Journal of Gastrointestinal Surgery (2019) 23:339–347
https://doi.org/10.1007/s11605-018-3891-x

ORIGINAL ARTICLE

Anastomotic Location Predicts Anastomotic Leakage After Elective Colonic Resection for Cancer

Thibault Voron[1,2] · Matthieu Bruzzi[1,2] · Emilia Ragot[1] · Franck Zinzindohoue[1,2] · Jean-Marc Chevallier[1,2] · Richard Douard[1,2] · Anne Berger[1,2]

Received: 23 January 2018 / Accepted: 16 July 2018 / Published online: 3 August 2018

Abstract

Background Anastomotic leakage (AL) is a potential feared complication after colorectal resection, which is associated with an increased risk of postoperative mortality and frequently requires additional surgery. The aim of this study was to assess major independent risk factors for AL after elective colonic resection for cancer, including anastomotic location.

Methods Among 1940 consecutive patients referred to our institution for colorectal adenocarcinoma, 1025 patients had elective colonic resection with intraperitoneal anastomosis without diverting stoma. Risk factors were assessed among preoperative, operative, and histological data.

Results Clinical AL was observed in 36 patients (3.5%) with 24 patients requiring revisional surgery (67%). In multivariate analysis, endoscopic impassable tumor and colo-colic or ileo-colic anastomosis were independent risk factors for AL. The occurrence of AL was associated with poor overall (43.1 months vs. 146.4 months; $p < 0.001$) and disease-free survival (40.5 months vs. 137.3 months; $p = 0.003$).

Conclusion Anastomotic leakage occurs more frequently after colo-colic and ileo-colic anastomosis than after intraperitoneal colorectal anastomosis.

The right colectomy appears to be at higher risk of AL, with a greater risk of surgical intervention than after an elective left colectomy. Ileo-colic anastomosis should be avoided in cases of suboptimal conditions.

Keywords Colonic resection · Colorectal cancer · Anastomotic leakage · Right colectomy · Prognostic factors

Introduction:

With an estimated 1,360,000 new cases diagnosed in 2012, colorectal cancer is the third most frequently diagnosed cancer and the fourth leading cause of cancer-related death in the world.[1] In 70% of these newly diagnosed patients, a curative treatment could be done, mainly based on resection of the colorectal tumor with immediate intestinal continuity restoration except in emergency situations including obstruction and perforation. Despite advances in anastomotic techniques, postoperative monitoring and diagnostics, an anastomotic leak (AL) remains a feared complication after colorectal resection, which has an incidence and consequences that have not changed appreciably during the past 20 years. In recent publications, the incidence rate of AL ranges widely from 1 to 16%[2–6] depending on the definition of AL chosen and patient-inclusion criteria.

The consequences of these leaks are well known, including longer hospital length of stay, an increase in postoperative mortality and morbidity rates,[7] and potentially the need for another surgery in order to create a definitive or temporary diverting stoma. Moreover, among patients with colorectal cancer, anastomotic leakage seems to increase the risk of cancer recurrence and diminishes overall survival.[8–11] Anastomotic leakage is therefore a dreaded complication that severely impacts patient quality of life and increases the cost of medical care. Thus, the occurrence of stage IIIb postoperative complications according to Clavien-Dindo's classification after colorectal resection, such as anastomotic leakage requiring surgery, increases full inpatient costs from $26,420 to $95,550(USD).[12]

✉ Thibault Voron
Thibault.voron@gmail.com

1 Department of General, Digestive and Oncological Surgery, Georges Pompidou European Hospital, AP-HP, Assistance Publique-Hôpitaux de Paris, 20-40 rue Leblanc, 75908 Paris, France

2 Faculté de Médecine Paris Descartes, Paris, France

Recently, it has been demonstrated that the surgeon's clinical judgment is not accurate in predicting anastomotic leakage after intestinal surgery.[13] Therefore, an accurate risk assessment for anastomotic leakage is needed in order to help tailor treatment in colorectal surgery.

Unfortunately, the majority of studies designed to assess risk factors for anastomotic leakage included numerous and various situations. Thus, most studies have included both colic resection with intraperitoneal anastomosis and rectal resection with extra-peritoneal anastomosis, while it has been shown that the rate of anastomotic leakage greatly increased after extra-peritoneal anastomosis.[5,14–16]

Those studies also included patients with proximal diversion through a stoma, while it has been demonstrated that this stoma reduces the consequences that are feared when AL occurs.[17,18]

It therefore seems important to distinguish colonic resection with anastomosis performed during an emergency and a resection performed electively to limit cohort heterogeneity and focus on risk factors for leakage after elective colonic resection.

Thus, the aim of this study was to assess major independent risk factors for anastomotic leakage after elective colonic resection for cancer and notably identify the impact of the location of anastomosis on this risk of leak. Treatment of such a leakage depending on the type of anastomosis performed and consequences of these leakages has also been assessed.

Patients and Method

Patients

From January 1990 to December 2015, 1940 consecutive patients were referred to our institution for colorectal adenocarcinoma; medical data were included in a prospectively maintained database. Among these patients, 1025 fulfilled the following inclusion criteria: colic resection with intraperitoneal anastomosis, without proximal diversion through a stoma, during elective surgery. A flow chart of the patient selection is presented in Fig. 1.

Preoperative Investigations

Preoperative assessment included a complete medical history with familial and personal cancer history, obesity, ongoing anticoagulant treatment, complete colonoscopy when possible, or at least until the tumoral stenosis, allowing the clinician to locate the colic adenocarcinoma, and abdominopelvic and chest computed tomographic scans. The suitability of patients for colonic resection was discussed during multidisciplinary weekly meetings of surgeons, oncologists, pathologists, and radiologists. Preoperative chemotherapy would be proposed in patients with potentially resectable metastatic colonic adenocarcinoma. The American Society of Anesthesiologists (ASA) score was used to stratify patients according to their preoperative risk. This score was assigned at the time of surgery by the anesthesiologist according to the following guidelines: ASA 1, normal healthy patient; ASA 2, patient with mild systemic disease; ASA 3, patient with severe systemic disease; ASA 4, patient with severe systemic disease and a constant threat to life.

Postoperative Outcomes

Morbidity and mortality at 30 days and 90 days were recorded in our database, according to Clavien-Dindo's classification of surgical complications.[20]

The outcome of interest was the presence of clinical AL during the first 90 postoperative days, defined as a leakage of bowel content and/or gas from the surgical connection between the two bowel segments into the abdomen with either spillage or collection around the anastomotic site or extravasation through a wound or drain. Clinical manifestation of this AL could either be fever, abscess, septicemia, peritonitis, and/or organ failure. Finally, AL or its consequences must be confirmed by an imaging technique (computerized tomography scan, magnetic resonance imaging, echography) or during surgery.

The treatment of such an anastomotic leakage was considered medical when the fistula could be treated only by antibiotics and/or when the fistula was externalized by a drain placed during the initial surgery. Radiologic treatment was defined by the realization of drainage during the postoperative period. Surgical treatment for the anastomotic leakage was defined by another surgery with or without stoma placement.

Pathological Analysis

Specimens were examined by pathologists with expertise in digestive diseases. Retrieved lymph nodes, surgical margins, and mural extension of the tumor were systematically examined. TNM stages were defined according to the seventh edition of the UICC/TNM classification.[21]

Curative resection (R0) was defined by the lack of any tumor macroscopically or microscopically detectable after resection. An R1 resection indicates microscopic residual tumor (positive margins), and R2 indicates macroscopic residual tumor.

Follow-up

All patients had follow-up control monitoring at 6-month intervals for at least 5 years. This control monitoring included physical examination, tumor marker evaluation, and alternatively either abdominal echography and chest radiography or chest and abdominopelvic computed tomography scans.

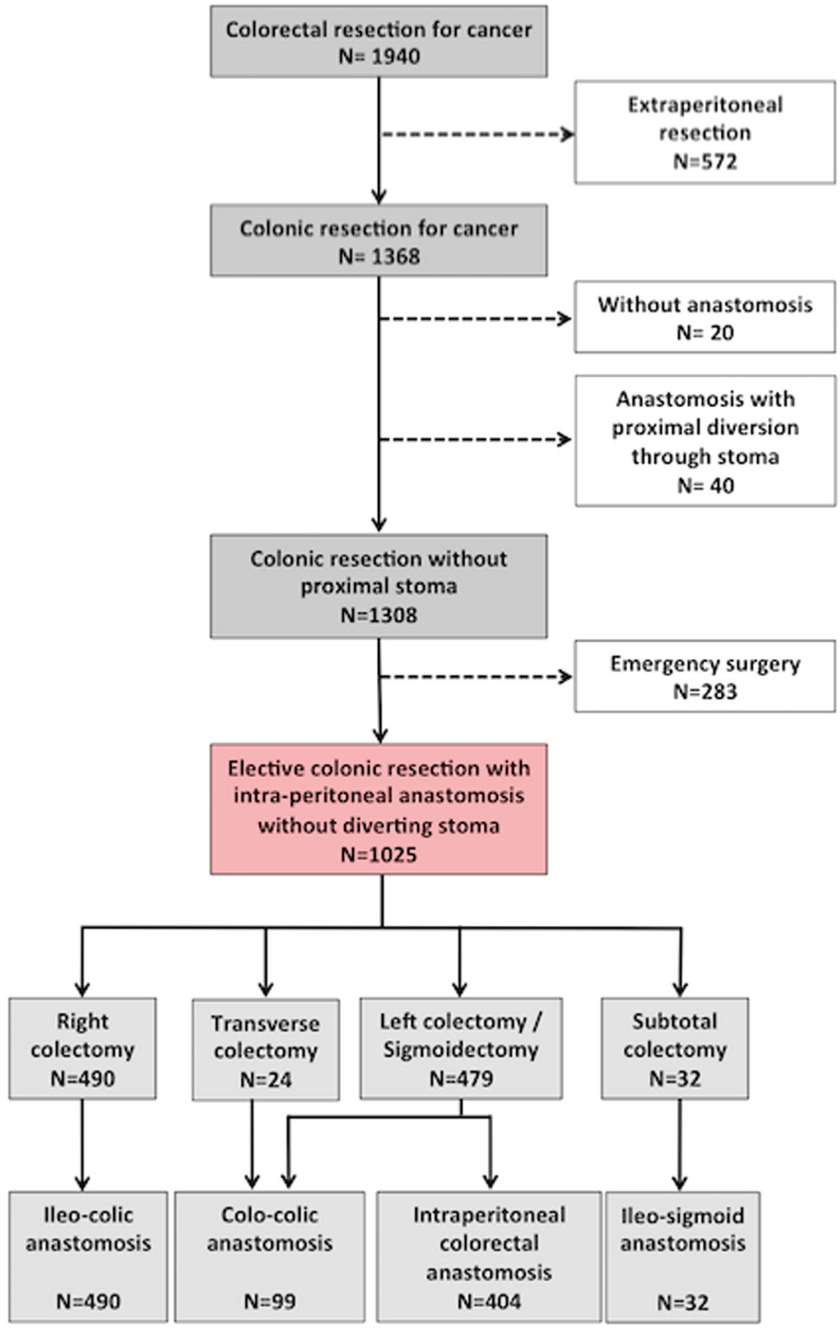

Fig. 1 Flow chart of the study

Histological, cytological, or specific radiological proof was required for the diagnosis of recurrence if a recurrence was suspected. Locoregional recurrence was defined as being located in anastomotic sites or in the regional resection area. Distant recurrences included peritoneal carcinomatosis, liver metastasis, and metastasis in other extra-abdominal sites. The last information from included patients was updated in December 2015.

Statistical Analysis

Categorical data were compared by the chi-square test or Fisher's exact test. The independent-samples *t* test or Mann-Whitney's test was used for continuous data. To consider potential confounders that assess anastomotic leak risk factors, a multivariate analysis was performed using binary logistic regression with a stepwise procedure, including non-redundant variables chosen by univariate analysis. The 0.1 level was defined for systematic entry into the model. Survival rates and recurrence rates were calculated using the Kaplan-Meier method and included postoperative deaths. These survival curves were calculated from the date of surgery, and all causes of death were considered for survival estimation. The log-rank test was used to compare survival curves. All statistical analyses were performed using SPSS for Mac version 22.0 (SPSS Inc., Chicago, IL). A p value ≤ 0.05 was considered significant.

Results

Risk Factors of Anastomotic Leakage

Among the 1025 patients electively operated on for colon cancer between 1990 and 2015, 490 patients had a right colectomy (47.8%), 24 had a **transverse** colectomy (2.3%), 479 (46.7%) had a left colectomy, and 32 (3.2%) received a subtotal colectomy (Fig. 1). To restore intestinal continuity, ileo-colic anastomosis was performed in 490 patients (always after right colectomy), colo-colic anastomosis was performed in 99 patients (24 after **transverse** colectomy and 75 after left colectomy), 404 intraperitoneal colorectal anastomoses were performed (always after left colectomy), and 32 ileo-sigmoid anastomoses were performed.

During the study period, 36 anastomotic leakages were diagnosed, representing a rate of leakage after elective colonic resection for cancer of 3.5%. The distribution of those leaks during the study period was harmonious, with an annual rate ranging from 0 to 8.7% (Fig. 2).

Among these 36 anastomotic leaks, 20 (55.5%) were observed after ileo-colic anastomosis, 7 (19.4%) after colo-colic anastomosis, 7 (19.4%) after intraperitoneal colorectal anastomosis, and 2 (5.5%) after ileo-sigmoid anastomosis, leading to leak rates of 4.1%, 7.1%, 1.7%, and 6.2% after ileo-colic, colo-colic, intraperitoneal colorectal, and ileo-sigmoid anastomosis, respectively. In univariate analysis, four variables were associated with a high risk of leakage, including preoperative obesity defined by a body mass index (BMI) greater than 30 kg/m^2 ($p = 0.030$), endoscopic impassable tumor ($p = 0.018$), tumor location ($p = 0.010$), and type of anastomosis ($p = 0.034$) (Table 1). Thus, compared to an intraperitoneal colorectal anastomosis, the risk of leakage was multiplied by 2.41 ($p = 0.047$) after an ileo-colic anastomosis, by 4.32 ($p = 0.008$) after a colo-colic anastomosis and by 3.78 ($p = 0.106$) after an ileo-sigmoid anastomosis.

During the study period, five expert surgeons in colorectal surgery performed colonic resection. The rate of anastomotic leakage ranged from 0 to 4,7% without any statistical difference ($p = 0.181$) (Table 1), even after analysis according to the type of anastomosis performed (data not shown).

After including potential confounding factors in the multivariate analysis such as age, sex, personal, or familial cancer history, ASA score and tumor stage, the independent risk factors for anastomotic leakage were determined to be obesity (HR = 5.404; $p = 0.012$), endoscopic impassable tumor (HR = 2.109; $p = 0.032$), and ileo-colic anastomosis (HR = 2.562; $p = 0.035$) or colo-colic anastomosis (HR = 3.890; $p = 0.014$) (Table 2).

Management of Anastomotic Leakage

Treatment of anastomotic leakage varied depending on the site of anastomosis. When the afferent segment was

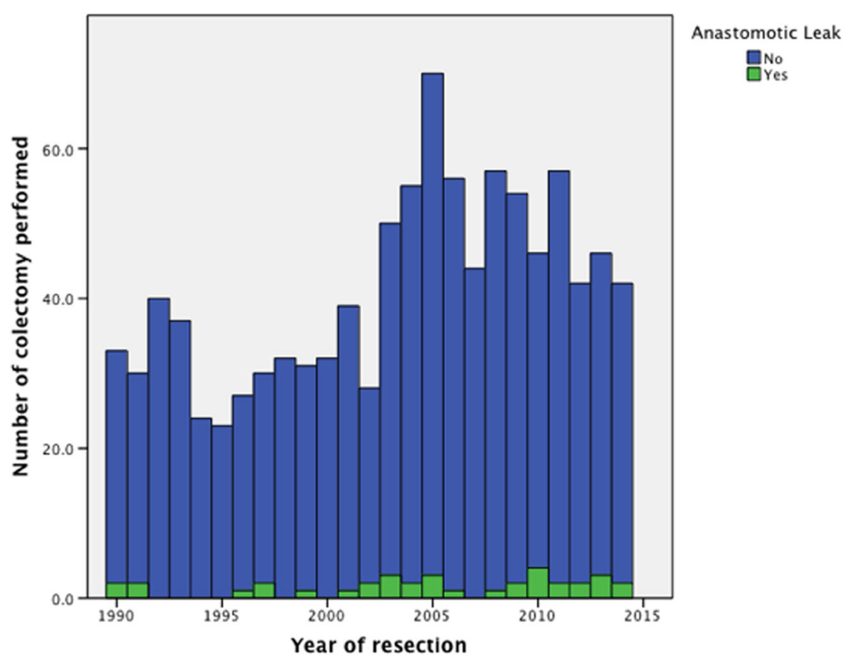

Fig. 2 Distribution of anastomotic leakage during the study period

Table 1 Prognostic factors for anastomotic leakage after elective colic resection (univariate analysis)

Variables	Whole population ($N = 1025$)	No anastomotic leak (N)	Anastomotic leak (N)	p value
Age > 70	553 (54.0)	536 (54.2)	17 (47.2)	0.410
Male gender	502 (49.0)	482 (48.7)	20 (55.6)	0.421
Family history of cancer	75 (7.3)	71 (7.2)	4 (11.1)	0.328
Personal history of cancer	119 (11.6)	114 (11.5)	5 (13.9)	0.599
ASA score 3–4	239 (23.4)	227 (23.0)	12 (33.3)	0.151
Obesity	20 (2.0)	17 (1.7)	3 (8.3)	0.030
Anticoagulant	57 (5.6)	53 (5.4)	4 (11.1)	0.135
Endoscopic impassable tumor	353 (34 .4)	334 (33.8)	19 (52.8)	0.018
Tumor location				0.010
Right colon	458 (44.7)	440 (44.5)	18 (50.0)	
Transverse colon	84 (8.2)	78 (7.9)	6 (16.7)	
Left colon	109 (10.6)	102 (10.3)	7 (19.4)	
Sigmoid	374 (36.5)	369 (37.3)	5 (13.9)	
Type of resection				0.098
Right colectomy	490 (47.8)	470 (47.5)	20 (55.6)	
Transverse colectomy	24 (2.3)	22 (2.2)	2 (5.6)	
Left colectomy	141 (13.8)	134 (13.5)	7 (19.4)	
Sigmoidectomy	338 (33.0)	333 (33.7)	5 (13.9)	
Subtotal colectomy	32 (3.1)	30 (3.0)	2 (5.6)	
Type of anastomosis				0.034
Ileo-transverse anastomosis	490 (47.8)	470 (47.5)	20 (55.6)	
Colo-colic anastomosis	99 (9.7)	92 (9.3)	7 (19.4)	
Intraperitoneal colorectal anastomosis	404 (39.4)	397 (40.1)	7 (19.4)	
Ileo-sigmoid anastomosis	32 (3.1)	30 (3.0)	2 (5.6)	
Preoperative treatment	13 (1.3)	13 (1.3)	0	1
Surgeon				0.181
Surgeon A	453 (44.2)	433 (43.8)	**20 (55.6)**	
Surgeon B	190 (18.5)	181 (18.3)	**9 (25)**	
Surgeon C	65 (6.3)	65 (6.6)	**0**	
Surgeon D	85 (8.3)	84 (8.5)	**1 (2.8)**	
Surgeon E	232 (22.6)	226 (22.9)	**6 (16.7)**	
pT stage				0.431
pTis-T1-T2	255(25.0)	244 (24.8)	11 (30.6)	
pT3-T4	766 (75.0)	741 (75.2)	25 (69.4)	
pN stage				0.123
pN0 - N1	835 (81.9)	809 (82.3)	26 (72.2)	
pN2 - N3	184 (18.1)	174 (17.7)	10 (27.8)	
Positive lymph node status	398 (39.1)	382 (38.9)	16 (44.4)	0.500
pM stage	197 (19.2)	187 (18.9)	10 (27.8)	0.185
pTNM stage				0.339
Stage 1 or 2	219 (21.4)	209 (21.1)	10 (27.8)	
Stage 3 or 4	806 (78.6)	780 (78.9)	26 (72.2)	

the small bowel, a surgical treatment was preferred (68.2%); colic afferent segments typically received either medical or radiological treatments (64.3%; $p = 0.056$). The full description of treatments carried out according to the type of anastomosis performed is detailed in Fig. 3.

Table 2 Prognostic factor for anastomotic leakage after elective colic resection (multivariate analysis)

Variables	HR	95%CI	*p* value
Age > 70	–	–	–
Male gender	–	–	–
Personal cancer history	–	–	–
Familial cancer history	–	–	–
Anticoagulant	–	–	–
Obesity	5.404	1.444–20.223	0.012
ASA score 3–4	–	–	–
Endoscopic impassable tumor	2.109	1.065–4.175	0.032
Preoperative treatment	–	–	–
pT 3–T4	–	–	–
Positive lymph nodes	–	–	–
Metastatic disease	–	–	–
Type of anastomosis (ref: intraperitoneal colorectal anastomosis)			0.068
Ileo-colic anastomosis	2.562	1.066–6.156	0.035
Colo-colic anastomosis	3.890	1.313–11.524	0.014
Ileo-sigmoid anastomosis	3.776	0.727–19.621	0.114

Consequences of the Occurrence of Anastomotic Leakage

The occurrence of anastomotic leakage after colonic resection for cancer had both short- and long-term consequences. In this study, 20 patients died during the first three postoperative months, leading to a global postoperative mortality rate of 1.95%. This postoperative mortality rate was higher when an AL occurred (11.1%) compared to the group of patients who did not have AL (1.6%; $p = 0.004$), corresponding to an odds ratio of 6.9.

Long-term Outcomes

Follow-up data were available for all patients with a mean length of follow-up in the surviving patients of 73.2 months (95%CI 68.6–77.8 months). During follow-up, 321 patients died (31.3%), and the mean overall survival (OS) for all patients was 144.5 months (95%CI 133.9–155.2 months) with a 5-year OS rate of 65.5%. There were 16 deaths (44.4%) among the 36 patients with AL and 305 deaths (30.8%) among the 989 patients without AL. Patients with AL had a significantly shorter mean overall survival than patients without AL (43.1 months vs. 146.4 months; $p < 0.001$) (Fig. 4).

The recurrence rate in our study was 37.7% (386 patients), and the estimated mean of disease-free survival (DFS) was 135.6 months (95%CI 125.2–146.1 months). During the follow-up period, 18 patients (50%) with AL and 368 patients (37.2%) without AL presented tumor recurrence or died. Patients with AL had a significantly shorter mean DFS than

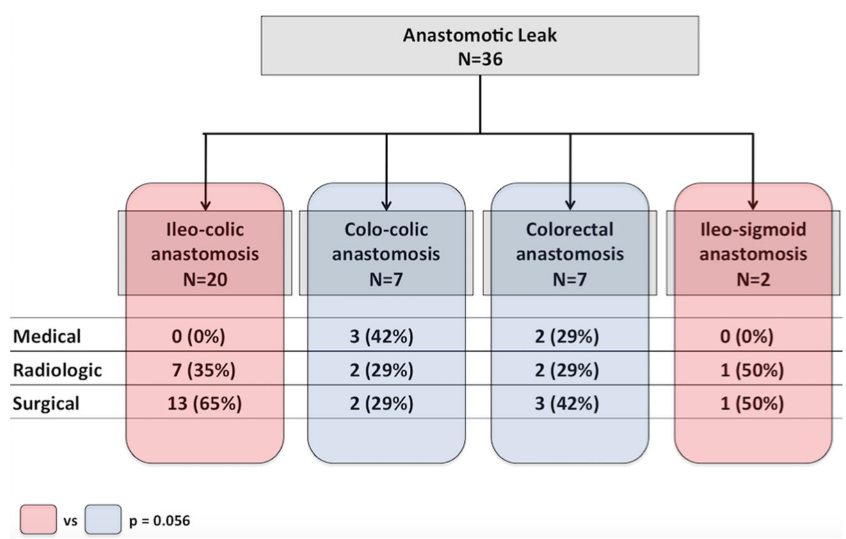

Fig. 3 Management of anastomotic leakage depending on the location of the anastomosis

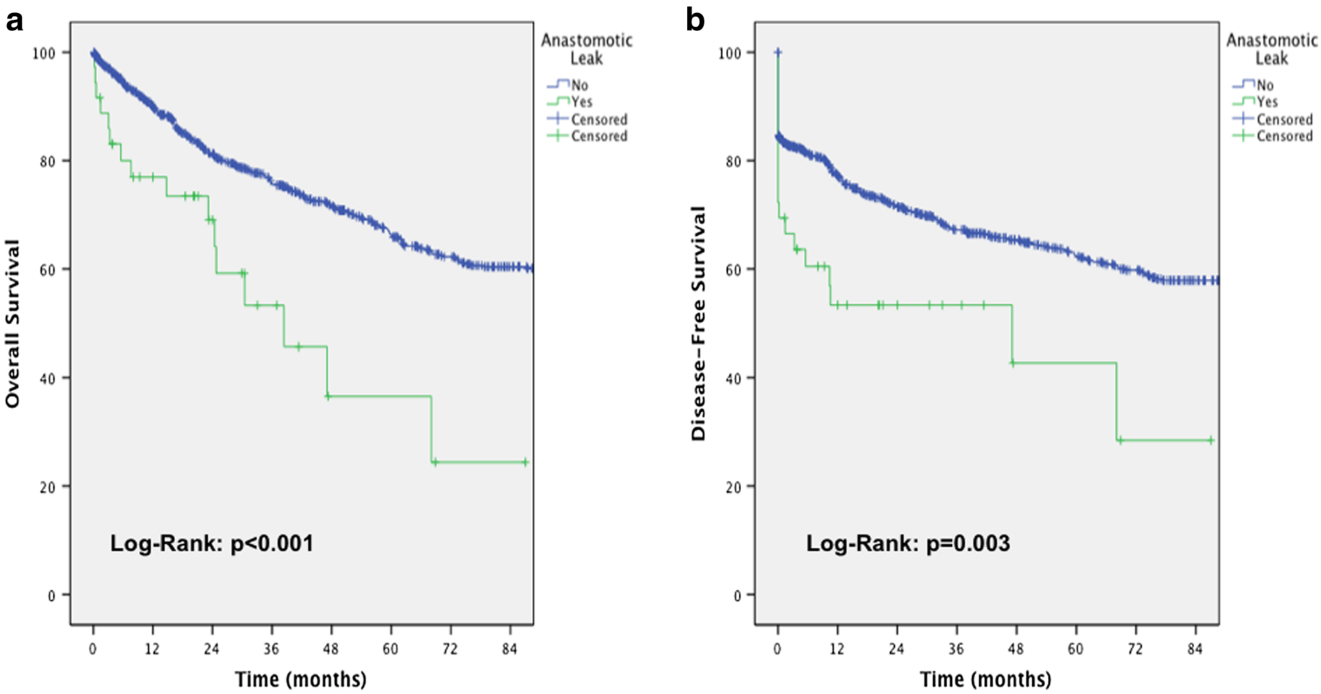

Fig. 4 **a** Overall survival curves for patients with or without anastomotic leakage. **b** Disease-free survival curves for patients with or without anastomotic leakage

patients without AL (40.5 months vs. 137.3 months; $p = 0.003$) (Fig. 4).

Discussion

This large retrospective study shows that AL occurs more frequently after colo-colic and ileo-colic anastomosis than after intraperitoneal colorectal anastomosis. Thus, segmental left colectomy and right colectomy appear as being more at risk of AL than elective left colectomy, which contradicts the generally held belief that ileo-colic anastomoses are less prone to leaks than intraperitoneal colorectal anastomoses.[22]

The impact of the location of an anastomosis on the risk of anastomotic leakage after colonic resection for cancer has rarely been studied previously and has presented contradictory results.[3,4,19,22] Bakker et al., in a nationwide audit, showed that right colectomy was associated with a lower rate of AL than left colectomy, while transverse resection was associated with higher risk of AL.[23] Conversely, in a retrospective study, Marinello et al. showed an increased risk of leakage after ileo-colic anastomosis compared to colorectal anastomosis,[3] while Frasson et al. found no difference in the rate of anastomotic leakage according to the type of colonic resection performed.[4] Agreeing with Bakker,[23] Marinello,[3] and Alves,[24] we found that colo-colic anastomosis is associated with the highest risk of AL after colic resection for cancer (HR = 3.890; $p = 0.014$) followed by ileo-colic anastomosis (HR = 2.562; $p = 0.035$). This finding can be explained first by the greater difficulty in assessing the blood supply to anastomosis after ileo-colic or colo-colic anastomosis than after intraperitoneal colorectal anastomosis, where the rectal segment is usually well vascularized. Second, this result reflects the greater tolerance of our surgeons to perform ileo-colic and colo-colic anastomosis in suboptimal circumstances (such as with an obese patient with numerous comorbidities and an impassable tumor at the preoperative endoscopy) compared to achieve a colorectal anastomosis, even if intraperitoneal. In this latter case with unfavorable circumstances, it is more common to perform either a proximal diverting stoma or to not perform anastomosis, Thus, patients with ileo-colic (26.7%) or colo-colic anastomosis (33.3%) more frequently had an ASA score > 3 than patients with colorectal anastomosis (16.8%; $p < 0.001$). To reduce the risk of AL after elective right colectomy or segmental left colectomy, a colic resection without anastomosis or temporary diverting stoma should be discussed in such selected high-risk patients. In our study, the overall AL rate is slightly lower than the AL rate observed in other studies, which also included emergency colic resections.[3,4,7,10,11,19,22,25] However, colonic resections performed during an emergency are associated with an increased AL rate compared with elective colonic resection.[19,23,26] Thus, our AL rate is comparable to other studies that assess the risk of AL after elective colonic resection.[14,27]

Among the other prognostic factors associated with an increased risk of AL in our study, obesity is a factor already found in a majority of studies and considered in the nomogram established recently by Frasson to assess the risk of anastomotic leakage after colonic resection.[4] Finally, an endoscopic impassable tumor is also found to be an independent risk factor for AL. Thus, even if there is no clinical obstruction, the endoscopic impassable tumor presumably caused distension of the afferent digestive segment, which in turn can weaken the anastomosis. Some risk factors for anastomotic leakage could not be analyzed in our retrospective study, such as serum albumin and type of anastomosis (i.e. hand-sewn/stapled, end-to-end/end-to-side/side-to-side, isoperistaltic, or anisoperistaltic), which is a limitation of our study. However, no trend in the rate of anastomotic leakage during the study period was observed, which argues for a low impact of the suture technique on anastomotic leakage occurrence.

The second main result of this study is the different management strategies for AL based on the type of afferent segment: ileum or colon. Management of AL is preferentially surgical when an AL occurred after ileo-colic or ileo-sigmoid anastomosis (68.2%), while it is medical or radiological after colo-colic or colorectal anastomosis (64.3%). This difference observed in the management of the AL **may be** related to the different kinds of fistula content. Thus, the content from ileal leakage is more fluid than the content from colic leakage; the risk of enteral peritonitis is higher after ileal leakage than after colic leakage, which evolves more frequently to an abscess. To our knowledge, this difference in the management of AL after right or left colectomy has not previously been described. However, Bakker et al. show a lower risk of death after AL after left and transverse colectomy than after right colectomy.[23] This result could be explained by the difference in the management of AL after ileo-colic fistula and colo-colic fistula.

Finally, this study confirms the negative impact of the occurrence of an AL, namely an increase in the relative risk of postoperative mortality (odds ratio for death in postoperative period was 6.9) and a poor overall (43.1 months vs. 146.4 months; $p < 0.001$) and disease-free survival (40.5 months vs. 137.3 months; $p = 0.003$).

With the growing development of enhanced recovery after colorectal surgery and the shortening of the inpatient postoperative period,[28–31] research on the predictive factors of AL is essential, especially after ileo-colic and colo-colic anastomosis. Assessing the decrease in the fistula rate also involves intraoperatively detecting patients with a high risk of AL.

Author Contribution Study conception and design: Voron, Douard, Berger

Acquisition of data: Voron, Bruzzi, Ragot

Analysis and interpretation of data: Voron, Zinzindohoue, Chevallier, Douard, Berger

Drafting of manuscript: Voron, Douard, Berger

Critical Revision: Voron, Bruzzi, Ragot, Zinzindohoue, Chevallier, Douard, Berger

References

1. Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;**136**:E359–86. https://doi.org/10.1002/ijc.29210
2. Blumetti J, Chaudhry V, Cintron JR, *et al.* Management of Anastomotic Leak: Lessons Learned from a Large Colon and Rectal Surgery Training Program. *World J Surg* 2014;**38**:985–91. https://doi.org/10.1007/s00268-013-2340-y
3. Marinello FG, Baguena G, Lucas E, *et al.* Anastomotic leaks after colon cancer resections: Does the individual surgeon matter?. *Colorectal Dis* 2015;562–9. https://doi.org/10.1111/codi.13212
4. Frasson M, Flor-Lorente B, Rodríguez JLR, *et al.* Risk Factors for Anastomotic Leak After Colon Resection for Cancer. *Ann Surg* 2015;**262**:321–30. https://doi.org/10.1097/SLA.0000000000000973
5. Trencheva K, Morrissey KP, Wells M, *et al.* Identifying Important Predictors for Anastomotic Leak After Colon and Rectal Resection. *Ann Surg* 2012;1. https://doi.org/10.1097/SLA.0b013e318262a6cd
6. Kockerling F, Rose J, Schneider C, *et al.* Laparoscopic colorectal anastomosis: risk of postoperative leakage. Results of a multicenter study. Laparoscopic Colorectal Surgery Study Group (LCSSG). *Surg Endosc* 1999;**13**:639–44.
7. Alves A, Panis Y, Trancart D. Factors associated with clinically anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. *World J Surg* 2002;499–502. https://doi.org/10.1007/s00268-001-0256-4
8. Mirnezami A, Mirnezami R, Chandrakumaran K, *et al.* Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg* 2011;**253**:890–9. https://doi.org/10.1097/SLA.0b013e3182128929
9. Marra F, Steffen T, Kalak N, *et al.* Anastomotic leakage as a risk factor for the long-term outcome after curative resection of colon cancer. *Eur J Surg Oncol* 2009;**35**:1060–4. https://doi.org/10.1016/j.ejso.2009.02.011
10. Kube R, Mroczkowski P, Granowski D, *et al.* Anastomotic leakage after colon cancer surgery: A predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. *Eur J Surg Oncol* 2010; **36**:120–4. https://doi.org/10.1016/j.ejso.2009.08.011
11. Krarup P-M, Jorgensen LN, Harling H. Management of anastomotic leakage in a nationwide cohort of colonic cancer patients. *J Am Coll Surg* 2014; **218**:940–9. https://doi.org/10.1016/j.jamcollsurg.2014.01.051
12. Vonlanthen R, Slankamenac K, Breitenstein S, *et al.* The Impact of Complications on Costs of Major Surgical Procedures. *Ann Surg* 2011; **254**:907–13. https://doi.org/10.1097/SLA.0b013e31821d4a43
13. Karliczek A, Harlaar NJ, Zeebregts CJ, *et al.* Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. *Int J Colorectal Dis* 2009; **24**:569–76. https://doi.org/10.1007/s00384-009-0658-6
14. McDermott FD, Heeney A, Kelly ME, *et al.* Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015;**102**:462–79. https://doi.org/10.1002/bjs.9697
15. Buchs NC, Gervaz P, Secic M, *et al.* Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. *Int J Colorectal Dis* 2008; **23**:265–70. https://doi.org/10.1007/s00384-007-0399-3
16. Boccola M A, Buettner PG, Rozen WM, *et al.* Risk factors and outcomes for anastomotic leakage in colorectal surgery: A single-institution analysis of 1576 patients. *World J Surg* 2011; **35**:186–95. https://doi.org/10.1007/s00268-010-0831-7
17. Shiomi A, Ito M, Maeda K, *et al.* Effects of a diverting stoma on symptomatic anastomotic leakage after low anterior resection for rectal cancer: A propensity score matching analysis of 1,014 consecutive patients. *J Am Coll Surg* 2015; **220**:186–94. https://doi.org/10.1016/j.jamcollsurg.2014.10.017
18. Peeters KCMJ, Tollenaar RAEM, Marijnen CAM, *et al.* Risk fac-

tors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005; **92**:211–6. https://doi.org/10.1002/bjs.4806
19. Bakker IS, Grossmann I, Henneman D, *et al.* Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *Br J Surg* 2014; **101**:424–32. https://doi.org/10.1002/bjs.9395
20. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg* 2004; **240**:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae
21. Edge SD, Compton C, Fritz A, *et al.* Colon and Rectum. In: Springer, ed. *AJCC Cancer Staging Manual*. New York: 2010.173–206.
22. Veyrie N, Ata T, Muscari F, *et al.* Anastomotic leakage after elective right versus left colectomy for cancer: prevalence and independent risk factors. *J Am Coll Surg* 2007;**205**:785–93. https://doi.org/10.1016/j.jamcollsurg.2007.06.284
23. Bakker IS, Snijders HS, Grossmann I, *et al.* High mortality rates after non-elective colon cancer resection: results of a national audit. *Color Dis* 2016;:n/a-n/a. https://doi.org/10.1111/codi.13262
24. Alves A, Panis Y, Mathieu P, *et al.* Postoperative Mortality and Morbidity in French Patients Undergoing Colorectal Surgery. *Arch Surg* 2005;**140**:278–83. https://doi.org/10.1001/archsurg.140.3.284
25. Kwaan MR, Al-Refaie WB, Parsons HM, *et al.* Are Right-Sided Colectomy Outcomes Different From Left-Sided Colectomy Outcomes? Study of Patients With Colon Cancer in the ACS NSQIP Database. *JAMA Surg* 2013;**148**:504–10. https://doi.org/10.1001/jamasurg.2013.1205
26. Panis Y, Maggiori L, Caranhac G, *et al.* Mortality After Colorectal Cancer Surgery. *Ann Surg* 2011;**254**:738–44. https://doi.org/10.1097/SLA.0b013e31823604ac
27. Hyman N, Manchester TL, Osler T, *et al.* Anastomotic leaks after intestinal anastomosis: It's later than you think. *Ann Surg* 2007; **245**:254–8. https://doi.org/10.1097/01.sla.0000225083.27182.85
28. Kehlet H. Fast-track colorectal surgery Perioperative. *Lancet* 2008; **371**:792–3. https://doi.org/10.1016/S0140-6736(08)60357-8
29. Anderson ADG, McNaught CE, MacFie J, *et al.* Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* 2003; **90**:1497–504. https://doi.org/10.1002/bjs.4371
30. Khoo CK, Vickery CJ, Forsyth N, *et al.* A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* 2007;**245**:867–72. https://doi.org/10.1097/01.sla.0000259219.08209.36
31. Gatt M, Anderson ADG, Reddy BS, *et al.* Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* 2005;**92**:1354–62. https://doi.org/10.1002/bjs.5187