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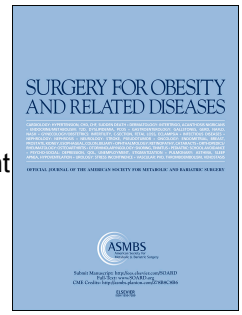

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Luca Dittrich, Marie-Valerie Schwenninger, Klaus Dittrich, Johann Pratschke, Felix Aigner, Jonas Raakow

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Marginal ulcers after laparoscopic Roux-en-Y gastric Bypass – Analysis of the amount of daily and lifetime smoking on postoperative risk

Luca Dittrich[1,2], Marie-Valerie Schwenninger[2], Klaus Dittrich[2], Johann Pratschke[1], Felix Aigner[1], Jonas Raakow[1]

[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health
Department of Surgery, Charité Campus Mitte, Campus Virchow Klinikum
Charitéplatz 1
10117 Berlin, Germany

[2]Landesklinikum Korneuburg
Wiener Ring 3-5
2100 Korneuburg, Austria

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Corresponding author
Luca Dittrich
Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health
Department of Surgery, Charité Campus Mitte, Campus Virchow Klinikum
Charitéplatz 1
10117 Berlin, Germany
Tel. +49-30-450-522012
Fax: +49-30-450-522922
luca.dittrich@charite.de

Short Title: Marginal ulcers after laparoscopic RYGB

Marginal ulcers after laparoscopic Roux-en-Y gastric Bypass – Analysis of the amount of daily and lifetime smoking on postoperative risk

Introduction

A common postoperative complication following laparoscopic Roux-en-Y gastric bypass (LRYGB) is the development of marginal ulcers (MUs) at the gastrojejunal anastomosis. Several risk factors, such as smoking, seem to have an impact on the development of MUs.

Objective

Very little is known about how much smoking increases the risk. We therefore reviewed our patients regarding their smoking behavior and the development of MUs after LRYGB.

Setting

Primary Care Hospital; University Hospital

Methods

This study included 249 patients who underwent LRYGB surgery between 2010 and 2015 with at least 2 years of follow-up at a single institution. This retrospective analysis focused on the development of marginal ulcers after LRYGB, the time of appearance, and possible risk factors.

Results

A total of 27 (10.8%) patients in this study developed MUs. The majority of MUs (66.7%) occurred within the first postoperative year. Smoking is an independent and statistically significant predictor of the development of MUs with a 4.6-fold greater risk (p=0.003). Light, moderate and heavy daily smokers have the same rate of MUs (17.4% vs. 17.1% vs. 17.9%, respectively). Light smokers with less than 10 cigarettes per day are at significantly increased risk for MUs compared to nonsmokers (17.4 vs. 4.2%, respectively; p=0.027). Former and current smokers are at comparable risks for MUs (13.3% vs. 17.5%, respectively; p=0.685).

Conclusion

The described incidence of 10.8% shows that marginal ulcers are one of the most important and frequent complications after LRYGB. Smoking at every intensity is associated with an extraordinary risk of MU formation after LRYGB and therefore, smoking cessation prior to bariatric surgery must be strongly recommended.

Keywords: Marginal Ulcer, Laparoscopic Roux-en-Y Gastric Bypass, Smoking

Introduction

Since 1975, obesity has tripled worldwide. It is defined as a body mass index (BMI; kg/m^2) greater than or equal to 30 kg/m^2. In 2016, over 650 million adults (over 18 years) were found to be suffering from obesity [1].

In comparison to conservative treatments and/or lifestyle changes, bariatric surgery leads to an even greater and longer lasting weight loss, as well as a remarkable reduction of risk factors in patients with obesity [2, 3]. Originally developed and described by Wittgrove AC, et al. in 1994, the laparoscopic Roux-en-Y gastric bypass (LRYGB) has become one of the most common and effective therapies for obesity among the variety of bariatric procedures [4, 5].

The LRYGB and other bariatric surgeries are known to be very safe procedures with an excellent surgical outcome and a low incidence of early and late complications [6, 7]. Early postoperative complications that occur within 30 days after LRYGB include anastomotic strictures and anastomotic and staple line leaks [8, 9]. Late surgical complications after gastric bypass are anastomotic stenoses, gastrogastric fistulas and internal hernias [10, 11]. Additionally, marginal ulcers (MUs) are possible late complications with a wide range of incidences in recent literature from 0.6 to 25%[12].

A marginal or anastomotic ulcer, used synonymously in the medical literature, is defined as a peptic ulcer at or in close contact with the gastrojejunal anastomosis (e.g., the gastric pouch or jejunal mucosa). Typically observed symptoms are abdominal pain, nausea or vomiting, dysphagia, symptoms of obstruction or hematemesis [13]. Several risk factors are supposed to have an impact on the pathogenesis of an MU: local ischemia, the size and position of the pouch [14], and extrinsic factors such as the use of nonsteroidal inflammatory drugs (NSAIDs) or

corticosteroids [15, 16]. Smoking has also been shown to be a significant risk factor for the development of MUs [12, 17]. However, as smoking is a very widespread term encompassing occasional or social smoking to very high daily smoking, nothing is known about the amount of smoking being a risk factor for MUs. To the best of our knowledge, no previous research has investigated the risk of formerly smoking, the amount of daily smoking or lifetime tobacco exposure (LTE) on the development of MUs.

The aim of the present study was therefore to review our results regarding the incidence and possible risk factors influencing the development of marginal ulcers following LRYGB for the treatment of severe obesity. Our particular focus was on the influence of current or former smoking habits, the amount of current smoking and the amount of lifetime tobacco exposure on the development of MUs. Further, we evaluated complications associated with MUs and our treatment regime.

Materials and Methods

Patients who underwent a laparoscopic Roux-en-Y gastric bypass between January 1, 2010 and December 31, 2015 with a follow-up time of at least two years after surgery were included in this study, leading to a total study population of 249 patients. All operations were performed by the same specialized surgeon with more than 30 years of experience in bariatric surgery in high volume centers. Due to restrictive medical guidelines and insurance reglementation in the author´s country and limitations by the hospital operator, the center currently only performs approximately 100 bariatric procedures per year with a 1-year follow-up rate of approximately 70%. A detailed retrospective analysis was performed, including demographics (age, gender, preoperative BMI), preoperative diagnostics and

surgeries (e.g., preoperative gastroscopy, gastric banding, vertical banded gastroplasty (VBG)), the presence of comorbidities (e.g., diabetes mellitus (DM), arterial hypertension, coronary heart disease) and technical characteristics of the surgery (length of biliary/alimentary limb, type of circular stapler).

This analysis focused on the development of marginal ulcers after LRYGB, its location (anastomotic, jejunal, gastric pouch), the time of appearance, risk factors and complications.

A BMI ≥40 kg/m^2 or ≥35 kg/m^2 with at least one comorbidity, such as diabetes mellitus, arterial hypertension or cardiac and vascular diseases, was required for the indication of bariatric surgery. Further inclusion criteria were previous bariatric surgery with weight regain, dilatation of the esophagus, gastric band migration and staple line rupture after laparoscopic VBG. Preoperative dietary consultation, psychological assessment and gastroscopy were required. Every patient with diagnosed preoperative *Helicobacter pylori* infection received a standardized eradication therapy [(18)].

Surgery

The same standardized surgical technique was performed throughout the observational period, based on the original LRYGB technique described by Wittgrove, et al. [(4)]. Nevertheless, modifications due to personal experiences were made.

The first step was to identify the esophagogastric junction to ensure the possibility of creating a gastric pouch. The biliopancreatic limb (BPL) was measured between 80-150 cm, lifted antecolic to the stomach and fixed there (3-0 Vicryl®). Depending on the presence of comorbidities, such as diabetes mellitus, the biliary limb was created with a minimum length of 110 cm. The length of the alimentary limb was set between

80-150 cm. The entero-anastomosis was performed with a linear stapling device (EC60: Ethicon Echelon 60 mm Stapler, 340 mm®) side to side.

The creation of a gastric pouch with a volume of 50-70 ml started with insertion of the calibration tube. The stomach was dissected 5-7 cm distal to the esophagogastric junction at the lesser curvature. The first linear stapler was positioned at a 90° (degrees) angle. Gastrotomy was performed near the greater curvature to insert the anvil of the circular stapler (Ethicon Endoscopic Curved Intraluminal Stapler ILS 25®, Touchstone CSC25®, Medtronic DST Series™ EEA™ 25® / Premium Plus CEEA™ 25®) into the stomach to prepare the gastrojejunostomy close to the lesser curvature and through the staple line. The gastric pouch was completed with two or three reload cartridges. GORE® SEAMGUARD® (Bioabsorbable Staple Line Reinforcement) was used to minimize the risk of staple line bleeding. Then, the circular stapler was inserted into the previously opened alimentary limb and connected with the anvil, completed the gastrojejunostomy. The integrity of the stapling doughnuts was verified, and a histopathological examination was performed to detect gastric inflammation at the anastomosis. Subsequently, an inspection of the circular-stapled anastomosis (CSA) was realized by a leak test with a colored liquid (Patent blue®). If there were any concerns regarding the integrity of the gastrojejunal anastomosis, intraoperative endoscopy was performed.

Postoperative treatment and follow-up

On the first postoperative day, every patient performed a contrast medium swallow (gastrograffin) and received proton pump inhibitors (PPI; Pantoprazol®). 40 mg twice daily for 4 weeks. After this initial period, they were prescribed 40 mg once a day for

6 months. Routine clinical observation was performed 2, 6 and 12 months after surgery.

Postoperative gastroscopy was realized only when indicated for symptoms such as pain, obstruction, nausea/vomiting or bleeding. Marginal or anastomotic ulcers were defined as described above, with the appearance of a peptic ulcer at or in close proximity to the gastrojejunal anastomosis (e.g., the gastric pouch or jejunal mucosa). In this study, the term “marginal ulcer” will be used preferentially. MUs were verified by visualization and histological examination and defined gastroscopically by their location (anastomotic, jejunal, gastric pouch). Once an MU was diagnosed, treatment was initiated with a 6-8 week regimen containing PPI 40 mg once a day and sucralfate 1 g 3 times a day. In the case of a bleeding ulcer, the dosage of PPI was increased to 40 mg twice daily. The ulcer was defined as healed either with the ceasing of symptoms after 6-8 weeks or via endoscopic control. Further gastroscopy was only conducted when the patient’s symptoms were persistent. Recurrent ulcers were defined as emerging ulcers within the first 6 to 8 weeks in a different location than a prior ulcer or after healing of a prior ulcer independent of the time after surgery. The same concept was applied to a third ulcer and so on. In case of MU recurrence or re-recurrence the conservative medical treatment consisted of 40mg PPI twice a day and 1g of sucralfate three times a day.

Smoking

A current smoker was defined as a patient who smoked cigarettes or similar types of tobacco products at the time of the operation. A former smoker was defined as a patient who had quit smoking at the time of the operation. The amount of current smoking was divided into three subgroups: light smokers with <10 cigarettes per day

(CPDs), moderate smokers with 10-20 CPDs and heavy smokers with >20 CPDs. Lifetime tobacco exposure was also divided into three subgroups: low with under 10 pack years (PYs), moderate with 10-30 PYs and high with over 30 PYs. A pack year was defined as twenty cigarettes smoked every day for one year.

Smoking cessation was recommended to all patients prior to bariatric surgery. But according to the guidelines for bariatric surgery in the authors countries smoking cessation is not mandatory prior to the operation and therefore active smoking is no contraindication for a LRYGB.

Statistics

To assess risk factors, location, and time of appearance of MUs after LRYGB, we performed survival analysis (Cox regression). The follow-up time was defined as the diagnosis of an MU within a total observation time of at least 2 years. The same period without incident represented event-free survival. To adjust the Cox regression for potential confounders, various factors such as age, gender, NSAID usage, alcohol consumption and others were taken into consideration.

The correlation between different characteristics (smoking, NSAID usage, technical parameters of the operation) and the development of MUs was analyzed by use of unadjusted survival analysis. Adjustment for multiple tests was not performed.

A p-value of less than 5% ($p < 0.05$) was determined to be statistically significant. Results presented as the median additionally indicate the lower (Q1) and upper (Q3) quartile (25%, 75%, respectively) in brackets.

Statistical analysis was performed using IBM SPSS Statistics 25.0.0.0 (SPSS, Inc., Chicago, Illinois).

Results

Throughout the entire course of the study, 249 patients underwent LRYGB. Table 1 shows the demographic and clinical characteristics of the patients. The mean age was 45.5 (±12.7) years, with the majority of the patients being female (74.3%). The mean preoperative BMI was 43.1 (±6.2) kg/m^2, the total weight loss (TWL) was 19.4 (±7.8) kg, and the BMI difference was 8.5 (±3.6) kg/m^2 after 74 days (median). More than half of the patients (n=129, 51.8%) were classified as smokers with a mean of 18.2 (±13.1) CPDs and 22.7 (±17.5) pack years at the time of operation.

In the 5-year study period with 2 years of follow-up, 27 (10.8%) patients developed MUs (Table 2). The majority of MUs (66.7%) occurred within the first postoperative year (205 days [median]), and two patients (7.4%) suffered from early MU formation (≤30 days). The latest developed MU was reported 1296 days (43.3 months) after LRYGB. Primary MUs were mainly localized exactly at the gastrojejunal anastomosis (74.1%), and the remaining quarter of MUs were found in the jejunum (18.5%) and the gastric pouch (7.5%). Only one ulcer-associated complication required surgical therapy because of ulcer perforation (3.7%). All patients with primary MUs received PPI therapy, and 81.5% additionally received sucralfate. 81.5% of the patients (n=22) developing a MU were smokers. After the initial diagnosis of a MU smoking cessation was recommended to all of them, but only two patients actually stopped smoking. In one the MU healed under conservative treatment, the other developed a recurrence. MU recurrence was diagnosed in 14 cases (51.9%). In eight of these cases (57.1%) the MU was found at the same localization as the primary MU. All patients received conservative medical treatment with PPI and sucralfate. MU re-recurrence was diagnosed in 5 (35.7%) patients and in 60% of these at the same

localization as the recurrence. Again, all patients received PPI and sucralfate as therapy with therapy success in all five patients.

Table 3 shows the univariate analysis of the risk factors leading to the development of MUs. The only significant factor leading to an almost 5-fold increased risk of the occurrence of MUs is smoking (p=0.002). The length of the biliary limb (<110 vs. ≥110 cm) and the alimentary limb (<130 vs. ≥130 cm) does not seem to be a risk factor for the development of MUs. A TWL ≥15% within a short period of time is not shown to be a risk factor for developing MUs. Other factors, such as cardiac and vascular diseases, do not significantly influence the incidence of MUs due to the low number of appearances in this sample.

The multivariate analysis in Table 4 confirms the results of the univariate analysis of the risk factors associated with MU. Smoking is an independent and statistically significant predictor of the development of postoperative MUs with a 4.6-fold greater risk. The 95% confidence interval for the odds ratio was from 1.70 to 12.45 (p=0.003). Analogous to the univariate analysis, the other risk factors do not demonstrate a significant impact on the development of MUs.

The influence of smoking on the appearance of MUs is demonstrated in Table 5. The present findings do not show statistical significance between current and former smokers (p=0.685). Additionally, smokers were divided into various groups comparing pack years and cigarettes per day. Light, moderate and heavy daily smokers show comparable rates of MUs (17.4% vs. 17.1% vs. 17.9%, respectively). There is also no difference in the rate of MUs regarding the intensity of lifetime tobacco exposure. Comparing light smokers with fewer than 10 CPDs and non-smoking patients shows a significantly higher rate of developing MUs for the light smokers (17.4 vs. 4.2%, respectively; p=0.027). The risk for an MU for patients with

low LTE and fewer than 10 pack years is also significantly higher than the risk of nonsmokers (13.9% vs. 4.2%, respectively; p=0.048).

Discussion

In the present study, 249 patients who underwent LRYGB were reviewed to evaluate the incidence, risk factors and complications of MUs.

Ten percent (n=27) of patients suffered from MUs after LRYGB, and among these, the majority occurred within the first postoperative year (66.7%; n=18). Previous studies showed a wide range, from 0.6 to 25% incidence of MUs, after LRYGB [12, 19, 20]. The most common risk factors suspected to influence the development of MU are *H. pylori* (HP) colonization, usage of NSAIDs, and tobacco and alcohol consumption. In the present study, smoking was a significant risk factor for MUs, but we further investigated whether the amount of smoking and the intensity of LTE influence the rate of MUs. Additionally, we proposed that the length of the biliary and alimentary limbs or the TWL might influence the development of MUs after LRYGB.

Fifty-one percent of the patients were regular smokers. Twenty-two of the 27 (81.5%) patients who suffered from MUs after LRYGB were smokers, which made smoking the major risk factor with a 4.9-fold greater risk in the univariate analysis and a 4.6-fold increased risk in the multivariate analysis for developing MUs after LRYGB.

Among frequently smoking patients, 11.8% developed MUs within the first postoperative year compared to 2.5% of the nonsmokers. Within two years after LRYGB, the appearance of MUs was observed in 13.4% of the smokers, in contrast to 3.3% of the nonsmokers. Recent literature confirms the results observed in our study. Azagury et al. reported a 2.5-fold greater risk for smokers to develop MUs [21]. A systematic review published by Coblijn et al. in 2014, including 41 studies with

17,000 patients, showed a correlation between smoking and the occurrence of marginal ulcers, as well as a reduced healing capacity between smokers and nonsmokers with MUs [12]. Fringeli et al. noticed the same influence of persistent smoking on the development of ulcerations at the gastrojejunostomy after LRYGB. Seventy-five percent of the study population were regular smokers at the time of the complication [19]. However, to the best of our knowledge, no previous research has investigated the influence of the amount of daily smoking or the intensity of LTE on marginal ulcers. Our present results demonstrate three things. First, there is no difference in the risk for marginal ulcers for current and former smokers. Second, the amount of smoking, measured in cigarettes per day, and the intensity of LTE, measured in pack years, have no influence on the rate of MUs. Finally, even light smokers with less than 10 CPDs and patients with less than 10 PYs have a significantly increased risk for the development of MUs compared to nonsmokers. To summarize, smoking at every intensity is associated with an extraordinary risk of MU formation after LRYGB. The exact influence of smoking on the pathogenesis of MUs is still unclear, but factors such as local ischemia - due to, e.g., mesenteric vascular disease - are likely to predispose patients for the development of MUs. Until now, case reports have mainly emphasized gastric and local ischemia followed by ulcerations, which could be part of the pathomechanism of MUs after LRYGB [22-24].

Very few studies have highlighted the complication rates regarding the length of the bypassed limbs in LRYGB. The length of the biliopancreatic limb (BPL) in patients who underwent LRYGB in this current series was measured between 80 and 150 cm. In patients with comorbidities such as diabetes mellitus and/or a BMI ≥50 kg/m^2, the minimum length of the BPL was 110 cm. In this study, we compared patients with a BPL ≥110 cm after LRYGB to those with a BPL ≤110 cm with regard to MU formation.

When the BPL was ≥110 cm, the risk of MU occurrence was 1.2 to 1.5 times higher but was not significantly different from that for shorter BPLs. An increased BPL length (200 cm) was shown to correlate with more nutritional deficiency (iron, vitamin D and calcium) compared with a BPL length of 60 cm, but the complication rate regarding MU formation did not differ (9% vs. 9%; overall 8.6%)[25]. A prospective analysis of 150 patients who underwent LRYGB with a BPL length of 200 cm reported MUs in 25 patients (16.6%), which confirms the results of recent literature [26]. The length of the alimentary limb in this study also varied between 80 and 150 cm and did not show a significant influence on the postoperative rate of MUs. Although the literature is scarce, hypotheses that an increased BPL length or a shorter alimentary limb length relative to the distal jejunal mucosa favor the appearance of MUs at the gastrojejunostomy do not seem to be valid.

Analogous to the BPL length, the TWL was not shown to have an impact on marginal ulcers. During a systematic study of the existing literature, we could not find any former studies that investigated the influence of TWL on MU formation, which confirms that the present series is the first to show the effect of TWL.

The main location of the MUs was exactly at the gastrojejunal anastomosis (74.1%), and the remaining quarter of MUs were divided among the jejunum (18.5%) and the gastric pouch (7.5%). In the literature, there are only a few studies that provide information about the exact location of MUs. Slightly different results are presented in the study by Azagury et al., where most of the MUs were located at the gastrojejunostomy (50%) or at the jejunum (40%)[21].

The great majority of MUs (66.7%) occurred within the first year after LRYGB. Two patients (7.4%) suffered from MU formation ≤30 days after the operation. The mean time until ulceration was 358 days (11.9 months). The latest-developed MU was

reported 1296 days (43.2 months) after LRYGB. The literature differentiates between the formation of MUs that appear within the first year, defined as early MUs, and those that appear after the first year, defined as late MUs. The occurrence of early MUs is more likely than that of late ulcerations [17, 19, 27, 28].

Patients with MUs received standardized treatment with PPIs. The successful treatment of MUs was determined as the absence of symptoms. Subsequent repeat endoscopy was only performed when the patient's symptoms were persistent. In approximately 50% of the patients with MUs, ulcer recurrence was diagnosed within the first 6 to 8 weeks at a different location than a prior ulcer or after healing. All patients with ulcer recurrence were treated conservatively. Despite the standardized treatment of MUs with PPIs, the incidence of ulcer recurrence is still high and often requires surgery [13, 17, 29].

Only one patient required surgical treatment following an MU due to perforation (3.7%). The patient had persistent NSAID consumption. The perforated ulcer was treated laparoscopically with interrupted sutures, lavage and drainage. Simultaneously, an endoluminal stent was placed endoscopically. Perforation of the marginal ulcer is a severe complication with a high morbidity and mortality rate [30, 31]. Risk factors for perforation seem to be similar to those of the development of MUs [31].

We acknowledge some limitations in this present study in addition to the fact that it is a retrospective analysis. Data regarding the smoking behavior of the patients were collected at the time of the operation and at irregular time intervals during the follow-up but not with the same accuracy as at the initial interview. However, to the best of our knowledge, none of the patients stopped smoking or changed the amount of smoking postoperatively. Former smokers were defined according to the definition of

the United States Centers for Disease Control and Prevention as patients who had smoked at least 100 cigarettes in their life but had stopped smoking at the time of the operation, but we have no reliable data on the time interval between when they had quit smoking and the operation. We are therefore not able to distinguish between former smokers who had quit smoking either right before or months or years before the operation. We are also not able to calculate the risk of MU development for very light, occasional or so-called social smokers with less than five CPDs. These results would have been very interesting, especially compared with the risk for an MU of nonsmoking patients, but the number of cases in our analysis was too small for a reliable statement.

Conclusion

Numerous risk factors have been discussed that favor the development of MUs, but smoking at any intensity seems to be one of the key factors as demonstrated in this present analysis. Neither the amount of daily smoking nor the lifetime tobacco exposure seems to influence the rate of marginal ulcers. Even light smokers and patients with a low LTE are at significantly increased risk for MUs postoperatively. Therefore, smoking cessation prior to bariatric surgery must be strongly recommended. In addition, we suggest further investigations of the risk for MUs in former and very light smokers.

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Table 1 Patient and Clinical Characteristics (n=249)

Age	(years)	45.5 (±12.7)
Sex	Male	64 (25.7%)
	Female	185 (74.3%)
Height	(cm)	168.0 (±9.4)
Weight preoperative	(kg)	122.1 (±23.5)
BMI preoperative	(kg/m^2)	43.1 (±6.2)
Follow-up time TWL (Q1;Q3)	(days)	74.0 (57.5; 115.5)
TWL	(%)	19.4 (±7.8)
BMI difference	(kg/m^2)	8.5 (±3.6)
Comorbidities	Diabetes mellitus	33 (13.3%)
	Arterial hypertonia	92 (36.9%)
	Peripheral arterial occlusive disease	1 (0.4%)
	Thromboembolic event	14 (5.6%)
	Coronary heart disease	7 (2.8%)
	Cardiac insufficiency	3 (1.2%)
	Cardiac arrythmia	1 (0.4%)
	COPD	9 (3.6%)
Smoking		129 (51.8%)
Amount of Smoking (n=129)	(Cigaretts/day)	18.2 (±13.1)
	(Pack years)	22.7 (±17.5)
Biliary limb	(cm)	107.3 (±12.9)
Alimentary limb	(cm)	121.4 (±12.3)

All values as numbers and percentage or as mean ± Standard Deviation (SD)

BMI Body-mass-index, TWL Total Weight Loss, COPD Chronic obstructive pulmonal disease

Table 2 Characteristics of Marginal ulcer

Primary MU	Diagnose overall		27 (10.8%)
	Localization*	Anastomosis	20 (74.1%)
		Pouch	2 (7.5%)
		Jejunum	5 (18.5%)
	Therapy	PPI	27 (100%)
		Sucralfate	22 (81.5%)
		Surgery	1 (3.7%)
	Smoking		81.5%
MU recurrence	Diagnose overall		14 (51.9%)
	Localization*	Anastomosis	10 (71.4%)
		Pouch	2 (14.3%)
		Jejunum	3 (21.4%)
	Therapy	PPI	14 (100%)
		Sucralfate	14 (100%)
	Smoking		78.6%
MU re-recurrence	Diagnose overall		5 (35.7%)
	Localization*	Anastomosis	2 (40.0%)
		Pouch	-
		Jejunum	4 (80.0%)
	Therapy	PPI	5 (100%)
		Sucralfate	5 (100%)
	Smoking		100%

All values as numbers and percentage or as median
*multiple selection possible

MU Marginal ulcer, PPI Proton pump inhibitor

Table 3 Univariate analysis of Risk factors associated with MU

		n	Rate MU	OR	95% CI	p-Value
Smoking	No	120	4.2%		Reference	
	Yes	129	17.1%	4.90	1.80-13.40	0.002
Diabetes mellitus	No	216	10.2%		Reference	
	Yes	33	15.2%	1.58	0.55-4.49	0.396
Prior Helicobacter pylori	No	205	11.2%		Reference	
	Yes	24	12.5%	1.13	0.31-4.08	0.852
Arterial hypertension	No	157	12.1%		Reference	
	Yes	92	8.7%	0.69	0.29-1.70	0.406
Cardiac/Vascular Disease	No	229	11.8%		Reference	
	Yes	20	0	0.57	0.24-1.40	0.209
Alcohol	No	171	11.1%		Reference	
	Yes	78	10.3%	0.91	0.38-2.19	0.841
NSAID praeoperative	No	223	11.7%		Reference	
	Yes	26	3.8%	0.30	0.04-2.33	0.251
NSAID postoperative	No	78	9.0%		Reference	
	Yes	171	11.7%	1.34	0.54-3.32	0.523
Sex	Female	185	10.8%		Reference	
	Male	64	10.9%	0.99	0.40-2.46	0.978
Revisional surgery	No	206	10.2%		Reference	
	Yes	43	14.0%	1.43	0.54-3.78	0.427
Biliary limb	<110cm	154	9.1%		Reference	
	≥110cm	95	13.7%	1.59	0.71-3.54	0.260
Alimentary limb	<130cm	143	10.5%		Reference	
	≥130cm	104	11.5%	1.11	0.50-2.50	0.794
TWL	<15%	46	10.9%		Reference	
	≥15%	111	8.1%	0.72	0.23-2.29	0.582

CI Confidence interval, MU Marginal ulcer, NSAID Non-steroidal anti-inflammatory drug, OR Odds-ratio, TWL Total Weight loss

Table 4 Multivariate analysis of Risk factors associated with the appearance of MU

	OR	95% CI	p-Value
Nicotine (yes)	4.69	1.64-13.44	0.004
Diabetes mellitus (yes)	2.50	0.68-9.22	0.168
Prior Helicobacter pylori (yes)	1.05	0.26-4.17	0.945
Arterial hypertension (yes)	0.57	0.20-1.62	0.289
Alcohol (yes)	0.73	0.27-1.95	0.525
NSAID praeoperative (yes)	0.21	0.03-1.79	0.154
NSAID postoperative (yes)	1.16	0.40-3.32	0.787
Revisional surgery (yes)	1.33	0.43-4.13	0.620
Biliary limb (≥110cm)	1.16	0.45-2.98	0.945
Alimentary limb (≥130cm)	1.09	0.43-2.76	0.863

CI Confidence interval, MU Marginal ulcer, NSAID Non-steroidal anti-inflammatory drug, OR Odds-ratio

The multivariate analysis is age and gender adjusted.

Table 5 Influence of Smoking (n=129) on the appearance of MU

		n	Rate MU	OR	95% CI	p-value
Smoking	Current	114	17.5%	1.38	0.29-6.61	0.685
	Former	15	13.3%		Reference	
Smoking	Light	23	17.4%		Reference	
	Moderate	35	17.1%	0.98	0.25-3.95	0.980
	Heavy	56	17.9%	1.03	0.29-3.70	0.961
Smoking	No	120	4.2%		Reference	
	Light	23	17.4%	4.84	1.20-19.67	0.027
LTE	Low	36	13.9%		Reference	
	Moderate	60	18.3%	1.39	0.44-4.39	0.573
	High	33	18.2%	1.38	0.38-5.03	0.627
LTE	No	120	4.2%		Reference	
	Low	36	13.9%	3.71	1.01-13.63	0.048

CI Confidence interval, LTE Lifetime tobacco exposure, MU Marginal ulcer, OR Odds-ratio

Highlights

1. Smoking at every intensity is associated with an extraordinary risk of MU after LRYGB

2. Increased BPL or shorter alimentary limb length do not seem to favour MU formation