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Billroth II reconstruction in gastric cancer surgery: A good option for Western patients

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ABSTRACT

Purpose: The aim of this study is to report the short and long-term results of a cohort of patients who underwent Billroth II (BII) Distal Gastrectomy (DG) for gastric cancer (GC), in a tertiary referral Western center.

Methods: From January 2005 to December 2015, a prospective observational study was conducted in candidate patients to elective gastrectomy for cancer.

Results: Among 514 patients observed with GC, a series of 258 patients underwent BII DG for middle/lower third GC. Postoperative mortality and complication rates were 1.5% and 12.4% respectively.
The overall and disease-free 5-year survival rates were 78% and 69%, respectively.
Young age, lymph nodes retrieved, radicality of resection, and early tumor stages were independent positive prognostic factors at multivariate analysis for 5-year overall survival.
Abdominal complications and advanced tumor stages negatively influenced 5-year disease-free survival at multivariate analysis.

Conclusion: BII provides excellent results in terms of short and long-term prognosis and should be regarded as an acceptable reconstructive option following DG for GC.

Introduction

Gastric cancer is the fourth most common malignancy and the third leading cause of cancer death worldwide.[1] Surgery is the mainstay of curative treatment. For most tumors affecting the distal part of the stomach, radical distal gastrectomy (DG) is the recommended operation.[2] However, the choice of reconstruction after DG remains controversial. Billroth I (BI), Billroth II (BII), and Roux-en-Y gastrojejunostomy (RY) are all acceptable options.[3] BI gastroduodenostomy is a common reconstruction technique especially in Japan and Korea where the tumors are mostly diagnosed at an early stage. Conversely, in most of the other parts of the world, BII and RY gastrojejunostomy are the most commonly performed, in relation to the more frequent GC diagnosis at locally advanced stages.

Technically, BII is a simpler procedure to perform, but it is associated to a high rate of post-operative bile reflux that can lead to potential histologic alteration of the gastric mucosa and to the clinical syndrome called alkaline gastritis.[4–7]

In order to prevent bile reflux and its clinical consequences, the RY gastrojejunostomy was more recently introduced as alternative technique. Comparative studies have shown functional advantages as compared to both BI and BII reconstructions.[5,8,9] However, RY is a more complex surgical procedure since two anastomoses are needed and it has its own complications, such as the Roux stasis syndrome[10–13] leading to the postoperative onset of delayed gastric emptying, nausea and vomiting.

Both these functional and technical controversies reflect in the absence of a general consensus on the best reconstructive technique after DG.

At this regard, the aim of this observational study is to evaluate the efficacy of BII reconstruction after DG and to assess both the early and long-term results related to this technique.

MATERIALS and METHODS

All patients who underwent DG with BII reconstruction for GC at

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the Department of Digestive Surgery, "A. Gemelli" Foundation IRCCS, Catholic University of Rome, Italy, from January 2005 to December 2015 were retrospectively reviewed from a prospectively maintained database. Institutional review board approval had been obtained for the research purpose use of the data, stemming out from standard clinical practice, since no additional interventions were planned (observational study). All surgical procedures were performed by the same surgical team.

We recorded hospital morbidity and mortality, type of treatment, histologic type according to Lauren,[14] and demographic characteristics, tumor size, location, and gross appearance according to Borrmann.[15] The disease was staged according to the 8th Edition of the American Joint Committee on Cancer and the International Union Against Cancer Staging System (UICC).[16,17] Based on categories established by the Japanese Gastric Cancer Association,[18] the regional extent of nodal involvement after radical procedures was also recorded.

All patients were operated on according to the intention-to treat method. Those with potentially curable lesions were treated by DG and D2 lymphadenectomy. Patients with stage IV disease and noncurable lesions (distant metastases, peritoneal carcinomatosis, and N4 nodal involvement) at the preoperative evaluation were treated by DG and perigastric (D1) lymphadenectomy with the intent to control specific symptoms and to obtain a survival advantage.

For D2 lymphadectomy, node dissection was performed according to the Japanese Gastric Cancer Association Rules.[18] At the end of the operation, the surgeon resected all lymph nodes from the surgical specimen and identified their distribution and tumor location according to the classification by the Japanese Gastric Cancer Association.[18]

Intestinal continuity was restored by means of BII gastrojejunostomy in all cases. Technically, a loop of jejunum 10–15 cm distal to the duodeno-jejunal flexure was brought up to the remnant stomach in an isoperistaltic antecolic fashion. The anastomosis was constructed over the posterior wall of the stomach in a transverse plane at least 2 cm from the gastric remnant staple line. An enterotomy and a gastrostomy were created either for a manual anastomosis or to allow for entry of linear cutting 60–75 mm stapler. The stapler entry point was closed with a hand-sewn suture.[19]

Based on definitive pathologic findings, the potentially curative operations were classified as radical (R0-microscopic tumor free) or as R1-microscopic residual disease-according to the presence or absence of residual tumor. Palliative resection (among patients with stage IV disease) was classified based on R2 macroscopic disease left behind. Frozen section were not routinely used in the evaluation of margins, but only in the suspicion of a possible tumor infiltration. In case of a positive frozen section this led to conversion to a total gastrectomy. If final margins were R1, in no case was considered reoperation.The patients were monitored for 30-day postoperative complications and mortality.

Postoperative complications were considered in a time period of 30 days from surgery and defined as a severity of grade 2 or more according to the Clavien-Dindo classification.[20] All postoperative complications were captured in the database during hospitalization or at the first follow up, by telephone contact, within 30 days from surgery. Heart burn symptom and biliary reflux at 6 months were confirmed by endoscopic examination and biopsy.[21]

Postoperative mortality was defined as death within 30 days from surgery.

As far as combined treatments are concerned, perioperative chemotherapy was administered according to the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) protocol.[22] Adjuvant regimens highly varied over the 30 years spanned by this series. As previously reported,[19] the decision to administer adjuvant chemotherapy was made by medical oncologists. This resulted in heterogeneous indications for chemotherapy, treatment protocols, and number of cycles performed.

All patients included in the study were regularly followed up with a standardized protocol.[23]

Statistical analysis

Statistical analysis was performed using commercially available software (SPSS® for Windows version 20.0; Chicago, IL).

Results are given as mean (SD). The statistical significance of the difference between mean values was evaluated using the *t*-test. Categorical variables were assessed by the $\chi 2$ test, using the Fisher's exact test correction where appropriate.

Overall survival curves and local control curves were estimated by the Kaplan–Meier method. To assess the prognostic importance at univariate analysis, survival curves for each variable were compared by log rank test, for both overall survival and local control. Variables found to be significant at univariate analysis were entered into a multivariate Cox regression model. The critical significance level of 0.05 was chosen.

Results

During the study period, a total of 545 patients underwent total or partial gastrectomy. In 289 cases (53%) a DG was performed. For the study purposes, 31 patients who underwent RY DG were excluded from the analysis. Therefore, the study population consisted of 258 out of 545 (47.3%) patients who underwent DG with BII reconstruction for a primary GC.

Twenty-two patients (8.5%) received neoadjuvant therapy.

Patients demographics, surgical details, and pathologic characteristics are shown in Table 1.

The majority of tumors, as expected, were located in the lower third (66.3%), while the remnant (33.7%) in the middle third.

Table 1
Patient characteristics.

Characteristic	Total (N = 258)
Gender	
Male	140 (54.3)
Female	118 (45.7)
Age	
<65	108 (41.9)
≥65	150 (58.1)
Neo-adjuvant therapies	
Yes	22 (8.5)
No	236 (91.5)
Tumor location	
Lower third	171 (66.3)
Middle third	87 (33.7)
Lauren classification	
Intestinal	143 (55.4)
Diffuse	88 (34.1)
Mixed	27 (10.5)
Borrmann Classification	
I	49 (19)
II	117 (45.3)
III	67 (26)
IV	14 (5.4)
V	11 (4.3)
TNM	
I	76 (29.5)
II	76 (29.5)
III	79 (30.6)
IV	27 (10.4)
Lymph nodes retrieved (mean; sd)	36.76 (±13.0)
Multivisceral resections	36 (14.0)

Values in parentheses are percentages.

Histologic evaluation was available for all the resected specimens. Most adenocarcinomas showed intestinal type differentiation (55.4%).

The mean number of lymph nodes retrieved was 36.76 (±13.0). A non-curative resection (R1-2) was documented in 61 patients (23.6%); 42 R1 and 19 R2, respectively.

The mean length of postoperative hospital stay was 6.5 (±5.7) days.

Heartburn symptom and biliary reflux at 6 months were 8.3% and 9.2%, respectively.

Five patients (1.9%) had anastomotic leakage.

Complications requiring prolonged hospitalization or additional surgery (Clavien-Dindo grade ≥2) occurred in 32 (12.4%) of 258 patients.

Four (1.5%) of 258 patients died during the perioperative period, in three cases as a result of abdominal sepsis secondary to anastomotic leakage, and in one case as a result of acute myocardial infarction.

After surgical resection, 135 patients (52.3%) received systemic adjuvant chemotherapy.

The median follow-up was 87 months (range, 9–162 months). Excluding 15 patients lost during the study period and 4 patients who died during the postoperative hospital stay, follow up was completed in 239 cases (92%). At the last evaluation, 143 (59.8%) patients had died. During follow-up, no patient developed cancer of the gastric stump.

For the entire cohort of the study, the overall survival (OS) at 5 years was 78% (Fig. 1), while the 5-year disease-free survival (DFS) for all patients without metastatic disease (231 patients) was 69% (Fig. 2).

An univariate and multivariate analysis of the effect of prognostic factors on the 5-year OS and DFS (Tables 2–5) has been conducted.

At univariate analysis, OS was significantly affected by age (≥65), tumor stage (early stages), number of lymph nodes retrieved (≥15), and radicality of resection (R0) (Table 2). The multivariate analysis, as shown in Table 3, revealed the same factors as significant predictors of OS.

At multivariate analysis, the most important independent negative prognostic factors were young age (<65), lower lymph node harvested (<15), advanced tumor stages (III-IV), and palliativeresections (R1/R2).

Five-year DFS was strongly associated with tumor stage, radicality of resection, and postoperative complications onset at univariate analysis (Table 4). The same features have been confirmed as independent prognostic factors at the multivariate analysis (Table 5).

Discussion

Great controversy is still present in the literature regarding the best reconstructive technique after distal or subtotal gastrectomy.

For instance, BI gastroduodenostomy is more frequently performed in Japan and Korea, where most of the GCs are diagnosed at an early-stage. The anastomosis can be done with minimal tension and is also more physiological, as it maintains a normal passage of food into the duodenum and it allows easy access to the bile duct.

However, in a recent study from Japan comparing BI and RY for gastric cancer, a higher rate of reflux gastritis was evidenced in the BI group, despite there was no difference in terms of body weight and nutritional status between the two study cohorts.[3]

Conversely, in Western countries, where the majority of GCs are diagnosed as locally advanced and bulky, BII and RY techniques are more commonly performed. BII is a simpler technique; only one anastomosis is needed, leading, consequently, to a lower rate of anastomotic leakage and related complications. On the other hand,

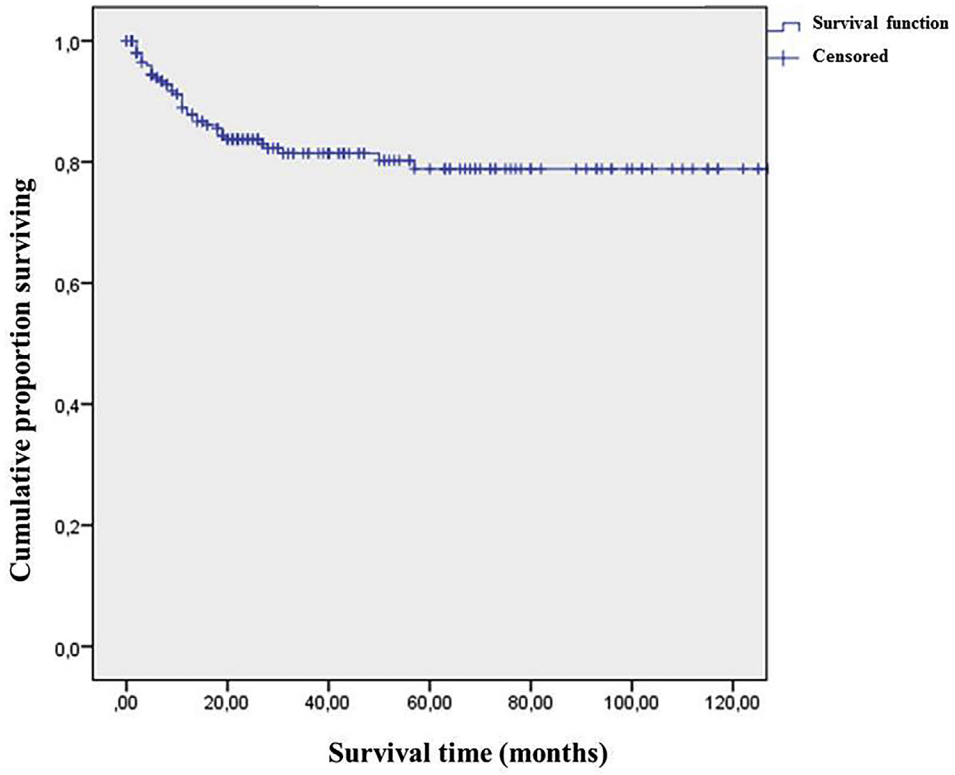

Fig. 1. 5-Year overall survival for all patients of the study group.

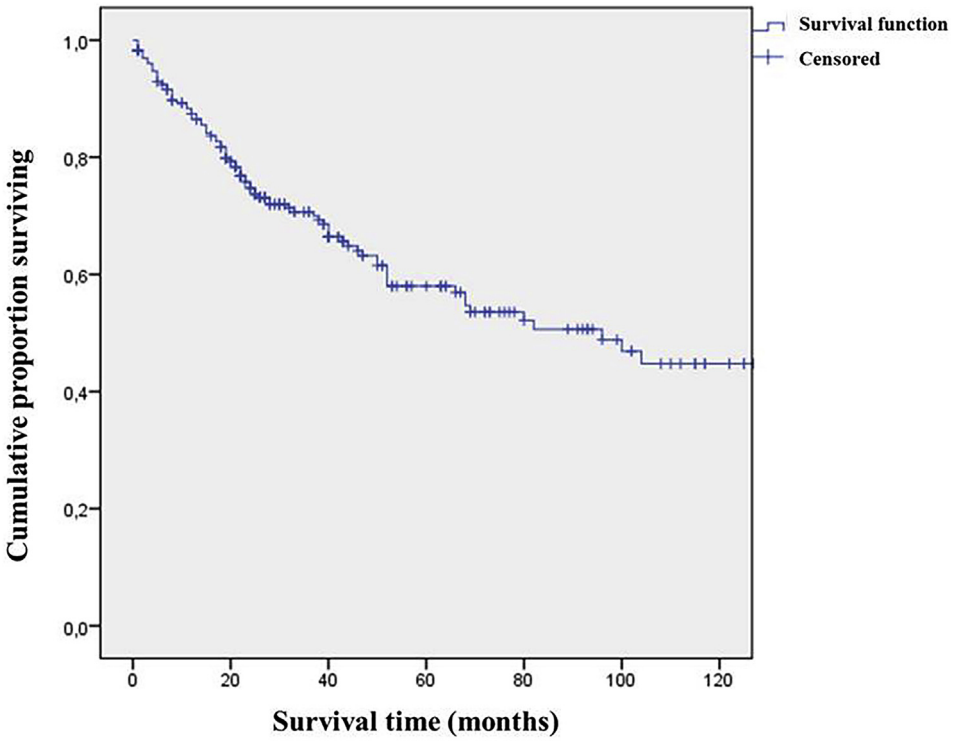

Fig. 2. 5-Year disease-free survival for all patients without metastatic disease.

BII is associated with the potential postoperative onset of bile reflux.[4,6,7] The persistence of reflux gastritis has been documented as risk factor for carcinogenesis at the gastric remnant.[6] Despite the addition of a Braun anastomosis to the conventional BII reconstruction was thought to reduce the post-operative bile reflux incidence, its role still remains uncertain24.

As compared to the BII reconstruction, RY technique has been demonstrated to significantly reduce the risk of bile reflux.[4,6,7] However, it is more complicated to perform since two anastomoses are needed and, moreover, the difficulty in assessing the bile duct during endoscopic retrograde cholangiopancreatography (ERCP) is increased. In addition, up to 30% of patients may postoperatively develop the Roux stasis syndrome, which consists of delayed gastric emptying, nausea and vomiting due to the functional obstruction of the Roux limb.[10–13]

As result of these functional and technical controversies, no consensus is present in the literature on the best reconstructive technique to adopt after DG.

To the best of our knowledge, our study represents the largest experience in the Western literature analyzing the short- and long-term outcomes after DG and BII reconstruction for GC.

We demonstrated good results both in terms of postoperative recovery, with more than acceptable morbidity and mortality rates, and long-term survival.

Table 2
Factors affecting 5-year overall survival according to univariate analysis.

	All patients (n = 258)	5-year overall survival %	*P**
Gender			
Male	140 (54.3)	77	0.88
Female	118 (45.7)	69.3	
Age			
<65	108 (41.9)	59.7	0.002
≥65	150 (58.1.)	69.3	
Tumor location			
Lower third	171 (66.3)	66.9	0.98
Middle third	87 (33.7)	70	
Lauren classification			
Intestinal	143 (55.4)	78.7	0.45
Diffuse	88 (34.1)	67.8	
Mixed	27 (10.5)	65.4	
Borrmann classification			
I	49 (19)	76	0.73
II	117 (45.3)	69.5	
III	67 (26)	54.3	
IV	14 (5.4)	38.6	
V	11 (4.3)	23.5	
Tumor stage			
I	76 (29.5)	89.7	<0.001
II	76 (29.5)	74.4	
III	79 (30.6)	52.2	
IV	27 (10.4)	22.6	
Lymph nodes retrieved			
<15	51 (19.8)	56.8	0.026
≥15	207 (80.2)	72.6	
Radicality of Resection			
R0	197 (76.4)	71.7	<0.001
R1/2	61 (23.6)	22.2	
Patients with Complications (≥ grade II)			
Yes	32 (12.4)	40.9	0.1
No	226 (87.6)	70.2	

Values in parentheses are percentages. *Log rank test.

Table 3
Multivariate analysis factors affecting 5-year overall survival.

Variable	RR	95% CI	P value*
Age ≤65 vs > 65	1.68	1.05–2.69	0.03
Lymph node harvested <15 vs ≥ 15	0.56	0.33–0.96	0.03
Tumor stage (TNM) I-II vs III-IV	2.31	1.43–3.74	<0.001
Radicality of Resection R0 vs R1/R2	3.32	1.27–8.65	<0.001
Lymph node metastasis Negative vs Positive	1.4	0.79–2.48	0.24

RR: relative risk, 95% CI: 95% confidence interval.
* Cox regression.

Table 4
Factors affecting 5-year disease free survival according to univariate analysis (231 patient without metastatic disease).

	All patients (n = 231)	5- year disease free survival %	P*
Gender			
Male	125 (54.1)	64.2	0.41
Female	106 (45.9)	55.8	
Age			
<65	96 (41.6)	55.2	0.14
≥65	135 (58.4)	63.5	
Tumor location			
Lower third	153 (66.3)	62	0.66
Middle third	78 (33.7)	67.9	
Lauren classification			
Diffuse	80 (34.6)	57.9	0.28
Intestinal	125 (54.1)	71	
Mixed	26 (11.3)	59.2	
Borrmann classification			
I	35 (15.2)	64.1	0.39
II	104 (45)	68.3	
III	64 (27.7)	46.3	
IV	13 (5.6)	38.6	
V	15 (6.5)	23.3	
Tumor stage			
I	76 (32.9)	88.2	<0.001
II	76 (32.9)	70.7	
III	79 (34.2)	46.4	
Lymph nodes retrieved			
<15	47 (20.3)	57.8	0.79
≥15	184 (79.7)	65	
Radicality of Resection			
R0	197 (85.3)	66.3	<0.001
R1/2	34 (14.7)	19.7	
Patients with Complications (≥ grade II)			
Yes	21 (9.1)	50	0.01
No	210 (90.9)	79.9	

Values in parentheses are percentages.
* Log rank test.

With regard to the post-operative course, we reached a post-BII morbidity rate of 12.4% for Clavien-Dindo grade ≥2. These data are in line with other case series, here considering both the BII and RY reconstruction techniques.[5,9,25,26]

As matter of fact, Tran et al.,[26] in their multicenter study comparing BII and RY, reported a morbidity rate of almost 13% for both reconstructive techniques. Similarly, So et al.[9] documented a post-operative complication rate of Clavien-Dindo grade ≥2 of 14% and 17% for BII and RY, respectively. In both studies anastomotic leak rate was lower in BII group than the RY group, even if not statistically significant.

However, as compared to other studies, our observational analysis did not include any objective or subjective information on the postoperative rate of bile reflux, nutritional status and quality of life (QoL). At this regard, some issues should be raised. First, the presence of reflux may be asymptomatic in most patients. As consequence a subjective evaluation could be misleading.[7,27] Second, it is not rare to have difficulty in finding a correlation between symptoms and endoscopic findings.[7,27] Comparing BII and RY techniques, So et al.[9] found that reflux gastritis and heartburn symptoms were more prevalent on endoscopy among patients with BII reconstruction despite no statistical difference was detected between the two techniques. The authors justified their results with the short follow-up of 1 year performed. Conversely, another randomized controlled trial by Csendes et al.[5] where BII and RY reconstructions were compared in patients with duodenal ulcers with a mean follow up of 15 years, gastro-esophageal reflux and Barrett esophagus on endoscopy were significantly more frequent in the BII group. However, the underlying disease could have played a crucial role on the results obtained, and probably an analysis conducted on only GCs could have lead to different outcomes. With regard to our case series, the long median follow-up of 87 months let us to objectively quantify the consequences of a persistent bile reflux in terms of related risk of carcinogenesis in the gastric stump. As result, a zero incidence of gastric remnant cancer was documented at the last follow up. Surely, it would be of great interest a future subanalysis on the younger portion of the population involved, to better define the risk of carcinogenesis for patients with a longer life expectancy.

Regarding the long-term outcomes, the results we reached are even better than most of the other case series,[28] with a value of 78% and 69% for OS and DFS at 5 years, respectively. This variation may have been influenced by different factors. The TNM stage of our cohort accounted for almost 60% of patients with a stage I or II GC. This would have played a crucial role in the prolonged long-term survival as compared to other case series. As confirmed by our multivariate analysis and most of the other publications,[29] TNM stage is one of the most agreeable independent risk factor for OS. Additionally, both the number harvested and metastatic lymph nodes have been confirmed as further OS and DFS influencing factors. Our mean number of lymph nodes retrieved was 36.76 (±13.0), notably higher than the UICC guidelines recommendation, according to which at least 15 lymph nodes should be harvested to reach an adequate oncological radicality.[30] As already demonstrated, better long-term survival outcomes are obtained with the increased number of removed nodes.[30–33] This is due to the higher probability of detecting pathologic nodes with more nodes examined, leading to a more accurate stage specific survival estimation.[30–33]

Postoperative complications and advanced age resulted important prognostic indicators for DFS and OS, respectively. More specifically, the development of postoperative complications has been already reported as strictly influencing long-term survival in all patients undergoing gastrectomy for cancer, especially for the subgroup of advanced GCs.[34]

The influence of patients' age on OS is not surprising and it is linked to the well known concept of “elderly frailty”.[35]

Table 5
Multivariate analysis factors affecting 5-year disease free survival (231 patients without metastatic disease).

Variable	RR	95% CI	P value
Surgical complications Yes vs Not	3.8	1.33–10.98	0.013
Tumor stage (TNM) I-II/III-IV	3.98	1.75–9.06	<0.001
Radicality of Resection R0 vs R1/R2	1.98	1.42–3.61	0.003
Lymph node metastasis Positive vs Negative	2.08	0.63–2.87	0.22

RR: relative risk, 95% CI: 95% confidence interval.
*Cox regression.

Conclusions

The advantages of BII reconstruction, especially in elderly and advanced GC patients, may be resumed as follows: (1) the possibility to perform just one anastomosis and, therefore, less anastomotic complications; (2) shorter duration of surgery; and (3) less incidence of stomal ulcer due to the protection on the anastomosis by the biliary fluids.

However, higher incidence of heartburn symptoms, gastritis and potential onset of GC in the residual stomach should be taken into account, especially for younger patients with a long life expectancy.

In any case, we should consider that, in the past, the majority of

gastric resection were performed for benign peptic disease. Regarding all these new data available in the literature, all from GC populations, probably the type of reconstruction for cancer patients should be matter of a deeper investigation with a large sample prospective randomized trial.

The theoretical advantage of RY with regard to bile reflux gastritis is questioned in elderly patients with a poor prognosis, due to the disadvantage of an additional anastomosis that could be only detrimental.

Probably, in Western countries, a revaluation of BII reconstruction for locally advanced GC and elderly patients must be taken into consideration.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.03.009.

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