META-ANALYSIS

Meta-Analysis of Metformin on Recurrence Risk and Long-Term Survival in Patients with Diabetes and Renal Cell Carcinoma

Kai Xu, MM; Yinyin Ying, MM

ABSTRACT

Objective • To evaluate the effect of metformin on the survival of patients with diabetes mellitus complicated with renal cell carcinoma by Meta-analysis.

Methods • To collect the required data, we looked through the databases of the Cochrane Library, PubMed, and EMBASE, as well as the network for querying registration data from clinical trials (https://clinicaltrials.gov). Retrieve relevant ongoing or closed clinical trials. To avoid publication bias, the search process is limited to randomized controlled trials, and the search results are not limited to language, publication time, or other restrictions. All included studies need to be evaluated according to the quality evaluation standard of the Cochran system evaluation manual. The relevant data were statistically analyzed by Revman 5.3 software. In the evaluation of overall survival (OS) and progression-free survival (PFS), the index of hazard risk (HR) was selected in this paper.

Results • Eight cohort studies were included in the analysis. Partial and metastatic subgroup analysis of renal cell carcinoma demonstrated no significant effect of metformin on PFS, CSS, or OS. There was no evidence of publication bias, according to the findings.

Conclusion • This systematic review and meta-analysis found that metformin did not improve survival rates for diabetic patients with renal cell carcinoma. (*Altern Ther Health Med.* 2024;30(4):60-65)

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INTRODUCTION

Renal cell carcinoma is a highly malignant and most common tumor in the urinary system. It is a malignant tumor originating from the renal parenchyma and ureteral epithelial system, also known as renal adenocarcinoma, which accounts for roughly 80% to 90% of all kidney cancers.[1] Renal cell carcinoma accounts for 2%-3% of adult malignant tumors and about 20% of genitourinary malignant tumors in China, according to relevant surveys, ranking just behind bladder tumors as the most common genitourinary tumor.[2] The prevalence of renal cell carcinoma is twice as high in men as in women and increases with age, according to available data.[3] According to statistics, the peak age for developing renal cell carcinoma is between 40 and 55. On the other hand, the prevalence of diabetes has grown over time, paralleling the rise of modern society and modern ways of living. It has become another non-infectious chronic disease that endangers human health. At present, the prevalence rate of diabetes is about 11% in China. The effects of diabetes and its complications on patients' health and longevity are tragic. Although the mechanism is unclear, several studies have revealed that people with diabetes have a higher-than-average prevalence of cancer and a poorer-than-average prognosis for their malignancy.[4] It may be related to hyperglycemia, hyperinsulinemia, application of some hypoglycemic agents, or chronic inflammation in diabetic patients. The commonly used hypoglycemic drugs in the clinic include insulin and its analogs; Biguanides, such as metformin; Insulin-secreting agents, such as glibenclamide; α- Glucosidase inhibitors, such as acarbose; Insulin sensitizers, such as pioglitazone.[5] Metformin's favorable hypoglycemic effect, low rate of side effects, and its affordable price have led to its widespread use as a sound therapy for type 2 diabetes.[6]

Many studies have highlighted that the kidney is a targeted organ in patients with diabetes mellitus (DM), which is a common chronic disease in patients with renal cell carcinoma. The prevalence of DM was found to be high in the early-stage renal cell cancer population analyzed by surveillance and SEER (11 190 individuals).[7] At the same

time, the diagnosis of DM is also related to the high probability of renal cell carcinoma. A recent meta-analysis of 97 studies showed that 820 900 patients reported a moderate association between renal cancer mortality and DM diagnosis. Several indicators of poor overall survival of renal cell carcinoma in patients with DM, including tumor recurrence, were found in the Surveillance, Epidemiology, and End Results (SEER) Program database analysis. In contrast, other studies have found that people with DM and renal cell cancer have lengthy lifetimes. It is unclear how DM affects individuals with renal cell carcinoma's long-term prognosis. Some studies have shown that high glucose (Hg) can significantly enhance the proliferation and migration of renal cell carcinoma cells.[8] Metformin is now widely accepted as a first-line therapy option for people with type 2 diabetes (T2DM) and it has even gained international recognition. Evans et al proposed metformin can reduce the incidence of cancer in diabetic patients. The potential antitumor effect of metformin has attracted the attention of researchers at home and abroad. Metformin is a well-tolerated derivative of bi-guanide, which can regulate blood glucose levels and reduce the risk of DM complications.[9] Population-based studies have shown that diabetic patients who take metformin have a better prognosis for cancer treatment and a lower risk of developing cancer. Some in vitro and ex vivo studies have demonstrated the ability of metformin to fight tumor breast, colorectal, and prostate cancer and other tumor cells. The mechanism is that metformin can act on the cell cycle, activate apoptotic signaling pathways, promote apoptosis of cancer cells, or make the cell cycle stagnate, thereby inhibiting the proliferation of tumor cells.[10] Compared with other hypoglycemic drugs, metformin can delay or even reverse the drug resistance of tumors and improve the prognosis of tumor patients. Metformin affected the prognosis of patients with stage II–IV renal cell carcinoma treated with first-line chemotherapy, according to retrospective research. The prognosis of individuals with renal cell carcinoma is still dismal despite advancements in surgical techniques, radiotherapeutic approaches, and novel chemotherapy medicines.[11] Therefore, it is necessary to emphasize the development of new methods to improve the effectiveness of current treatment. Some published studies have reported that metformin treatment can improve the survival of patients with DM; However, many inconsistencies have been found in the existing literature.[12] Therefore, we did a systematic assessment and meta-analysis to offer trustworthy and up-to-date evidence of the effect of metformin treatment on the survival of patients with renal cell carcinoma and further examine its association based on histological subgroups.

METHODS

literature retrieval strategy

We searched the Cochrane Library, PubMed, and EMBASE. Two researchers searched independently from the establishment of the database to September 2016. The retrieval words include metformin, renal cell carcinoma, diabetes mellitus, survival rate, and prognosis. English search terms include "metformin", "renal cell carcinoma", "kidney carcinoma", "survival", and "diagnosis". Subject words and free words work together in the retrieval approach. To avoid publication bias, the search process is limited to randomized controlled trials, and the search results are not limited to language, publication time, or other restrictions. At the same time, we also searched the clinical trial data query registration website (https://clinicaltrials.gov)To retrieve relevant ongoing or closed clinical trials. For the retrieved review literature, further consult the references to avoid missing literature as much as possible.

literature selection and inclusion

Independently, our two researchers screened all the literature. The inclusion criteria were as follows: (1) All patients were untreated patients with renal cell carcinoma; (2) The exposure factor was Metformin; (3) All included studies were randomized controlled prospective studies; (4) The endpoint was the prognosis or mortality of renal cell carcinoma; (5) The literature provides hazard ratio (HR) or other information that can calculate HR, such as Cox regression curve. Before entering the full-text screening link, the two researchers performed a preliminary screening based on the titles, abstracts, and types of studies contained in the aforementioned literature. If the retrieved research does not meet the above requirements, it will be excluded, and the corresponding exclusion reasons will be given. Specific exclusion criteria: (1) Inclusion of randomized controlled prospective clinical studies in patients with non-renal cell carcinoma; (2) Clinical studies that are in progress or whose results have not been published; (3) Clinical studies with repeated publication of research data. If there is any dispute in the process of literature inclusion or exclusion, it shall be judged and decided again after discussion and consultation with a third party.

Data extraction and literature evaluation

Cochrane's Handbook for Systematic Reviews of Interventions states that when assessing the quality of included studies, researchers should look for things like randomization, allocation concealment, blinding, data integrity, selective reporting of results, and other types of bias (such as premature study termination, obvious imbalance of baseline level, etc.). When evaluating each standard, "low risk", "high risk" and "unknown" are adopted. In case of any dispute during the evaluation, it shall be judged and decided again after discussion and consultation with a third party. The data were extracted by two researchers using pre-designed tables. The extracted contents include the first author of the study, publication year, study design type, sample size, average age, renal cancer type, tissue type, treatment plan, etc. The New Castle Ottawa standard is adopted for literature quality evaluation. If there is any inconsistency in the evaluation, it shall be decided through discussion.

Figure 1. The literature search process

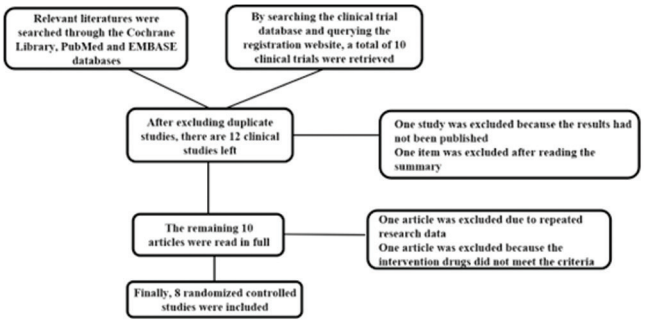


Figure 2. Risk of bias plot for quality evaluation according to various criteria

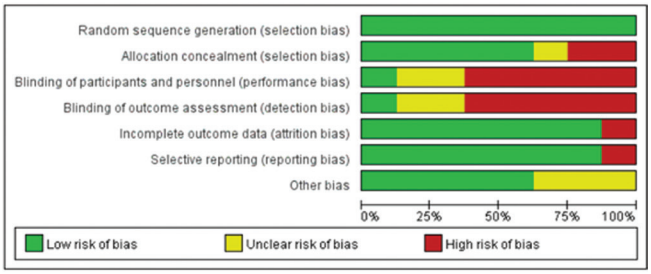
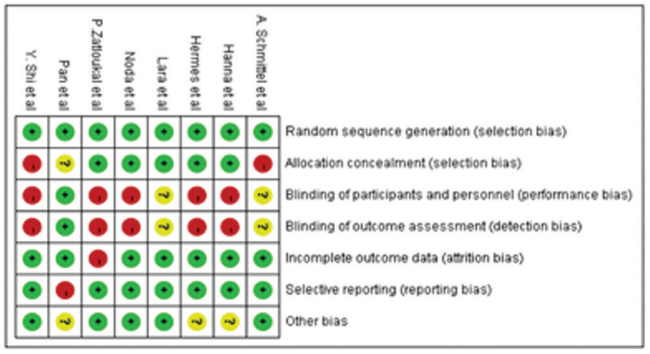


Figure 3. A detailed diagram depicting the outcomes of the quality assessment of the included studies



Definition of outcome indicators

Time to disease recurrence, death, or loss of follow-up after nephrectomy is called progression-free survival (PFS). Chronological survival (CSS) measures how long someone lives after receiving a diagnosis of renal cell carcinoma. OS measures how long it takes from when metformin treatment begins until the patient either dies or is lost to follow-up.

Statistical analysis

We pooled the HR values obtained after adjusting for the most influential confounders across studies to determine the overall HR and 95% CI. The I^2 test was employed to assess the degree of variation between studies. When the degree of heterogeneity was high enough to warrant its use ($I^2 > 50\%$), a random-effects model was employed. Otherwise, a model with fixed effects was employed. Overall effect values were also assessed using sensitivity analysis. For time event data such as PFS and OS, we use HR as the evaluation index; For binary variables such as disease control rate (DCR), we use risk ratio (RR) as the effect scale index. If the risk ratio of OS and PFS in the study cannot be obtained directly from the literature, relevant important data shall be extracted from the given survival curve, and the HR shall be calculated by using Engauge Digitizer version 4.1 software. We believe that when HR > 1, more death or disease progression occurred in the IP group; RR > 1 indicates that more related events have occurred in the IP group. Use Review Manager 5.3 to complete the above analysis.

RESULTS

literature search results

A total of 1060 articles as well as 7 clinical trials were retrieved. Duplicate studies were excluded based on the inclusion and exclusion criteria, and then those that were not relevant to the study were excluded by crisping the title and abstract, and then those that were in the study or whose status and results were unknown were also excluded. The remaining 39 articles were read in full. Finally, a total of 2089 patients were included in 8 articles, which had been published from 2002 to 2015. The flow chart of literature searches and screening is shown in Figure 1.

Characteristics of our study subjects

The median follow-up time was about 8 ~ 120 months. Volumes varied from 283 and 4468 in the sample. Participants' average ages differed from 59 to 67. Most studies corrected for the effects of common confounding factors, including gender, age, tumor stage, and so on. Two studies were aimed at patients with local renal cancer, one study was aimed at patients with metastatic renal cancer. More, there was one study that involved both types of patients, while the type of kidney carcinoma was not specified in one study. The full score of literature quality evaluation is 9, and the score of each study is 7 or more.

Quality evaluation results included in the study

As for the above research methods, according to the requirements of Cochran's system evaluation manual, we assessed how well the studies generated random sequences, hid distributions, used blinded settings, and reported their findings. Two researchers agreed that the overall quality of the included studies matched that of the systematic review and meta-analysis. The generation of random sequences in the included studies was evaluated as "low risk"; Two studies were rated as "high risk", one study was "unknown", and the rest were rated as "low risk". In terms of blind setting, four studies were served as "high risk", while there being two studies were evaluated as "unknown", and the rest were "low risk"; Only one study was rated as "high risk" in terms of completeness of outcome data and selective reporting of results, and the rest as "low risk"; Three studies had "unknown" other biases.

Effect of metformin upon progression-free survival in patients who had kidney cancer

A random-effects model was used because of significant inter-study heterogeneity. After summarizing the full HR values, it was found that metformin did not significantly

Figure 4. Effect of metformin upon progression-free survival in patients who had kidney cancer

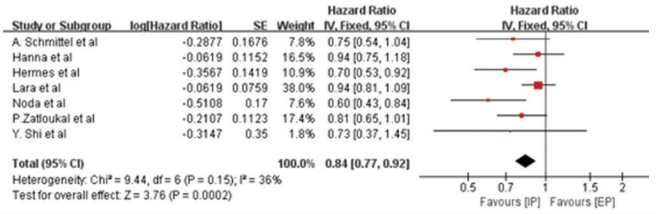


Figure 5. Effect of Metformin on cancer-related Survival in patients suffering from Kidney Cancer

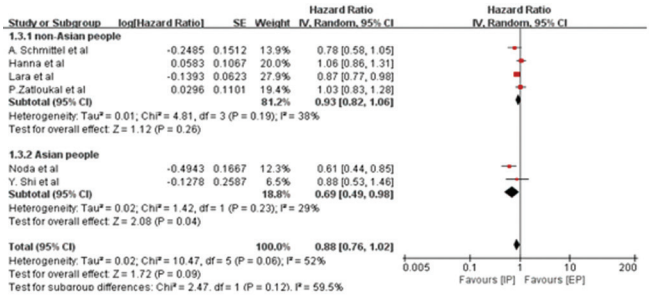
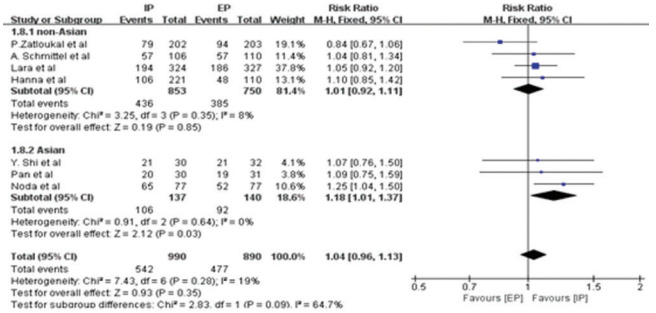


Figure 6. Metformin's impact on overall survival for kidney cancer patients



improve progression-free survival in patients with kidney cancer, regardless of metastasis or not. Sensitivity analysis found that the combined effect was still not statistically significant after excluding four studies.

Effect of Metformin on cancer-related Survival in patients suffering from Kidney Cancer

When analyzing CSS, five studies were included and divided into local and metastatic subgroups. The random effect model was utilized because of the substantial heterogeneity among the investigations. After summarizing all HR values, metformin did not significantly improve the cancer-related survival rate of patients with renal cancer, regardless of metastasis or not. Sensitivity analysis found that after excluding Psutka SP, there was a statistically significant aggregate effect. The overall effect was not statistically significant once the other four trials were removed.

Metformin's impact on overall survival for kidney cancer patients

Three studies were included in the analysis of OS, and the data were split into local and metastatic subgroups. The fixed effect model was utilized due to the lack of heterogeneity between trials. The overall survival rate of patients with kidney carcinoma, regardless of metastasis, was not significantly improved by metformin after summing all HR values. After excluding the influence of Psutka SP, the overall effect was still shown to be statistically significant. When the other three trials were taken out, the overall effect was not significant.

DISCUSSION

Metformin is a widely used first-line treatment for type 2 diabetes. However, as a multidrug, it can also modulate many diseases, including cancer, in addition to its hypoglycemic effect. Metformin has been linked to potential cancer-fighting effects in several studies, and the return visit survey also found that metformin can benefit some cancer patients. Researchers explored the effect of metformin on the survival rate of breast cancer and analyzed the clinical outcomes of 1215 breast cancer patients who underwent surgery from 1997 to 2013. 97 of them used metformin before being diagnosed, and 97 patients began using metformin after being diagnosed. Patients who used metformin before diagnosis had a 50% higher risk of dying compared to those who had never taken metformin, whereas those who started metformin after diagnosis had a 25% higher chance of surviving.[13] The use of metformin as a cancer prevention strategy has been controversial, and the relevant research results are inconsistent, but more analysis shows that the use of metformin is time-dependent. Some breast cancer patients may benefit from metformin, but those with breast cancer who use metformin before diagnosis may have more aggressive subtypes of cancer. This indicates the complexity of the interaction between basal metabolic risk and breast cancer outcomes and highlights the importance of multi-system cancer treatment. The results also showed that patients who used metformin were more likely to be diagnosed with cancer after the age of 50. However, in all the experimental groups, tumor size and disease progression were similar. Patients who took metformin after diagnosis were more likely to develop ER/PR-positive tumors, while those with metformin before diagnosis had a higher probability of having Her2+ and three negative breast cancers.[14] The study authors feel more investigation into metformin's impact on cancer recurrence is warranted. However, researchers believe that there is convincing biological evidence that the difference in tumor markers between breast cancer is related to the difference in tumor initiation mechanism in patients taking metformin.

Renal cell carcinoma is becoming more common every year in the global population. Although early detection is possible, there has been little improvement in survival rates. Multiple studies have also demonstrated that diabetes is a negative prognostic factor in renal cell carcinoma patients. Therefore, the treatment of diabetes may improve the survival of patients with renal cell carcinoma. Metformin is a first-line treatment for diabetes and has been shown to increase the

survival rate of several malignancies.[15] There is evidence that both insulin-dependent and insulin-independent mechanisms contribute to metformin's anticancer effect, but the precise mechanism is still unclear. Metformin inhibited cell proliferation in a time- and concentration-dependent manner, inhibited cell clone formation in a concentration-dependent manner, and induced cell cycle arrest in in vitro studies of renal cell carcinoma. In addition, the study also found that mice transplanted with metformin significantly reduced the size of the tumor. Although laboratory data indicate that metformin may have a potential therapeutic benefit for renal cell carcinoma, observational studies assessing the impact of metformin application upon survival have yielded conflicting results.[16]

The first published study was conducted by Hakimi AA and others to evaluate the relationship between the application of metformin and the survival results of 784 patients with renal cancer, of which 55 patients were treated with metformin. In this study, the patients involved fell within the categories of pT2 and pT3. The results showed that the application of metformin during surgery had a bad effect on DFS, but was beneficial to CSS.[17] However, there was no statistical significance between these associations. So it is very important to point out that this group of people is not limited to diabetes. Metformin users include all people with diabetes, while non-diabetic users include both people with and without diabetes; this suggests that diabetes may affect how long people with kidney carcinoma live. Psutka SP explored the correlation between metformin and survival outcomes in patients with renal cell carcinoma. The results expressed that metformin was more effective in renal cancer, but did not prolong survival. The number of patients treated with metformin reached 83. Two prospective randomized trials were conducted in these patients to assess changes in renal function and the occurrence of serious complications after treatment. Similar to the first study, the use of metformin did not exhibit statistically significant differences with DFS, CSS, and OS. The multifactor model variables in this investigation were chosen sequentially. So this result may be due to the lack of sample size. There are several problems with the choice of independent variables, which limits the comprehensive interpretation of the results shown by metformin users. A recent study by Cheng s et al. suggests that metformin showed significant efficacy in treating DFS and CSS in patients with localized renal cell carcinoma, yet in those with metastases, its efficacy was not as good. This study was adjusted for the karakiewicz score only. Although this assessment metric covers critical predictive variables, it does not take into account other predictive factors such as age and gender.[18]

The study conducted by Madhur Nayan et al. was not the first study to assess the relationship between metformin and renal cell carcinoma outcomes, but it was the first to apply a propensity score. The propensity score approach reduces the effect of confounding factors. Of course, this study has several limitations: first, it is an observational study, so it cannot prove causality; second, the study will have limitations due to its small sample size. Therefore, considering the prevalence of diabetes in treated renal cell carcinoma patients and the prevalence of metformin use in these patients as well, a multicenter or multi-population-based study may result in a larger population. Third, the exposure group was divided into different groups depending on whether metformin was administered after surgery.[19] Maybe some patients did not use metformin continuously after the operation, while those who were divided into non-metformin groups began to use metformin after the operation. But these problems are difficult for us to avoid. Despite the many limitations, however, the propensity to use score is consistent with previous studies indicating that the use of metformin is not effective in improving survival in diabetic patients after nephrectomy for nephrocalcinoma.

The lack of a beneficial therapeutic benefit of metformin in individuals with renal cell carcinoma is consistent with the majority of research. Perhaps the lack of sample size is the main reason, but at the same time, in the process of grouping, the random dressing change or intermittent withdrawal of patients may also be the factor affecting the difference between groups. Therefore, if we want to get results consistent with laboratory data, we may need a more rigorous clinical design and a larger sample of multi-center clinical research.

CONCLUSION

This systematic review and meta-analysis found that metformin did not improve survival rates for patients with renal cell carcinoma.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

FUNDING SOURCES

There are no funding sources to declare.

REFERENCE

1. Liu XD, Kong W, Peterson CB, et al. PBRM1 loss defines a nonimmunogenic tumor phenotype associated with checkpoint inhibitor resistance in renal carcinoma. *Nat Commun*. 2020;11(1):2135. doi:10.1038/s41467-020-15959-6
2. Teng L, Chen Y, Cao Y, et al. Overexpression of ATP citrate lyase in renal cell carcinoma tissues and its effect on the human renal carcinoma cells *in vitro*. *Oncol Lett*. 2018;15(5):6967-6974. doi:10.3892/ol.2018.8211
3. Mennitto A, Huber V, Ratta R, et al. Angiogenesis and Immunity in Renal Carcinoma: Can We Turn an Unhappy Relationship into a Happy Marriage? *J Clin Med*. 2020;9(4):930. doi:10.3390/jcm9040930
4. Syafruddin SE, Rodrigues P, Vojtasova E, et al. A KLF6-driven transcriptional network links lipid homeostasis and tumour growth in renal carcinoma. *Nat Commun*. 2019;10(1):1152. doi:10.1038/s41467-019-09116-x
5. Xiong Y, Zhang J, Song C. CircRNA ZNF609 functions as a competitive endogenous RNA to regulate FOXP4 expression by sponging miR-138-5p in renal carcinoma. *J Cell Physiol*. 2019;234(7):10646-10654. doi:10.1002/jcp.27744
6. Gao W, Li W, Xiao T, Liu XS, Kaelin WG Jr. Inactivation of the PBRM1 tumor suppressor gene amplifies the HIF-response in VHL-/- clear cell renal carcinoma. *Proc Natl Acad Sci USA*. 2017;114(5):1027-1032. doi:10.1073/pnas.1619726114
7. Liu J, Li M, Song B, et al. Metformin inhibits renal cell carcinoma in vitro and in vivo xenograft. *Urol Oncol*. 2013;31(2):264-270. doi:10.1016/j.urolonc.2011.01.003
8. Li Y, Hu L, Xia Q, Yuan Y, Mi Y. The impact of metformin use on survival in kidney cancer patients with diabetes: a meta-analysis. *Int Urol Nephrol*. 2017;49(6):975-981. doi:10.1007/s11255-017-1548-4
9. Hamieh L, McKay RR, Lin X, Moreira RB, Simantov R, Choueiri TK. Effect of Metformin Use on Survival Outcomes in Patients With Metastatic Renal Cell Carcinoma. *Clin Genitourin Cancer*. 2017;15(2):221-229. doi:10.1016/j.clgc.2016.06.017
10. Hakimi AA, Chen L, Kim PH, et al. The impact of metformin use on recurrence and cancer-specific survival in clinically localized high-risk renal cell carcinoma. *Can Urol Assoc J*. 2013;7(11-12):E687-E691. doi:10.5489/cuaj.1447

11. Kalogirou C, Schäfer D, Krebs M, et al. Metformin-Derived Growth Inhibition in Renal Cell Carcinoma Depends on miR-21-Mediated PTEN Expression. *Urol Int*. 2016;96(1):106-115. doi:10.1159/000441011
12. Psutka SP, Boorjian SA, Lohse CM, et al. The association between metformin use and oncologic outcomes among surgically treated diabetic patients with localized renal cell carcinoma. *Urol Oncol*. 2015;33(2):67.e15-67.e23. doi:10.1016/j.urolonc.2014.07.008
13. Li M, Liu J, Hu W, et al. [Effect of Metformin on Apoptosis of Renal Cell Carcinoma Cells in Vitro and Its Mechanisms]. *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University*. 2011;31(9):1504-1508. Accessed September 30, 2023. https://pubmed.ncbi.nlm.nih.gov/21945753/
14. Keizman D, Ish-Shalom M, Sella A, et al. Metformin Use and Outcome of Sunitinib Treatment in Patients With Diabetes and Metastatic Renal Cell Carcinoma. *Clin Genitourin Cancer*. 2016;14(5):420-425. doi:10.1016/j.clgc.2016.04.012
15. Wei M, Mao S, Lu G, et al. Valproic acid sensitizes metformin-resistant human renal cell carcinoma cells by upregulating H3 acetylation and EMT reversal. *BMC Cancer*. 2018;18(1):434. doi:10.1186/s12885-018-4344-3
16. Jang JH, Song IH, Sung EG, Lee TJ, Kim JY. Metformin-induced apoptosis facilitates degradation of the cellular caspase 8 (FLICE)-like inhibitory protein through a caspase-dependent pathway in human renal cell carcinoma A498 cells. *Oncol Lett*. 2018;16(2):2030-2038. doi:10.3892/ol.2018.8832
17. Nayan M, Finelli A, Jewett MAS, et al. Metformin Use and Kidney Cancer Outcomes in Patients With Diabetes: A Propensity Score Analysis. *Clin Genitourin Cancer*. 2017;15(2):300-305. doi:10.1016/j.clgc.2016.06.008
18. Zhang X, Zhang X, Huang T, Geng J, Liu M, Zheng J. Combination of metformin and valproic acid synergistically induces cell cycle arrest and apoptosis in clear cell renal cell carcinoma. *Int J Clin Exp Pathol*. 2015;8(3):2823-2828. Accessed September 30, 2023. https://pubmed.ncbi.nlm.nih.gov/26045790/
19. Cai X, Hu X, Cai B, et al. Metformin suppresses hepatocellular carcinoma cell growth through induction of cell cycle G1/G0 phase arrest and p21CIP and p27KIP expression and downregulation of cyclin D1 in vitro and in vivo. *Oncol Rep*. 2013;30(5):2449-2457. doi:10.3892/or.2013.2718