells as a new possible mechanism for anti-cancer effects of metformin. Biochem Pharmacol. 2020;174:113787.

20. Tang Z, Tang N, Jiang S, Bai Y, Guan C, Zhang W, Fan S, Huang Y, Lin H, Ying Y. The Chemosensitizing Role of Metformin in Anti-Cancer Therapy. Anticancer Agents Med Chem. 2021;21:949–62.

21. Saraei P, Asadi I, Kakar MA, Moradi-Kor N. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. Cancer Manag Res. 2019;11:3295–313.

22. Singh PP, Shi Q, Foster NR, Grothey A, Nair SG, Chan E, Shields AF, Goldberg RM, Gill S, Kahlenberg MS, Sinicrope FA, Sargent DJ, Alberts SR, Relationship Between Metformin Use and Recurrence and Survival in Patients With Resected Stage III Colon Cancer Receiving Adjuvant Chemotherapy: Results From North Central Cancer Treatment Group N0147 (Alliance), Oncologist, 2016; 21: 1509-1521.

23. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Ann Oncol. 2016;27:2184–95.

24. Miranda VC, Braghiroli MI, Faria LD, Bariani G, Alex A, Bezerra Neto JE, Capareli FC, Sabbaga J, Lobo Dos Santos JF, Hoff PM, Riechelmann RP, Phase 2 Trial of Metformin Combined With 5-Fluorouracil in Patients With Refractory Metastatic Colorectal Cancer, Clin Colorectal Cancer, 2016; 15: 321-328 e321.

Table

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Figures
Figure 1

(A) Outcome of metformin users (n=8) or non-users (n=24) (B) Outcome of metformin users (n=6) or non-users (n=17) who received systemic chemotherapy. Overall survivals (OS) were evaluated using the Kaplan-Meier method and p value was calculated with log-rank test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf