Analysis of Surgical Risk Factors in Tailoring Digestive Anastomosis

1

Mario Testini, Ilaria Fabiola Franco, Valentina Ferraro, Angela Gurrado, and Germana Lissidini

Failure of gastrointestinal anastomosis results in *leaks*, *fistulas* and dehiscence, still representing the major complication following abdominal surgery. Despite the improved perioperative assessment, the standardization of surgical technique, and the use of innovative devices, reported incidence of gastrointestinal anastomosis leakage ranges from 2 to 12 % [1–4], significantly increasing mortality (7–12 %), morbidity (20–30 %), and hospital resource utilization [5].

The anastomotic leakage rate is highly variable and strictly depending on the anastomotic site [6]: failure of esophagojejunostomy is a potentially catastrophic event, as a missed leakage of a colorectal anastomosis; on the contrary, gastroenteric or entero-enteric anastomosis leakage could be more often managed by a conservative approach. Therefore, anastomotic leakage represents one-third of overall mortality in colorectal surgery [6] and even more in esophagectomy and total gastrectomy [7–9].

The *risk factors* for anastomotic failure in digestive surgery (Table 1.1) can be divided into two groups:

(a) General
(b) Local also including factors related to surgical technique

Diabetes mellitus seems to have an important role on the anastomosis healing. Experimental studies demonstrated an increased anastomotic leakage in untreated diabetic rats vs diabetic one

Table 1.1 Risk factors of anastomotic leakage

General	Local
Age	Bowel preparation
Sex	Surgical technique
Diabetes mellitus	Mechanical or manual anastomosis
Nutritional state	Emergency surgery
Blood transfusion	Surgical skills
Uremia	Comorbidity
Anemia	Peritonitis
Preoperative radiotherapy	Bowel obstruction
Chemotherapy	Antibiotic therapy prophylaxis
Chronic obstructive pulmonary disease	Operative time
Cardiopathy	Protective ileostomy
Hypotension	Use of drain
Weight loss	High tension at anastomosis level
Obesity	Vascularization
Coagulopathy	Anastomosis site and number
Smoke	Positive surgical margins after resection (Flogosis, necrosis, neoplasia)
Corticosteroid therapy	
Metastatic disease	
Fluid and electrolyte disorders	

M. Testini, MD (✉) • I.F. Franco • V. Ferraro
A. Gurrado, PhD • G. Lissidini, PhD
Unit of Endocrine, Digestive and Emergency Surgery, Department of Biomedical Sciences and Human Oncology, University Medical School "A. Moro" of Bari, Piazza Giulio Cesare, 11, Bari 70124, Italy
e-mail: mario.testini@uniba.it; ilariafrn@libero.it; ferrarov.v@libero.it; angelagurrado@libero.it; germana.lissidini@ieo.it

G. Galloro (ed.), *Endoscopic Follow-up of Digestive Anastomosis*,
DOI 10.1007/978-88-470-5370-0_1, © Springer-Verlag Italia 2014

treated by insulin therapy. Obesity, anemia, hypotension, uremia, coagulopathy, age, and male sex are also reported in some experiences [1–5, 8]. Otherwise, a prolonged nonsteroidal anti-inflammatory drugs (NSAIDs) use yields a higher risk of anastomotic breakdown. NSAIDs result in an increased rate of anastomotic leakage after colorectal surgery during the postoperative treatment too; consequently, cyclooxygenase-2 selective NSAIDs should be used with caution after colorectal resections with primary anastomosis [10, 11]. Moreover, some authors [12, 13] consider intraoperative blood loss of 200 mL or more, blood transfusions (more than 2 U/24 h), and low albumin serum level (inferior than 3.0 g/L) as significant factors. Conversely, chronic hypovolemia and weight loss don't seem to be significant factors, while vascular disease, advanced tumor stage, radiotherapy (Figs. 1.1 and 1.2), and chemotherapy are associated with increased anastomotic leakage. However, localized and generalized leaks also have a significant negative impact on overall, cancer-related, and disease-free survival [1–8, 12–14].

Among the local factors, compelling evidence exists that intestinal bacteria play a predominant role in the pathogenesis of anastomotic leakage [15]. Moreover, some authors consider bowel obstruction (Fig. 1.3), while others don't confirm its relevance [13]. Sepsis appears to be associated with anastomosis leakage, also enhancing the collagenolytic effects of the collagenosis [16]. We believe that sepsis still represents an absolute contraindication to a single-stage anastomosis during emergency colorectal surgery, above all in the presence of endoabdominal multiple abscesses and collections. In these pathological evidences (Fig. 1.4), a prudent behavior is mandatory, with the performance of a *Hartmann* procedure. The leakage rate appears significantly higher in patients undergoing to emergency surgery than elective one [12, 17] (38.1 % vs 13.3 % in *Kim* experience [18], 13 % vs 3.9 % in our [13]). Moreover, a full bowel preparation allows greater intraoperative cleaning, reducing fecal contamination, even if *Harris* [19] suggests elective colon resection performed safely without preoperative mechanical bowel preparation.

The decrease of *mortality* and *morbidity* due to anastomotic leaks can be also gained by performing intraoperative pneumatic test, defunctioning ileostomy, and drain tube insertion, as reported by *Boccola* [14, 20].

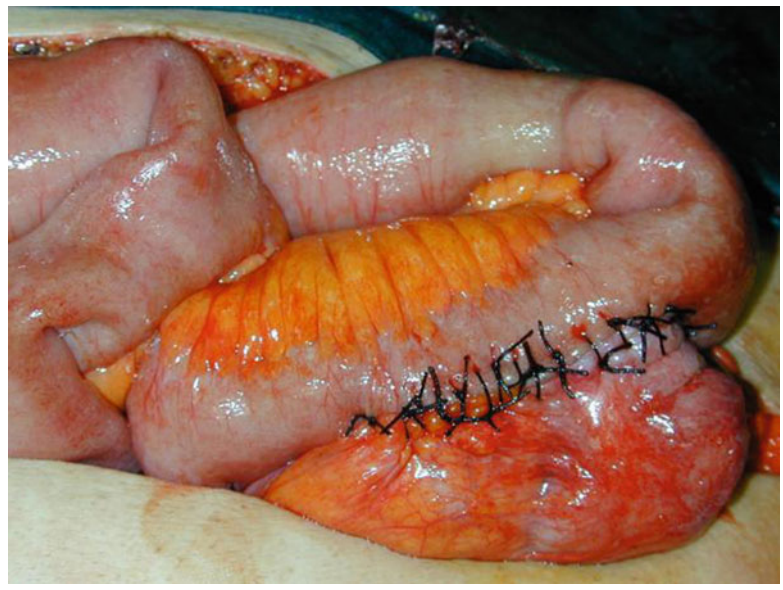

Fig. 1.1 Small bowel side-to-side anastomosis in a patient affected by volvulus following radiation enteritis

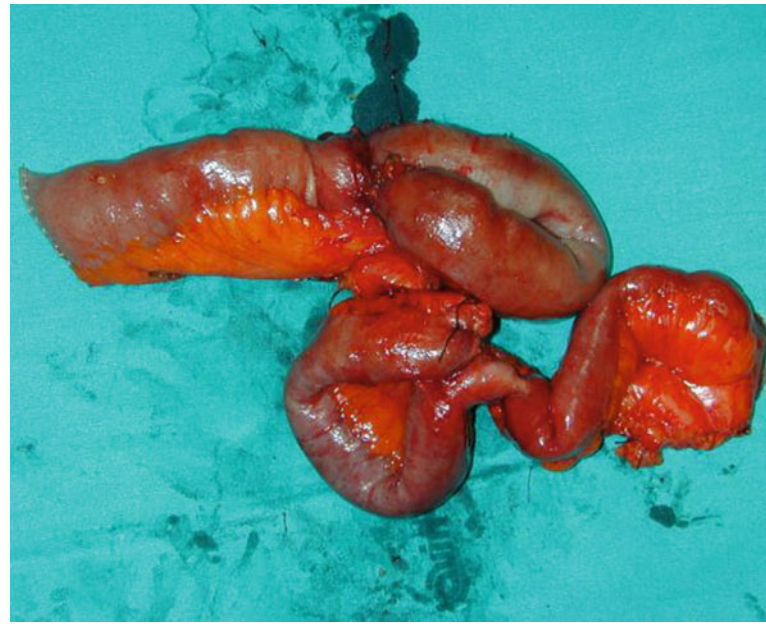

Fig. 1.2 Small bowel volvulus caused by radiation enteritis

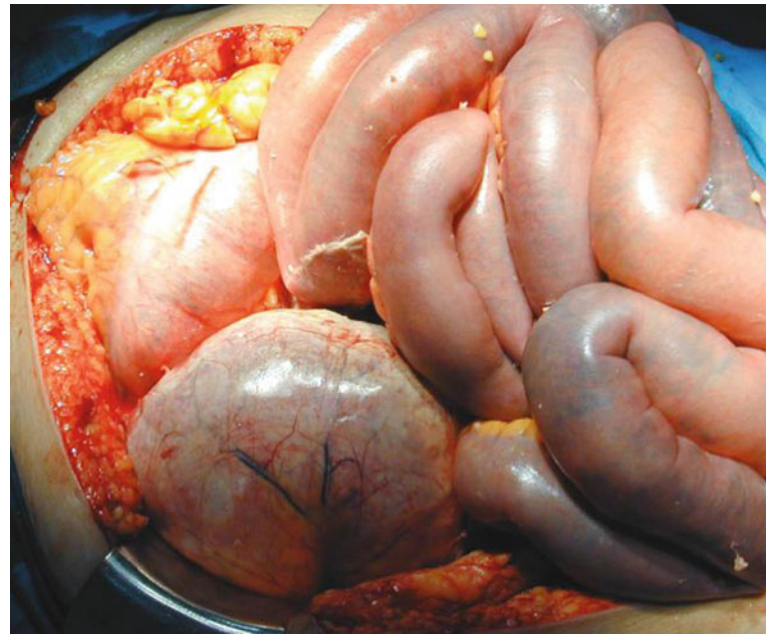

Fig. 1.3 Mechanical bowel obstruction with cecum diastase due to stenosis by carcinoma of the rectum

The choice of anastomosis remains at the discretion of the surgeon, largely depending on experience, patient's characteristics, and operative setting, even if there isn't a clear evidence for one technique over another [20]. Stapled anastomoses is associated with a significant lower leak rate regardless of anastomotic location [21], even if, as recently surprisingly reported by *Korolija* [21], anastomotic failures can be more than twice with stapled than hand sewn in the emergency general surgery.

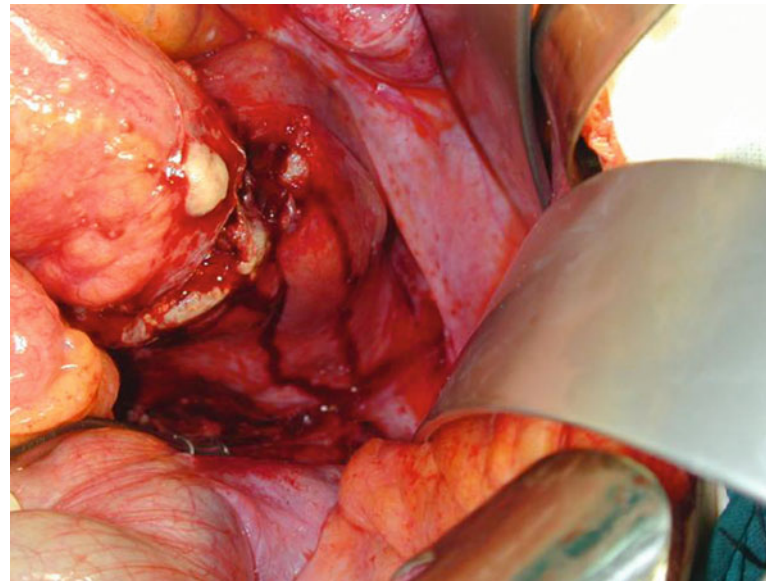

Fig. 1.4 Pelvic abscess from perforated carcinoma of the rectum

The anastomosis site represents one of the main problems in the digestive surgery. In fact, low colorectal [12, 14] as well as esophagus–jejunal [8, 9] anastomoses are associated with a higher incidence of failure. In this regard, *Montesani* reported re-peritonealizing and technical changes in the mechanical suture as useful in order to reduce failures following low anterior resection [22]. No differences in anastomotic colorectal leak are reported between laparoscopic and open surgery [23], even if a lower incidence in the laparoscopic one is reported in a recent review (3.0–17 % vs 0–23.0 %) [24]. The use of a protective stoma is controversial, with widespread use in some experience and markedly reduced or abolished in other [25]. In our opinion, according to *Hansen* [25], we justify the use of a protective ileostomy or colostomy only in situations with a high risk of failure as low colorectal anastomosis, difficult pelvic dissection, and risk patients. However, it is important to consider also the morbidity related to re-surgery and to the stoma management. Therefore, we believe that when an anastomotic failure appears, a late opening of a ghost-ileostomy could be not useful. A tension at the level of anastomosis resulting from an incomplete mobilization, an insufficient blood supply, and the absence of margins' integrity for necrosis, inflammatory disease, or cancer are univoquely accepted as high-risk local factors [1]. For these reasons a proper mobilization of the splenic flexure is essential to prevent the stretching on the anastomosis in left colon *resective surgery* [12]; otherwise, the low percentage of splenectomies of necessity reported in the literature does not justify different behaviors. Instead, the kind of disease does not seem to constitute a risk element [22] but a higher incidence of tumor recurrence resulting from the onset of dehiscence is reported in literature [14]. In univariate analysis [8], the patient age, the pulmonary insufficiency, the lymph node dissection, the combined resection of other organs, the omental resection, the operative time, the blood loss, the intraoperative blood transfusion, and the postoperative creatinine level were reported as significant factors influencing anastomotic healing. Also, a multivariate analysis [1] identified *pulmonary insufficiency* and duration of operation as predictors of anastomotic leakage.

Assembling the general and loco-regional with technical factors, we still agree with the multivariate analysis of *Golub* [3] that selected five statistically significant predictive parameters: chronic obstructive pulmonary disease (COPD), bowel obstruction, peritonitis, corticosteroids use, blood transfusion >2 U, and serum albumin level <3.0 g/L. Furthermore, a supplemental 80 %

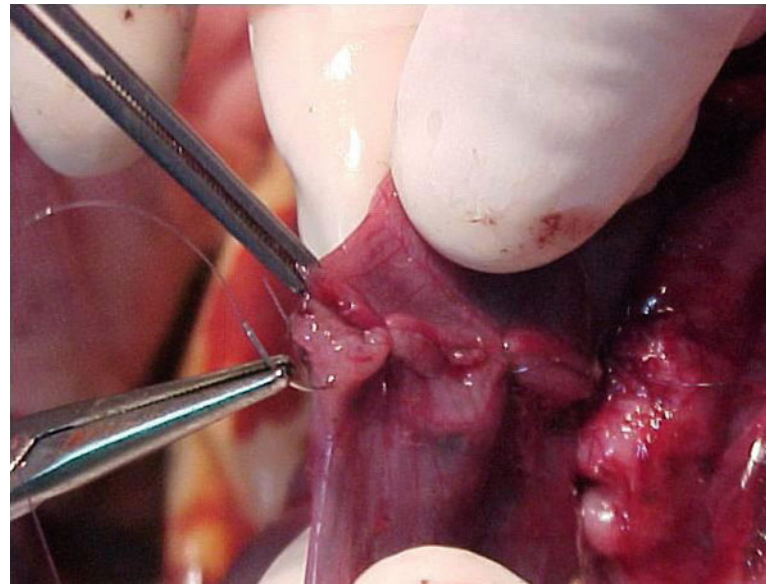

Fig. 1.5 Experimental study: small bowel anastomosis in the rabbit

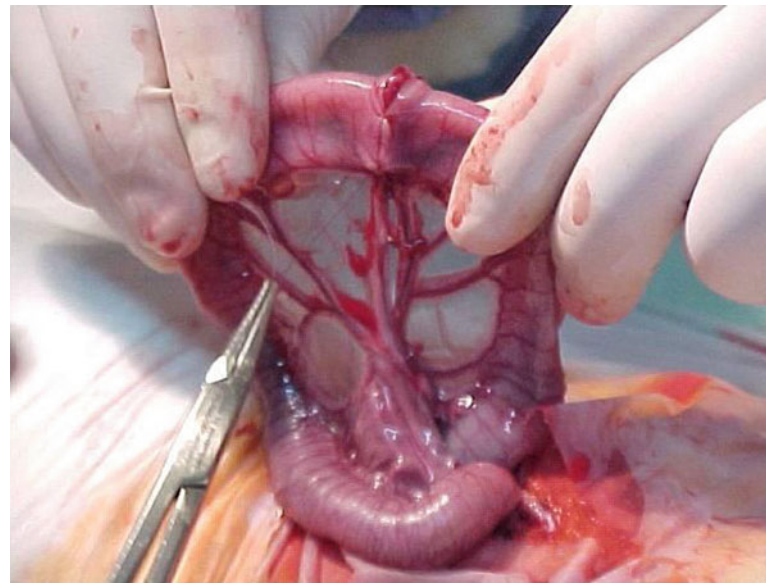

Fig. 1.6 Experimental study: colo-colic anastomosis in the rabbit

FiO2 during the rectal cancer surgery and immediate postoperative period reduces anastomotic failure [26].

Despite of the importance of general, local, or technical factors, at the base of the anastomosis failure could be an "innermost" *primum movens*, to look for both at the pathophysiological and biochemical levels. In fact, it is not otherwise possible to explain leakage in anastomoses performed under optimal conditions of elective surgery, using perfect technique, in patients without general risk factors.

Starting from this *rationale*, and from the higher leak rate in large than in small bowel anastomoses, we performed experimental studies comparing resected and anastomosed segments of small and large bowel (Figs. 1.5 and 1.6) using biochemical and tensiometric methods [27–29].

Previous experimental studies showed an early and massive deposition of collagen and a greater distress of the large compared with the small bowel. It is also well known the importance of the maturation of collagen in the anastomosis *healing process* and that an adequate *metabolic energy* is needed to realize healing process. Starting from these assumptions, our first study [27] was to analyze the process of oxidative phosphorylation (mitochondrial function) in colon and small bowel during the anastomotic process. The results of polarographic, spectrophotometric, and gel-electrophoresis analysis showed a prevalence of oxidative metabolism in the colic mitochondria compared with the small bowel, demonstrated by an increased activity of oxygen consumption and enzymatic respiratory. On the contrary, the small bowel showed a prevalence of glycolytic metabolism. Summarizing these results, the small bowel burns sugars through anaerobic glycolysis to produce energy for collagen deposition and healing process of anastomosis, and therefore is less influenced by the decrease of available oxygen occurring in the anastomotic area during surgical stress. By contrast, colon shows a metabolism mainly linked to the oxidative phosphorylation, presents a more difficult anastomotic healing process in absence of oxygen, and shows a greater risk of leak. This observation is confirmed by the decrement of biochemical parameters in colonic cells. In fact, at the end of the study, we observed a small bowel tissue biochemically identical to the preoperative one, while the colon tissue showed marked differences.

In the second phase of our experiments [29], we investigated if *biochemical differences* were also associated with motility and peristalsis. In fact, the aim was to verify in vitro how much the surgical stress could affect contractility of the smooth muscle (both spontaneous and agonist induced) of both organs, correlating these results to the biochemical parameters too. The results showed an anarchist contractility and late restart of colic peristalsis compared with an early and regular contractile activity of the small bowel. Such motor abnormalities may be the consequence of abnormal biochemical changes, because the ATP is necessary in the maintenance of membrane potentials, in calcium homeostasis, and in the actin–myosin interactions. The study showed that surgical stress determines abnormalities in the mitochondria of the smooth muscle, damaging the contractility. In consequence of a difficult process of collagen maturation and deposition, these changes are prevalent in the colon and may explain unexpected anastomotic leakage in the absence of apparent risk factors.

At confirm of these experimental results, an other retrospective study [30] showed a significant leakage rate (24.1 % vs 2.7 %, $P=0.001$) in patients who underwent colic resection, affected by COPD compared with patients not affected by COPD. COPD is characterized by a condition of chronic hypoxemia that determines a reduced peripheral oxygen delivery (DaO2). However, the mechanism of control of blood flow and of oxygen extraction at intestinal level let the consumption of oxygen (VO2) to be independent from DaO2; thus, the reduced DaO2 does not influence the VO2 in patients with COPD. On the contrary, during the healing process of colic anastomosis, the need of oxygen increases, both for higher metabolic request related to the oxidative phosphorylation and for the synthesis of collagen. In patients with COPD undergoing to resective surgery and colic anastomosis, these pathophysiologic changes inevitably relate the VO2 to the insufficient DaO2. Therefore, the correction of impaired oxygen tension could reduce the high incidence of anastomotic leak in patients with COPD. On the basis of these results, a preoperative evaluation of respiratory tract (chest X-ray, CT, spirometric tests, hemogasanalysis) is essential before colic resective surgery, especially in aged patients affected by COPD. Moreover, a perioperative oxygen therapy also may facilitate anastomotic healing.

In a further *experimental study* [31] we investigated in pigs if *pericardium bovine patch* (Tutomesh®) wrapping ileoileal and colo-colic anastomosis seals the suture line and promotes anastomotic healing. By using integrated and translational methodologies, we described intraoperative, histological, biochemical, tensiometric, and

electrophysiological evaluations performed on intestinal specimens.

Biologic materials have been introduced in general surgery as reinforcement of abdominal wall hernia in contaminated or potentially contaminated settings, when the use of alloplastic meshes is contraindicated [26–31]. In this respect, an innovative application of biologic patch could be their use as reinforcement of the gastrointestinal anastomotic suture line [7–9]. Therefore, the aim of the study was to verify if bovine pericardium patch improved the healing of anastomosis, when in vivo affixed on the hand-sewn suture line of large and small bowel anastomosis of the pigs.

A further end point was to verify if the patch was able to avoid anastomotic leakage in the presence of a deliberately incomplete left suture.

The results showed that the application of a patch wrapping the colic anastomosis produces a positive effect in the healing compared with untreated samples also showing, during follow-up, an almost full recovery [1–3, 26]. In the large bowel patch anastomosis group, the delay of oxidative stress in the early stage of reparative processes could prevent the damage of noble cells (like tissue stem cells), allowing a full restoration of tissue functions and also decreasing fibrotic reaction during the next stages of healing process. Under a condition of cellular oxidative stress, the protective effect of the patch is compatible with the histological observation of a moderate inflammatory infiltrate; moreover, the late increase of reacting oxygen species can be correlated with an appearance of a granulation tissue, without damages during the repairing process. Therefore, tensiometric evaluations in colic specimens suggested that the use of patch can preserve smooth muscle response to acetylcholine similar to the response of controls (specimens without anastomosis) in the early postoperative time (48 h–14 days), while the colic preparations with traditional anastomosis showed contractility alterations. In the ileum, the presence of pericardium bovine patch clearly prevents the alterations following the traumatic effect of surgery. However, pericardium bovine patch appears to modulate and counteract the traumatic effect of surgery. Overall, our results suggest that the application of the patch also improves the intestinal mucosal function, restoring the almost normal transport properties. In conclusion, the use of the pericardium bovine patch as *reinforcement* of the intestinal anastomosis could be safe and effective. Moreover, the leakage prevention in the presence of iatrogenic perforation is also unpublished before and it represents a surprising histopathological data. On the basis of these experimental results, we started a multicenter-controlled clinical trial in humans, comparing the outcomes of intestinal anastomosis performed with and without the bovine pericardium patch in risk patients.

In conclusion, despite studies regarding risk factors and prevention, the anastomotic leakage continues to be the most serious *complication* after *gastrointestinal tract surgery*. A thorough surgical technique, avoiding hazardous anastomoses without protective stoma, or without two-stage surgery in patients at risk, could allow a significant reduction of healing process failure. A tailored surgical approach to both patient's physiology and disease is the most important factor that influences anastomotic integrity after resective surgery. Further studies regarding innovative devices able to improve the healing process of anastomosis are needed.

References

1. Telem D, Chin E, Nguyen S et al (2010) Risk factors for anastomotic leak following colorectal surgery. A case–control study. Arch Surg 145:371–375
2. Kang CY, Halabi WJ, Chaudhry OO et al (2013) Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 148(1):65–71
3. Golub R, Golub RW, Cantu R Jr et al (1997) A multivariate analysis of factors contributing to leakage of intestinal anastomoses. J Am Coll Surg 184:364–372
4. Trencheva K, Morrissey KP, Wells M et al (2013) Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. Ann Surg 257(1):108–113
5. Snijders HS, Wouters MW, van Leersum NJ et al (2012) Meta-analysis of the risk for anastomotic leakage, the postoperative mortality caused by leakage in relation to the overall postoperative mortality. Eur J Surg Oncol 38(11):1065–1070

6. Branagan G, Finnis D, Colorectal Cancer Audit Working Group et al (2005) Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 48:1021–1026
7. Sierzega M, Kolodziejczyk P, Kulig J, Polish Gastric Cancer Study Group et al (2010) Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. Br J Surg 97(7):1035–1042
8. Deguchi Y, Fukagawa T, Morita S et al (2012) Identification of risk factors for esophagojejunal anastomotic leakage after gastric surgery. World J Surg 36(7):1617–1622
9. Markar SR, Arya S, Karthikesalingam A et al (2013) Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol 20(13):4274–81
10. Rutegård J, Rutegård M (2012) Non-steroidal anti-inflammatory drugs in colorectal surgery: a risk factor for anastomotic complications? World J Gastrointest Surg 4(12):278–280
11. Klein M, Gögenur I, Rosenberg J et al (2012) Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. BMJ 26(9):345, 1–13
12. Warschkow R, Steffen T, Thierbach J et al (2011) Risk factors for anastomotic leakage after rectal cancer resection and reconstruction with colorectostomy. A retrospective study with bootstrap analysis. Ann Surg Oncol 18(10):2772–2782
13. Testini M, Margari A, Amoruso M et al (2000) The dehiscence of colorectal anastomoses: the risk factors. Ann Ital Chir 71:433–440
14. Boccola MA, Buettner PG, Rozen WM et al (2011) Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg 35(1):186–195
15. Shogan BD, Carlisle EM, Alverdy JC et al (2013) Do we really know why colorectal anastomoses leak? J Gastrointest Surg 17(9):1698–1707
16. Miccini M, Borghese O, Scarpini M et al (2011) Anastomotic leakage and septic complications: impact on local recurrence in surgery of low rectal cancer. Ann Ital Chir 82(2):117–123
17. Matthiessen P, Hallböök O, Rutegård J et al (2007) Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 246:207–214
18. Kim JJ, Liang MK, Subramanian A et al (2011) Predictors of relaparotomy after nontrauma emergency general surgery with initial fascial closure. Am J Surg 202(5):549–552
19. Harris LJ, Moudgill N, Hager E et al (2009) Incidence of anastomotic leak in patients undergoing elective colon resection without mechanical bowel preparation: our updated experience and two-year review. Am Surg 75(9):828–833
20. Boccola MA, Lin J, Rozen WM et al (2010) Reducing anastomotic leakage in oncologic colorectal surgery: an evidence-based review. Anticancer Res 30(2): 601–607
21. Korolija D (2008) The current evidence on stapled versus hand-sewn anastomoses in the digestive tract. Minim Invasive Ther Allied Technol 17(3): 151–154
22. Montesani C, De Milito R, Chiappalone S et al (1992) Critical evaluation of the anastomoses in large bowel experience in 533 cases. Hepatogastroenterology 39:304–308
23. El-Gazzaz G, Geisler D, Hull T et al (2010) Surgery: risk of clinical leak after laparoscopic versus open bowel anastomosis. Surg Endosc 24(8):1898–1903
24. Hotta T, Yamaue H (2011) Laparoscopic surgery for rectal cancer: review of published literature 2000–2009. Surg Today 41(12):1583–1591
25. Hansen O, Schwenk W, Hucke HP et al (1996) Colorectal stapled anastomoses. Dis Colon Rectum 39:30–36
26. Schietroma M, Carlei F, Cecilia EM et al (2012) Colorectal infraperitoneal anastomosis: the effects of perioperative supplemental oxygen administration on the anastomotic dehiscence. J Gastrointest Surg 16(2):427–434
27. Testini M, Scacco S, Loiotila L et al (1998) Comparison of oxidative phosphorylation in the small vs large bowel anastomosis. Eur Surg Res 30(1): 1–7
28. Testini M, Piccinni G et al (1999) Wound healing of intestinal anastomosis after digestive surgery under septic condition. World J Surg 23:1315–1316
29. Testini M, Portincasa P, Scacco S et al (2002) Contractility in vitro and mitochondrial response in small and large anastomized rabbit bowel. World J Surg 26:493–498
30. Testini M, Miniello S, Piccinni G et al (2003) Correlation between chronic obstructive bronchial disease and colonic anastomosis dehiscence in the elderly. Ann Ital Chir 74:247–250
31. Portincasa P, Testini M et al (2011) The apposition of a resorbable pericardial Bovine patch (Tutomesh®) on intestinal anastomoses improves functional mucosal recovery in pig ileum and colon assessed by using chamber electrophysiological studies. Gastroenterology 140(5 suppl 1):S-656