Reply to the reviewers' comments

Dear Editor-in-Chief,

We thank you for your decision letter for our manuscript entitled "**Appraisal of gastric stump carcinoma and current state of affairs**". We have considered the reviewer's comments and provide below a point-by-point answer to each of them. Changes have been incorporated and highlighted in the revised manuscript. We are grateful to the reviewers for their comments which have helped us improve the manuscript. We hope that you will find this revised version suitable for publication in your esteemed journal.

With kind regards,

Authors

Response to comments

Reviewer 1

This topic is very well presented. This material will be a good basis for the development of modern methods of treatment and prevention of gastric stump carcinoma. The article is recommended for publication.

Reviewer 2

1. **The clinical data of cancer should be updated using data most recently.**
   As suggested by the reviewer, the clinical data has been updated.

2. **If the "diagnosis" could be a independent part would be better.**

   Diagnosis has been put as an independent part as suggested.

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Running Title: Gastric stump carcinoma

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Author contributions:

All the authors did the literature search. Ankit Shukla wrote the first draft of the review. Raja Kalayarasan conceptualized the work, supervised the writing, gave intellectual inputs. All the authors critically revised the manuscript.

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Review article

Appraisal of gastric stump carcinoma and current state of affairs

Abstract

Gastric stump carcinoma, also known as remnant gastric carcinoma, is a malignancy arising in the remnant stomach following gastrectomy for a benign or malignant condition. Enterogastric reflux and preexisting risk factors in a patient with gastric cancer are the major contributors to the development of gastric stump carcinoma. The occurrence of gastric stump carcinoma is time-dependent and seen earlier in patients operated on for malignant rather than benign diseases. The tumor location is predominantly at the anastomotic site towards the stomach. However, it can occur anywhere in the remnant stomach. The pattern of lymph node involvement and the type of surgery required is distinctly different compared to primary gastric cancer. Gastric stump carcinoma is traditionally considered a malignancy with a dismal outcome. However, recent advances in diagnostic and therapeutic strategies have improved outcomes. Recent advances in molecular profiling of gastric stump carcinoma have identified distinct molecular subtypes, thereby providing novel therapeutic targets. Also, reports of gastric stump carcinoma following pancreatoduodenectomy and bariatric surgery highlight the need for more research to standardize the diagnosis, staging, and treatment of these tumors. The present review aims to provide an overview of gastric stump carcinoma highlighting the differences in clinicopathological profile and management compared to primary gastric carcinoma.

Keywords: Gastric cancer; Gastritis; Carcinoma; Endoscopic surveillance; Gastric stump cancer; Remnant gastric carcinoma

Core tip: Gastric stump carcinoma is a rare malignancy with many unanswered questions regarding precise staging, molecular subtyping, and surgical management. The spectrum of its incidence is changing due to better medical management of peptic ulcer disease, increased survival of patients with malignancies, and malignancy in gastric stump following various other surgeries. The altered pattern of lymphatic spread deems further research to develop a newer staging system. Endoscopic surveillance with early gastric stump carcinoma detection made endoscopic resection and minimally invasive surgery feasible in selected patients with improved quality of life.

Introduction

Gastric carcinoma, with an incidence of 5.6 % and mortality of 7.7%, ranks fifth in incidence and fourth in mortality among all cancers, making it a worldwide health problem[1]. On the other hand, gastric stump or remnant gastric carcinoma is a less common entity and accounts for 2 to 6% of all gastric carcinoma and a pooled prevalence of 2.6%[2,3]. In 1922, Donald Church Balfour, a Canadian surgeon, first observed that patients undergoing gastric surgery for peptic ulcer disease had decreased survival due to the development of malignancy in the remnant stomach [4]. There has been a steady rise in gastric stump carcinoma from 1970 to the late twentieth century [5]. However, with a paradigm shift in the management of peptic ulcers to medical therapy, there is a decrease in the incidence of gastric stump carcinoma following benign disease. Surgical and systemic treatment advances have improved the postoperative survival of gastric carcinoma patients and those with pancreatic cancer who share similar risk factors due to changes in gastrointestinal continuity[5-7]. Also, screening programs for gastric cancer in high-incidence areas allowed early detection and better management of early gastric carcinoma. These factors could potentially increase the incidence of gastric stump carcinoma. Also, reports of gastric stump carcinoma in patients undergoing bariatric surgery could further increase the incidence of gastric stump carcinoma[8,9]. Compared to primary gastric carcinoma, gastric stump carcinoma is usually described as a malignancy with a dismal outcome with low resectability rates. The present review aims to highlight etiopathogenesis, the differences in the clinicopathological features, and the management of gastric stump carcinoma compared to primary gastric carcinoma. Also, recent advances in molecular typing of gastric stump carcinoma might open newer therapeutic options in the future[10].

Definition

Various definitions and nomenclature have been used for defining gastric stump carcinoma concerning the type of previous gastric surgery and the interval between the index gastric surgery and the development of malignancy. Some authors describe it as gastric cancer detected more than five years following gastric cancer surgery, while others recommend using a ten-year interval[11,12]. A few included all carcinoma arising in the remnant stomach regardless of the initial disease or duration following previous surgery as gastric stump carcinoma[13]. In Chinese literature, gastric stump carcinoma is defined as new cancer occurring in the residual stomach more than five or ten years after gastrectomy for benign diseases or gastric cancer, respectively[14]. The Japanese literature defines it as cancer in the remnant stomach following gastrectomy for benign disease or gastric cancer at least five years

after the primary surgery[15]. As there is no consensus on the definition it is imperative to have uniform definition to address various issues related to gastric stump carcinoma

Etiopathogenesis

Pathogenesis of gastric stump carcinoma is multifactorial and influenced by the indication for index gastric surgery and type of reconstruction[16-20]. Stump carcinoma tends to develop in a shorter period following index gastric surgery for a malignant etiology than benign causes. On average, it takes approximately 300 months for benign gastroduodenal diseases and 100 months for gastric cancer to turn into gastric stump carcinoma following primary gastric surgery[5,21]. However, irrespective of the initial gastric pathology, the shorter duration between index gastric surgery and the onset of stump carcinoma worsens the outcome [22-24]. In gastric carcinoma patients with a single lesion during index surgery, the transformation rate to gastric stump carcinoma has been reported to be 1.9% in 4 years [22]. A few studies have shown that Billroth II reconstruction has more preponderance for gastric stump carcinoma than Billroth I reconstruction [18-20]. While gastric stump carcinoma is commonly reported at the anastomotic site, it can occur anywhere in the remnant stomach[25]. Anastomotic site gastric stump carcinoma is common following Billroth II reconstruction, whereas it can occur anywhere in the gastric stump after Billroth I reconstruction [23,25]. However, a meta-analysis and a study from Sweden have documented that reconstruction type does not affect the risk of gastric stump cancer development, highlighting the multifactorial pathways in the genesis of gastric stump carcinoma[26,27].

Various physiological and anatomical alterations after partial gastric resection account for the occurrence of gastric stump carcinoma. Increased enterogastric reflux, and bacterial overgrowth secondary to vagotomy-induced achlorhydria are two dominant factors implicated in the pathogenesis. Bacterial overgrowth reduces dietary nitrates to nitrites resulting in overexposure of gastric mucosa to nitrosamines leading to metaplasia and dysplasia[28,29]. Hypochlorhydria also increases epithelial cell proliferation rendering the mucosa more susceptible to DNA damage [30,31]. Kaminishi et al. showed that the denervation of gastric mucosa encourages carcinogenesis in a rat model [32]. Miwa et al., documented that enterogastric reflux has carcinogenic potential in rats[31].]. It has been suggested that the hydrophobic nature of bile acids causes stress-induced oxidative DNA damage and reduces DNA repair in epithelial cells[33-35]. Enterogastric reflux changes the physiological environment and pH of the remnant stomach, making it susceptible to Epstein-Barr virus

infection and facilitating entry into epithelial cells, which is associated with the development of gastric stump carcinoma[36]. A few studies have documented Epstein-Barr virus infection rate of 22.2% to 41.2% in all patients following distal gastrectomy, with higher incidence following Billroth II compared to Billroth I reconstruction[23,37,38]. Higher frequency of Epstein–Barr virus infection that occurs in gastric stump carcinoma compared primary gastric cancer is an area of intense research.

The role of Helicobacter pylori in gastric stump carcinoma is questionable because gastroduodenal reflux hampers the growth of bacteria in the gastric stump [11,30]. However, some studies suggest that Helicobacter pylori-induced gastritis, in combination with bile reflux, stimulates cellular proliferation in the remnant stomach [39,40]. Hence, the role of Helicobacter pylori as a risk factor for gastric stump carcinoma remains an area of debate[41]. Attempts have been made to reduce the risk of gastric stump carcinoma by connecting the afferent and efferent limbs of the Billroth II reconstruction distal to gastrojejunostomy (Braun's anastomosis) to reduce the reflux. However, nuclear studies have revealed that Braun's anastomosis is inadequate in suppressing the biliopancreatic reflux in the fasting state as well as following fatty meals[42]. Also, the use of Roux-en-Y reconstruction, or placing a jejunal interposition graft, to reduce reflux have reduced but does not entirely eliminate the risk, as cases of gastric stump carcinoma have been reported even after these reconstructions[43-45]. In addition to the aforementioned risk factors, patients who underwent gastrectomy for malignancy have a gastric microenvironment that is already conducive to the development of remnant gastric carcinomas like atrophic gastritis and intestinal metaplasia [2]. Also, patients undergoing proximal gastrectomy for gastric cancer have more risk of gastric stump carcinoma compared to those undergoing distal gastrectomy [22,23]

Molecular biology

Detailed molecular characteristics of gastric stump carcinoma remain to be clarified because of its rarity. Studies have shown that Programmed death ligand 1 (PD-L1) expression in gastric stump carcinoma tumor cells is lesser than in primary gastric cancer. However, PDL-1 expression in tumor-infiltrating immune cells is higher in gastric stump carcinoma than in primary gastric cancer[33,46]. In patients with gastro-enteric reconstruction, PD-L1 overexpression in inflammatory cells is aimed at suppressing inflammation. However, it also contributes to the immune escape of tumor cells in patients with gastric stump carcinoma. As the expression of epidermal growth factor and human epidermal growth factor receptor 2

(HER2) is less HER2-targeted therapy may not frequently be applicable for treating gastric stump carcinoma [46]. Some authors reported that microsatellite instability was more common in gastric stump carcinoma compared to sporadic carcinoma stomach[33]. Also, the inactivation of hMLH1 and hMSH2 is more in Billroth II compared to Billroth I reconstruction[33,34]. Microsatellite instability and high PD-L1 expression suggest immunotherapy's role in managing gastric stump carcinoma. Also, C promoter polymorphism (IL-1B-31T) is associated with gastric stump carcinoma, with the T allele offering protection against gastric stump carcinoma[47]. A comprehensive understanding of molecular characteristics of gastric stump carcinoma may enable the selection of effective treatment options and the development of novel therapeutic strategies.

Histological transformation

According to the Lauren classification, two histological types of gastric carcinoma have been identified using hematoxylin and eosin staining, namely diffuse and intestinal type [48]. In gastric stump carcinoma, the histology of the tumor depends upon the location. Patients with tumors at the anastomotic site often have diffuse-type gastric cancer. Biliopancreatic reflux results in adenocystic proliferation of the gastric glands at the anastomotic site leading to a diffuse type of carcinoma[11]. Intestinal type is common in patients with gastric stump carcinoma located other than the anastomotic site. In the body of the remnant stomach, dysplasia ensues, leading to loss of gastric phenotype and resulting in intestinal type of carcinoma, which is attributed to the denervation of the gastric stump[32]. Another salient feature noticed on histology is that adjacent gastric mucosa in gastric stump carcinoma is less atrophic compared to proximal gastric carcinoma patients signifying a difference in the pathogenesis of gastric stump carcinoma[49]. Also, serosal tumor involvement seen in 37 to 48% of patients with remnant gastric carcinoma is significantly higher compared to 19% in proximal gastric carcinoma[50].

Pattern of lymph node involvement

The involvement of lymph nodes in gastric stump carcinoma is peculiar due to anatomical changes occurring after the type of primary surgery. Also, the pattern of lymph node spread is influenced by the indication of index gastric surgery. The lymphatic trunks are transected during the primary surgery, altering the lymphatic drainage pathways. Proximal gastric carcinoma normally drains along the celiac artery via lesser curvature, left gastric artery, and right cardiac lymph nodes. However, post-primary surgery, the draining pathway is

through greater curvature, posterior gastric, and splenic artery lymph nodes[11,16,51]. Tumors in the gastrojejunal anastomotic site tend to have higher jejunal mesentery lymph nodal involvement, which ranges between 7% and 46.8%. Also, they tend to have a higher stage at presentation and poor outcomes [15,52-54]. Overall proportion of patients with splenic hilar node involvement is significantly higher in gastric stump carcinoma compared to primary gastric cancer. Jejunal mesentery lymph node involvement is primarily encountered after Billroth II reconstruction[15,51]. Though mediastinal and paraaortic lymph nodal spread is reported, the exact incidence is not known, as clearance of these nodes is not routine for gastric stump carcinoma[51,55-57].

The total number of lymph nodes harvested following surgery for remnant gastric carcinoma is significantly less than primary gastric carcinoma, especially if the prior surgery was for gastric malignancy, as the nodes would have already been removed. Hence, the lymph node grouping used in the TNM classification for primary gastric carcinoma may not be appropriate for staging remnant gastric carcinoma[58]. Some authors have advocated the use of the lymph node ratio as a better prognostic marker and for selecting adjuvant therapy[58,59]. However, the lymph node ratio determined by dividing the number of positive lymph nodes by the total harvested nodes has different cut-off values in different studies[60-62]. Lack of standardization, primarily due to the limited sample size in the reported studies, limits the widespread use of lymph node ratio in gastric stump carcinoma. Hence, a novel staging system is required for gastric stump carcinoma, which considers the alterations of primary surgery and the type of reconstruction to accurately predict outcomes in these patients.

Management principles

The primary treatment of gastric stump carcinoma is radical surgical resection with lymphadenectomy and en bloc resection of involved adjacent organs[63-65]. As it is difficult to differentiate between tumor infiltration and inflammatory adhesions, en bloc resection of the involved adjacent organ is recommended. Most commonly resected adjacent organs are the spleen, transverse colon, jejunum, and distal pancreas[66]. In patients with gastric stump carcinoma following Billroth II reconstruction, a minimum of 10 cm of the jejunum distal to anastomosis is resected along with the ligament of Treitz and jejunal mesentery for better oncological outcomes[66-69]. Stump carcinoma infiltrating the esophagus requires cardiac, infradiaphragmatic, supradiaphragmatic, esophageal hiatal and lower thoracic lymphadenectomy. A few authors recommend splenic and paraaortic lymph node dissection

for advanced gastric stump carcinoma when they are involved[51,54,69,70]. However, the standard lymph node dissection in gastric stump carcinoma is yet to be defined. Major factors influencing overall survival in gastric stump carcinoma are T stage, R0 resection and the time interval between primary gastrectomy and remnant gastrectomy[24].

Conventionally, gastric stump carcinoma is managed with open surgical approach. However, recently minimally invasive approaches have been used to resect these tumors. Comapred to open surgery, minimally invasive surgery is associated with less blood loss, decreased morbidity, and similar 5 year survival rates [67,68]. Also the feasibility and comparable long term outcomes with endoscopic resection of early gastric stump carcinoma has been recently reported [71]. The overall survival and disease specific survival rates of 87.3% and 100% respectively was reported with endoscopic resection[71].

Current status of diagnosis

The poor outcome in patients with gastric stump carcinoma is primarily due to late diagnosis resulting in a presentation at an advanced stage with a poor resectability rate. As symptoms of gastric stump carcinoma are non-specific and often resemble the postgastrectomy symptoms, active endoscopic surveillance is an option for early diagnosis [72-74]. A few authors have suggested annual endoscopic surveillance from one-year post gastric cancer surgery to at least ten years. While surveillance endoscopy has been suggested following gastrectomy for the benign disease, it should be kept in mind that the primary diagnosis of a benign disease makes patients less compliant for future endoscopies[5,75]. Early detection of gastric stump carcinoma does not always require macroscopic lesions. Recent advances in endoscopic diagnostic techniques for diagnosis have resulted in the detection of early gastric carcinoma at an earlier stage, thereby facilitating endoscopic resection [76-80].

Appraisal of future perspectives

Several studies have documented en bloc resection and complete resection rates of 91% to 100% and 74% to 94%, respectively, for endoscopic submucosal dissection (Table 1)[71,80-88]. Perforation is relatively common after endoscopic gastric stump carcinoma resection and usually occurs at the anastomotic site[84,88]. As previously mentioned minimally invasive approach is increasingly used for gastric stump carcinoma. Studies comparing laparoscopic and open total gastrectomy for stump carcinoma have shown that laparoscopic surgery has less blood loss, more lymph node harvest, early post-operative recovery and lower complication rates[67,68,89-93]. However, all studies reported prolonged operative time compared to open

surgery (Table 2). Although 5 year survival rates were equivalent between both groups, most studies had short follow up [67,91,93].

Recently more studies are showing the association of gastric stump carcinoma with various other surgeries like pancreatoduodenectomy, bariatric surgery, and following gastric pull-up, though the numbers are not alarming [7,94-96]. Enterogastric reflux is the primary mechanism. Gastric stump carcinoma post pancreatoduodenectomy usually occurs at the gastrojejunostomy site and is frequently poorly differentiated[96]. Some authors have reported cases of remnant gastric carcinoma even after pylorus preserving pancreatoduodenectomy at the pancreaticogastrostomy site[97]. A few researchers consider pancreatoduodenectomy an emerging risk factor for gastric stump carcinoma as the survival post pancreatic cancer surgery is increasing[7,98]. Sleeve gastrectomy is one of the most common procedures performed for managing morbid obesity. A few studies have reported remnant gastric carcinoma 15 to 25 years after bariatric surgery[8,99]. Gastric stump carcinoma after Roux-en-Y gastric bypass is often reported in the excluded antrum followed by body, pylorus and fundus[100]. As the reported number of gastric stump carcinoma cases post-bariatric surgery is less, more studies are needed to document whether bariatric surgery represents a true risk factor for gastric stump carcinoma. However, it is reasonable to suggest post-bariatric surgery endoscopic surveillance in gastric cancer endemic regions. Well-designed epidemiologic studies are needed to investigate these new associations with gastric stump carcinoma thoroughly.

With the rise of targeted therapy in gastric carcinoma, the interest of researchers has grown in gastric stump carcinoma, too. High incidence of microsatellite instability and PD-L1 expression in gastric stump carcinoma suggests a possible role of immunotherapy in these patients[101, 102]. Prevalence of PTEN and SMAD 4 mutations in gastric stump carcinoma could also provide therapeutic targets[102]. The widespread availability of next-generation sequencing could facilitate molecular profiling of gastric stump cancer and the development of novel therapeutic strategies in the future.

Conclusion

Gastric stump carcinoma will not remain a rare clinical problem and may be more frequently encountered in the future. This entity still needs introspection and research concerning precise definition, appropriate staging and management. Owing to recent advances in diagnostic and therapeutic options, gastric stump carcinoma can be detected early and have survival equivalent to primary gastric carcinoma. Endoscopic management and minimally invasive surgery feasible in selected patients may offer a better quality of life. Recent advances

in the molecular biology of gastric stump carcinoma may help to develop novel therapeutic strategies.

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Table 1. Summary of endoscopic submucosal dissection for early gastric stump carcinoma

Authors [Reference](year)	**Number of patients (number of lesion)**	**En bloc resection, n (%)**	**Complete resection , n (%)**	**Perforation, n (%)**	**Bleeding, n (%)**
Takenaka et al [91] (2008)	31	30 (97)	23(74)	4 (13)	0
Hirasaki et al [92] (2008)	17	17 (100)	14 (82)	0	3 (18)
Hoteya et al [93] (2010)	40	-	38 (95)	1 (2.5)	2 (5)
Lee et al [94] (2010)	13	13 (100)	12 (92.3)	0	0
Nonaka et al [78] (2013)	139	131 (94)	118 (85)	2 (14)	2 (14)
Tanaka et al [95] (2013)	33	33 (100)	31 (94)	3 (9)	1(3)
Nishide et al [87] (2012)	58 (62)	59 (95)	53 (85)	11 (18)	5 (8)

Table 2. Overview of minimally invasive and open surgery for gastric stump carcinoma

Authors [Reference](year)	Country	No of patients Lap/open/robotic	Operative time Lap/open	Blood loss Lap/open	Postoperative hospital stay Lap/open	Conversion to open	Number of lymph nodes retrieved Lap/open
Son et al [100] (2013)	Korea	17/17/0	234.4/170 minutes	227.6/184.1 ml	9.3/9.3 days	8	18.8/22.3
Nagai et al [98] (2014)	Japan	12/10/0	362.3/270.5 minutes	65.8/746.3 ml	11.3/24.9 days	NA	23.7/15.9
Kwon et al [74] (2014)	Korea	10/58/8	266.2/203.3 minutes	182.2/193.1 ml	6/9 days	1	8/7
Kim et al [97] (2014)	Korea	17/50/0	197.2/149.3 minutes	NA	11.1/13.8 days	0	12.9/NA
Tsunoda et al [99] (2014)	Japan	10/6/0	325/289 minutes	55/893 ml	13/24 days	0	22/7
Otsuka et al [96] (2018)	Japan	7/20/0	364/309 minutes	70/1066 ml	13/27 days	0	22/12
Booka et al [75] (2019)	Japan	23/8/0	307.5/295.8 minutes	135.5/568.3 ml	10.6/21.3 days	2	8.8/6

Lap= laparoscopic, ml= milliliter, NA= Not applicable