

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2021 September 15; 13(9): 980-1212



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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJGO as 3.393; IF without journal self cites: 3.333; 5-year IF: 3.519; Journal Citation Indicator: 0.5; Ranking: 163 among 242 journals in oncology; Quartile category: Q3; Ranking: 60 among 92 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2020 is 3.3 and Scopus CiteScore rank 2020: Gastroenterology is 70/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*, Production Department Director: *Xiang Li*, Editorial Office Director: *Ya-Juan Ma*.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rosa M Jimenez Rodriguez, Pashtoon Kasi, Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

September 15, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Effect of oncometabolic surgery on gastric cancer: The remission of hypertension, type 2 diabetes mellitus, and beyond

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Author contributions: Cheng YX and Peng D contributed equally to this work; Zhang Wei conducted quality evaluation; Peng D and Cheng YX conducted data extraction; Tao Wei conducted figure painting; Cheng YX wrote the manuscript; Peng D, Cheng YX, Tao W and Zhang W conducted writing review and editing; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests.

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Abstract

This review summarizes the definition and surgical methods of oncometabolic surgery according to previous studies. Then, the authors discuss the beneficial effects observed after gastrectomy in gastric cancer (GC) patients with concurrent hypertension or type 2 diabetes mellitus (T2DM). The authors summarize the current studies analyzing the remission rate and the hypotheses of the mechanisms underlying these effects. The remission rate ranged from 42.5%-65.4% in T2DM patients and from 11.1%-57.6% among those with hypertension. Furthermore, the remission of T2DM could have an impact on overall survival rates as well. The mechanisms underlying the remission of hypertension and T2DM is unclear in current studies, but oncometabolic surgery is expected to be applied in clinical practice. In addition, the effect of oncometabolic surgery on other chronic metabolic comorbidities is expected to be proven in further studies. Therefore, the purpose of this review is to discuss the effects of oncometabolic surgery reported in current studies with a primary focus on the remission of hypertension and T2DM after gastrectomy in GC patients. The possibility of the remission of other metabolic comorbidities in GC patients who undergo oncometabolic surgery is also discussed.

Key Words: Gastric cancer; Type 2 diabetes mellitus; Hypertension; Remission; Oncometabolic surgery

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Core Tip: The purpose of this review is to discuss the effects of oncometabolic surgery observed in current studies, mainly including the remission of hypertension and type 2 diabetes mellitus after gastrectomy in gastric cancer (GC) patients, and to evaluate the possibility of the remission of other metabolic comorbidities in GC patients who

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Manuscript source: Invited manuscript**Specialty type:** Oncology**Country/Territory of origin:** China**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: May 27, 2021**Peer-review started:** May 27, 2021**First decision:** June 16, 2021**Revised:** June 24, 2021**Accepted:** July 29, 2021**Article in press:** July 29, 2021**Published online:** September 15, 2021**P-Reviewer:** Papazafiropoulou A, Salman A**S-Editor:** Fan JR**L-Editor:** A**P-Editor:** Ma YJ

undergo oncometabolic surgery.

Citation: Cheng YX, Peng D, Tao W, Zhang W. Effect of oncometabolic surgery on gastric cancer: The remission of hypertension, type 2 diabetes mellitus, and beyond. *World J Gastrointest Oncol* 2021; 13(9): 1157-1163**URL:** <https://www.wjgnet.com/1948-5204/full/v13/i9/1157.htm>**DOI:** <https://dx.doi.org/10.4251/wjgo.v13.i9.1157>

INTRODUCTION

Gastric cancer (GC) is the second most common digestive system cancer. As estimated by GLOBOCAN in 2018, the incidence of GC ranks fifth among all cancers, with 1 million new cases and 780 thousand deaths worldwide[1]. Radical resection plus standardized D2 Lymphadenectomy is the standard method for curative intention[2]. The 5-year survival rate of early GC patients has reached 90%, causing concern about these patients' quality of life after gastrectomy[3,4]. With the number of cancer-related deaths decreasing among postoperative GC patients, the control of chronic diseases has become another medical concern.

The initial and obvious purpose of bariatric surgery is to achieve weight loss and maintenance[5]. However, morbid obesity drastically elevates the risk of some chronic metabolic comorbidities, especially the most common diseases including hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, sleep apnea, and so on[6]. It has rapidly come under observation that bariatric surgery is effective in treating metabolic comorbidities in obese patients[7,8]. A meta-analysis including eleven randomized controlled trials reported by Cummings and Cohen provided class 1A evidence demonstrating the effect of bariatric surgery on T2DM remission[9]. Thus, the concept of metabolic bariatric surgery is gradually being developed.

To our knowledge, the extent of gastrectomy and reconstruction methods in bariatric surgery has a strong level of similarity with that in gastrectomy of GC patients. Therefore, surgeons began to pay close attention to the remission of hypertension or T2DM after gastrectomy in patients who suffer from concurrent GC and metabolic comorbidities[10,11]. Fortunately, this hypothesis was proposed in some previous studies of oncometabolic surgery[12,13]. It has been reported that insulin resistance improves and fasting blood glucose returns to normal after gastrectomy, although controversy regarding the mechanism underlying this remission still exists[14]. There was a retrospective study of 143 patients in which the hypertension remission rate after gastrectomy was evaluated[15], and it was relatively less than the T2DM remission rate reported in previous studies.

Although limited studies exist, the potential of oncometabolic surgery is nonnegligible. Therefore, the purpose of this review is to discuss the effect of oncometabolic surgery based on current studies, mainly including the remission of hypertension and T2DM after gastrectomy in GC patients, and to evaluate the possibility of the remission of other metabolic comorbidities in patients who undergo oncometabolic surgery.

CONCEPT OF ONCOMETABOLIC SURGERY

Oncometabolic surgery is a single operation that not only achieves tumor radical resection but also controls metabolic diseases, including hypertension and T2DM[10,16]. The extent of gastrectomy includes total gastrectomy and subtotal gastrectomy, and the reconstruction methods consist of Billroth I (B-I), Billroth II (B-II) and Roux-en-Y (RY) reconstruction (Figure 1). In a previous study, it was demonstrated that total gastrectomy with RY reconstruction had the highest remission rate[17]. In addition, Peng *et al*[18] considered that only the extent of gastrectomy influenced T2DM remission[18]. Similarly, Wang *et al*[19] found that total gastrectomy itself was closely related to hypertension remission[19]. Park *et al*[20] considered that long-limb RY reconstruction, which is closely associated with RY gastric bypass, was oncometabolic surgery[20]. However, we considered total gastrectomy and subtotal gastrectomy with all reconstruction methods, including B-I reconstruction, B-II reconstruction, RY

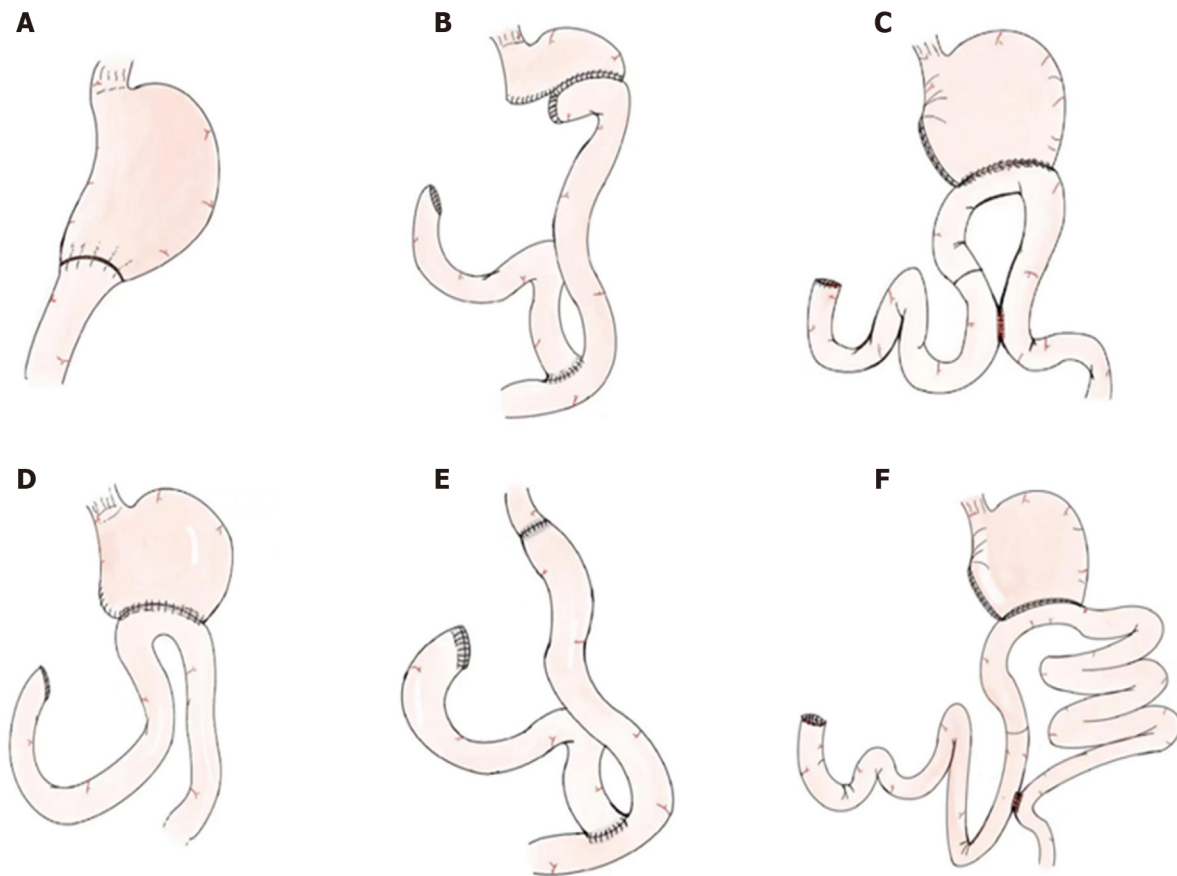


Figure 1 Schematic illustration of gastrectomy and reconstruction methods. A: Distal gastrectomy with Billroth I reconstruction; B: Distal gastrectomy with Roux-en-Y reconstruction; C: Distal gastrectomy with conventional uncut Roux-en-Y gastrojejunostomy; D: Distal gastrectomy with Billroth II reconstruction; E: Total gastrectomy with Roux-en-Y reconstruction; F: Distal gastrectomy with long-limb uncut Roux-en-Y gastrojejunostomy.

reconstruction, conventional uncut RY gastrojejunostomy, and long-limb uncut RY gastrojejunostomy, as oncometabolic surgeries.

T2DM REMISSION

GC patients can experience T2DM remission after gastrectomy, and the remission rate ranges from 42.5%-65.4% (Table 1)[13,14,17,21-26]. However, the factors predicting T2DM remission remain unclear. An *et al*[13] suggested that the degree of T2DM control was related to its duration[13]. Kim *et al*[17] analyzed the records of 385 patients and concluded that body mass index reduction was significantly correlated with T2DM remission. Total gastrectomy with RY reconstruction was reported to lead to higher remission rates than other surgical methods, however, whether the extent of gastrectomy or the reconstruction method played an important role in T2DM remission remains controversial[17]. Wang *et al*[21] reported that the extent of gastrectomy rather than the reconstruction method was the key factor affecting T2DM remission[21], but Choi *et al*[22] suggested that RY reconstruction played an important role in T2DM remission[22]. Peng *et al*[18] conducted a meta-analysis and reported that the extent of gastrectomy rather than the reconstruction method might play an important role in T2DM remission after gastrectomy in patients with GC[18]. However, there were only three studies in the subgroup analysis about the extent of gastrectomy on T2DM remission; therefore, the results might not be robust[17,18,21].

The remission of T2DM could also have an impact on overall survival. Wei *et al*[23] compared a remission group with a non-remission group and found that recovery from pre-existing T2DM after radical gastrectomy was associated with better overall survival; however, the study included only 67 patients, and larger studies are needed in the future[23].

The mechanism underlying T2DM remission after gastrectomy is unclear, but bariatric surgery might contribute to T2DM remission in a similar way. T2DM

Table 1 Oncometabolic surgery on type 2 diabetes

Ref.	Surgery	Sample size	CR + PR	CR	PR	Follow-up (mo)
Lee <i>et al</i> [14], 2012	RYTG, BI, BII, RYGJ	229	56.8%	19.7%	37.1%	NA
An <i>et al</i> [13], 2013	RYTG, BI, BII	64	57.8%	3.1%	54.7%	12
Wang <i>et al</i> [19], 2020	RYTG, BI, BII, RYGJ	69	43.5%	13.0%	30.5%	NA
Wei <i>et al</i> [23], 2014	RYTG, BII	67	59.7%	26.9%	32.8%	57.4
Kim <i>et al</i> [17], 2012	RYTG, BI, BII	385	45.5%	15.1%	30.4%	33.7
Zhu <i>et al</i> [24], 2015	RYTG, BI, BII	292	65.4%	55.5%	9.9%	24
Choi <i>et al</i> [22], 2017	RYTG, BI	40	42.5%	2.5%	40.0%	12
Kim <i>et al</i> [25], 2020	LLBR, BII	226	52.2%	4.9%	47.3%	12
Park <i>et al</i> [20], 2020	RYTG, BI, BII, RYGJ	52	63.5%	NA	NA	12

CR: Complete remission; PR: Partial remission; RYTG: Roux-en-Y total gastrectomy; BI: Billroth I reconstruction; BII: Billroth II reconstruction; RYGJ: Subtotal gastrectomy with Roux-en-Y gastrojejunostomy reconstruction; LLBR: Long-limb bypass reconstruction; NA: Not available.

remission was related to lifestyle changes, including decreased food intake, reduced body weight and intestinal malabsorption. Several theories explaining T2DM remission beyond lifestyle changes have been proposed. The foregut theory states that patients undergoing duodenal bypass experience anti-diabetic effects, and the hindgut theory states that early contact of unabsorbed nutrients with the distal intestine improves T2DM. Furthermore, hormones, including ghrelin, glucagon-like peptide (GLP)-1 and GLP-2, can influence T2DM remission.

HYPERTENSION REMISSION

GC patients also experience hypertension remission after gastrectomy. Peng *et al*[15] conducted a retrospective study of 143 patients who underwent gastrectomy and the resulting effects on hypertension and found that the hypertension complete remission rate was 55.3%. In addition, age and total gastrectomy were predictors of hypertension remission 6 mo after gastrectomy[15]. Wang *et al*[19] compared hypertension remission between total gastrectomy and subtotal gastrectomy in non-obese non-diabetic GC patients and found that total gastrectomy itself, beyond weight loss, was associated with hypertension remission[19]. Another study included 33 patients and found that 14 patients experienced hypertension remission 1 year after gastrectomy [20]. Kim *et al*[27] reported on 66 early GC patients undergoing gastrectomy and endoscopic submucosal dissection and found that the hypertension remission rate was 57.6%, and gastrectomy was a predictor of hypertension remission 1 year after surgery [27]. Lee *et al*[12] reported the largest number of patients ($n = 351$) from nationwide data, and after a follow-up of 36.7 mo, only 11.1% of patients experienced hypertension remission; however, the results analyzed were based on nationwide data, and limited baseline information was available[12]. Therefore, the hypertension remission rate after gastrectomy was 11.1%-57.6% (Table 2), and Peng *et al*[15] proposed that total gastrectomy is an oncometabolic surgery that can cure younger patients with concurrent GC and hypertension[15].

There were some limitations because of the limited number of studies. Previous studies reported on the remission of hypertension; however, the follow-up time was short, and hypertension might reoccur in long term follow-up. In addition, the improvement of sodium absorption dysfunction, instead of weight loss, might be the factor leading to better management of blood pressure. However, no studies have reported the lifestyle factors of patients after gastrectomy, including physical exercise, drinking and smoking, and these lifestyle factors might also play an important role in hypertension remission.

Furthermore, the mechanism underlying hypertension remission is still unknown. It is hypothesized that the levels of some hormones, such as renin, angiotensin II, aldosterone, adiponectin, GLP-1, and tumor necrosis factor, might cause blood pressure fluctuations. However, a previous study found no difference in serum levels of these indicators before and after surgery. Thus, more experiments need to be carried

Table 2 Oncometabolic surgery on hypertension

Ref.	Country	Surgery	Sample size	CR + PR	CR	PR	Follow-up (mo)
Peng <i>et al</i> [15], 2020	China	RYTG, BI, BII, RYGJ	143	55.3%	46.9%	8.4%	6
Wang <i>et al</i> [21], 2014	China	RYTG, RYGJ	16	93.8%	100%	87.5%	12
Park <i>et al</i> [26], 2017	Korea	uRYGJ, LLBR	33	42.4%	NA	NA	12
Kim <i>et al</i> [27], 2019	Korea	RYTG, BI, BII, RYGJ	66	57.6%	45.5%	12.1%	12
Lee <i>et al</i> [28], 2017	Korea	RYTG, BI, BII, RYGJ	351	11.1%	NA	NA	36.7

CR: Complete remission; PR: Partial remission; RYTG: Roux-en-Y total gastrectomy; BII: Billroth II reconstruction; BI: Billroth I reconstruction; RYGJ: Subtotal gastrectomy with Roux-en-Y gastrojejunostomy reconstruction; uRYGJ: Subtotal gastrectomy with uncut Roux-en-Y gastrojejunostomy reconstruction; LLBR: Long-limb bypass reconstruction; NA: Not available.

out in the future.

FUTURE PERSPECTIVE

Evidence for the effects of bariatric surgery (also referred to as metabolic surgery) on T2DM remission has been demonstrated in previous studies. Metabolic surgery is expected to become an alternative for the treatment of T2DM in the future, instead being used only for weight loss[28]. Similarly, it is notable that gastrectomy has the same metabolic effect as bariatric surgery on patients with concurrent GC and metabolic comorbidities. Thus, oncometabolic surgery, which has been considered a developing concept in recent years, has the ability to improve the quality of life of patients with metabolic comorbidities[10,16]. Surgeons continuously improve traditional gastrectomy techniques to benefit patients. T2DM remission after gastrectomy has been found to be associated with better overall survival outcomes [23], but there is no previous evidence demonstrating a relationship between hypertension remission and overall survival outcomes. Short follow-up times are the current obstacle to the observation of the remission of comorbidities that may influence long-term survival rates after gastrectomy.

In addition, the focus of attention in oncometabolic surgery research has been T2DM rather than hypertension or other metabolic comorbidities. The effects of oncometabolic surgery on other metabolic comorbidities, such as fatty liver disease, hyperglycemia and hyperosmotic syndrome, leukodystrophy, hyperlipidemia, gout, and osteoporosis, are expected to be evaluated in the future. With the maturation of the concept of oncometabolic surgery, the opportunity to treat both GC and metabolic diseases through a single operation is possible. Therefore, a larger sample size and basic medical experiments are needed in future research.

CONCLUSION

With the maturation of the concept of oncometabolic surgery, the opportunity to treat both GC and metabolic diseases through a single operation is possible.

ACKNOWLEDGEMENTS

We acknowledge all the authors whose publications are referred in our article.

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