Long-term oncologic outcomes following anastomotic leak after anterior resection for rectal cancer: does the leak severity matter?

LONG-TERM ONCOLOGIC OUTCOMES FOLLOWING ANASTOMOTIC LEAK AFTER ANTERIOR RESECTION FOR RECTAL CANCER: DOES THE LEAK SEVERITY MATTER?

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Abstract

Background: The evidence regarding the impact of anastomotic leak (AL) after anterior resection (AR) for rectal cancer on oncologic outcomes is controversial, and there are no data about the prognostic relevance of the International Study Group of Rectal Cancer (ISREC) AL classification. The aim was to evaluate the oncologic outcomes in patients with AL after AR for rectal cancer. The prognostic value of the ISREC AL grading system was also investigated.

Methods: It is a retrospective analysis of a prospectively collected database including all patients undergoing curative elective AR for rectal cancer (April 1998-September 2013). AL severity was defined according to the ISREC criteria. A multivariable analysis was performed to identify predictors of poor survival.

Results: A total of 532 patients underwent curative AR (69% laparoscopic) for rectal cancer. The overall AL rate was 7.9%: 15 grade B and 27 grade C ALs. With a median follow-up of 80 (range, 12-266) months, 5-year overall survival (OS) was 67.2% in patients with AL and 86.5% in those without AL (P=0.001). Five-year disease-free survival (DFS) was 50.5% and 80.3%, respectively (P<0.001). Local recurrence and distant metastases developed more frequently in AL patients (P<0.05). Grade B AL and no administration or delay of adjuvant chemotherapy were independent predictors for poorer OS and DFS. Grade B AL independently affected also the administration of adjuvant chemotherapy. Circulating C-reactive protein levels at two weeks after AL treatment were higher in grade B than grade C patients (P=0.006) and in patients with tumor relapse (P=0.011).

Conclusion: AL after curative AR for rectal cancer and impaired use of adjuvant chemotherapy are associated with poor survival. Postoperative systemic inflammation seems to be more sustained in grade B than grade C AL patients, with possible adverse impact on long-term survival.

Key words: Rectal cancer; anastomotic leak; anterior resection; ISREC grading system; survival.

Introduction

Anastomotic leak (AL) following anterior resection (AR) for rectal cancer is a severe surgical complication, that is associated with increased postoperative morbidity, ~~high~~ significant mortality, long hospital stay, high costs, poor functional results and impaired quality of life [1-5].

Even though AL has also been associated with adverse oncologic outcomes, the interpretation of the current evidence requires caution, since the studies are heterogenous in treatment protocols, design and follow-up. Moreover, different definitions of AL have been used in the published studies [6-7].

In 2010, the International Study Group of Rectal Cancer (ISREC) proposed a definition and a clinical grading system of AL after AR, in order to standardize the reports of the studies and to improve the clinical management of rectal cancer patients who experience postoperative AL [8]. The clinical relevance of the ISREC AL grading system has been then validated by several studies [9-12], showing that grade B and C leaks should be considered as separate entities, since ~~the~~ short-term outcomes vary according to the severity of AL. However, it is unclear if the severity of AL may have an impact also on long-term survival [13,14].

The aim of this study was to investigate the oncologic outcomes in patients with AL after AR for rectal cancer classified according to the ISREC AL grading system.

Materials and Methods

This is a retrospective analysis of a prospective institutional review board-approved database, including all consecutive patients who underwent AR with a primary anastomosis and total mesorectal excision (TME) for ~~the~~ mid- and lower rectal cancers, or partial mesorectal excision (PME) for upper rectal cancer at our Institution between April 1998 and September 2013. The location of the tumor was assessed by rigid proctoscopy and classified as follows: lower rectum (distal tumor margin less than 5 cm from the anal verge), mid-rectum (5–10 cm from the anal verge) and upper rectum (10–15 cm from the anal verge).

Patients with metastatic disease, acute bowel obstruction, tumor perforation, synchronous colorectal cancers, T1 rectal cancers treated with local excision by transanal endoscopic microsurgery and previous history of rectal surgery were excluded from the analysis.

Preoperative long-course neoadjuvant chemoradiation therapy (CRT) was discussed in a multidisciplinary setting and recommended to patients staged as T3-4N0-2M0. Adjuvant chemotherapy (CT) was recommended after a clinical oncologic evaluation within 8 weeks after surgery to all patients undergoing neoadjuvant CRT and to those with a postoperative diagnosis of stage 2 with high risk factors (G3, pT4, lymphovascular invasion, positive margins, number of lymph nodes <12) or stage 3 rectal cancer. The type of adjuvant CT [5-fluorouracil-based chemo-regimen (5-FU/leucovorin) was administered until August 2004, while 5-FU/leucovorin with oxaliplatin regimen was used since September 2004] and the timing of adjuvant CT were both recorded. Administration of adjuvant CT was defined as delayed when started more than 8 weeks after AR.

The surgical technique has been previously described [15,16]. Defunctioning ileostomy was fashioned at the end of all TMEs with coloanal anastomosis and in selected patients with low colorectal anastomosis at discretion of the operating surgeon, depending on the intraoperative evaluation of the quality of the colorectal anastomosis.

Follow-up protocol included clinical examination, serum carcinoembrionyc antigen assay every 3 months, and liver ultrasound every 6 months for the first 2 years, then annually. A CT scan of chest, abdomen and pelvis was performed every year. A colonoscopy was performed at 1 year, then every 3 years.

The following data were prospectively collected in the database: patient's characteristics [age, sex, body mass index (BMI), comorbidities assessed using the Charlson Comorbidity Index (CCI) [17], American Society of Anesthesiologists (ASA) score, indication for neoadjuvant CRT, rectal tumor site], operative variables (surgical approach, type of rectal resection, reason for conversion, fashioning a protective stoma), and short-term (within 30 days from surgery) outcomes, including C-reactive protein levels, morbidity classified according to Clavien Dindo classification [18], resumption of gastrointestinal function, length of hospital stay). Electronic medical charts were reviewed in details when patient's characteristics or postoperative data were missing in the database.

The definition of postoperative AL was clinical: in the presence of fever, clinical signs of peritonitis, discharge of gas, pus or bowel contents from the drainage tube, patients underwent a CT scan to confirm the diagnosis. AL severity was categorized according to the ISREC grading system. Patients were not screened for asymptomatic AL: only ALs requiring antibiotics with/without a endoscopic or radiological intervention (grade B) or a reoperation (grade C) were taken into account.

Oncologic outcomes included overall survival (OS), disease-free survival (DFS), local recurrence (LR) and distant metastases (DM) rates.

Statistical analysis

Quantitative data are given as median and range and categorical data are expressed as percentages. Statistical analysis among the groups was performed using χ^2 test or the Student's *t* as appropriate. Univariable OS and DFS rate analyses were performed using the Kaplan–Meier method and the differences between the groups were assessed with the log-rank test.

OS was calculated from the date of AR to the date of death from any cause. Patients alive were censored at the date of last examination by an oncologist. DFS was calculated from the date of AR to the date of recurrence. Patients alive with no recurrence were censored at the date of last oncologic evaluation. Time to LR or DM was calculated from the time of AR to date of recurrence.

A multivariable Cox regression analysis to identify independent risk factors for poorer DFS and OS ~~were~~ was separately performed in both the entire study population and in patients with indication for adjuvant CT. A full series of 13 variables were included in the univariable analysis; only the exploratory variables with a P value ≤0.200 were included in the multivariate model. The following variables were considered: age, gender, surgical approach, tumor location, grade of tumor differentiation, pT staging, number of lymph nodes harvested, lymph node ratio (number of positive nodes divided by total nodes harvested), lymphovascular invasion, TME completeness, AL, other complications graded as Clavien Dindo ≥3, blood transfusions, no/delayed administration of adjuvant CT. Administration of adjuvant CT was included only in the univariate and multivariate analysis limited to the subgroup of patients with indication for adjuvant CT. Results are reported as hazard ratio (HR) with 95% confidence intervals (CI).

A multivariable analysis was also performed to identify factors affecting the administration of adjuvant CT among patients with indication for adjuvant CT. The following variables were considered: age, gender, CCI, surgical approach, tumor location, AL, other complications graded as Clavien Dindo ≥3, blood transfusions. Results are reported as odds ratio (OR) with 95% confidence intervals (CI).

All p values were 2-sided. A level of 5% was set as the criterion for statistical significance. The statistical analysis was performed using SPSS version 19 (Copyright © SPSS Inc., 2000) and SYSTAT Version 10 (Copyright © SPSS Inc., 2000).

Results

Between April 1998 and September 2013, 532 patients underwent AR for non-metastatic rectal cancer. Overall AL rate was 7.9% (42/532): 15 grade B and 27 grade C ALs according to the ISERC grading system. Four (0.8%) patients died within 90 days of cardiac complications and 6 (1.1%) patients were lost to follow-up, leaving 522 patients available for the 5-year oncologic analysis. Overall median follow-up was 80 (range, 12-266) months; median follow-up of patients alive at the time of the oncologic analysis was 86.5 (range, 60-266) months.

The group of patients with AL (AL+ group) and the group of patients without AL (AL- group) were similar in age, gender, body mass index, ASA score, number of comorbidities, CCI, tumor site, use of neoadjuvant CRT (16.7% vs. 24.1%, P=0.369), surgical approach, conversion rate, diverting stoma creation rate at the time of index surgery (45.2% vs. 49.8%, P=0.685), postoperative complications graded by using the Clavien-Dindo classification and pathology. (**Table 1**).

Table 2 summarizes the characteristics of grade B and grade C patients. Though there was no statistically significant difference, there was almost a four-fold and two-fold higher use of neoadjuvant CRT (33.3% vs. 7.4%, P=0.077) and diverting stoma at the time of index operation (66.7% vs. 33.3%, P=0.079), respectively for patients who had grade B compared to grade C AL.

~~There was a trend towards a more frequent use of neoadjuvant CRT (33.3% vs. 7.4%, P=0.077) and creation of a diverting stoma at the time of index operation (66.7% vs. 33.3%, P=0.079) in grade B than in grade C patients.~~ In the grade B group, AL was treated by endoscopic vacuum therapy in our GI Endoscopy unit (N=9, 60%) or antibiotics and interventional drainage (N= 6, 40%). No patients who had endoscopic vacuum therapy required surgery. Grade C ALs were surgically managed by placing a drainage and fashioning a diverting stoma (N=12, 44.4%), by performing a Hartmann procedure (N=10, 37.1%), or a laparotomy and drainage of the pelvic collection (N=5, 18.5%).

Overall survival

~~The~~ Five~~5~~-year OS rate was significantly worse in the AL+ group (67.2% vs. 86.5%, P=0.001). At univariable analysis, poor grading of tumor differentiation, tumor staging >pT2, lympho-vascular invasion, and LNR of 0.25 or more, and AL were risk factors for ~~a~~ poorer OS (**Table 3**). Grade C AL and other grade ≥3 complications were not associated with poor OS (**Table 3**). At multivariate analysis, tumor staging >pT2, lymphovascular invasion, a LNR of 0.25 or more and grade B AL were found to be independent predictors of poorer OS (**Table 3**).

Disease-free survival

Five~~The 5~~-year DFS rate was significantly lower in the AL+ group (50.5% vs. 80.3%, P<0.001). At univariable analysis, poor grading of tumor differentiation, tumor staging >pT2, lympho-vascular invasion, and LNR of 0.25 or more, and AL were risk factors for ~~a~~ poorer DFS (**Table 4**). Grade C AL and other grade ≥3 complications were not associated with poor DFS. Multivariate analysis showed that tumor staging >pT2, lymphovascular invasion and a LNR of 0.25 or more and grade B AL were independent predictors of poorer DFS (**Table 4**).

Local recurrence

At 5 years after surgery, 6 (14.3%) AL+ patients and 24 (4.9%) AL- patients developed LR (P=0.029). ~~The median~~ Median time between AR and LR was 21.5 (range, 13-40) months among AL+ patients and 18.5 (6-64) months among AL- patients (P=0.770).

Distant metastases

At 5 years, distant metastases developed in 17 (40.5%) AL+ patients and in 83 (16.9%) AL- patients (P<0.001). ~~The m~~Median time to diagnose DM was 15.5 (range, 4-62) months among AL+ patients and 20 (range, 3-93) months among AL- patients (P=0.575). Two patients developed both LR and DM.

Grade B and C AL patients: C-reactive protein levels

Circulating levels of C-reactive protein (CRP) at two weeks after treatment of AL were significantly higher in grade B than grade C patients [48.7 (10.8-117.7) vs. 22.4 (1.9-48.2) mg/dl; P=0.006], in patients who did not undergo a Hartmann procedure [38.2 (10.8-117.7) vs. 8.2 (1.9-48.2) mg/l; P=0.046] and in patients who experienced tumor relapse [41.7 (8.2-117.7) vs. 14.4 (1.9-48.2) mg/dl; P=0.011].

Grade B and C AL patients: long-term survival

There were no significant differences in both 5-year OS and DFS rates between grade B and grade C group (55.1% vs. 73%; P=0.232, and 30.3% vs. 62.4%, P=0.126, respectively) (**Fig. 1**). No statistically significant differences in OS and DFS were observed between the 10 patients undergoing a Hartmann procedure and the 32 patients receiving radiological/endoscopic treatment, diverting stoma or reintervention with drainage (75% vs. 59.7%, P=0.537 and 66.7% vs. 42.7%, P=0.622).

Administration of adjuvant CT and survival

A total of 331 patients had indication for adjuvant CT. Adjuvant CT was more likely not administered or delayed more than 8 weeks after AR in AL+ patients than in AL- patients (60.6% vs. 35.9%, P=0.010). The multivariate analysis showed that age, CCI >2, open AR and grade B AL were independent factors associated with no CT administration or delay. Gender, tumor location, blood transfusion, grade C AL and other grade ≥3 complications did not affect the use of adjuvant CT (**Table 5**).

The multivariate analyses for risk factors for poor OS and DFS in this group of patients (**Tables 6** and **7**) showed that lymph node ratio of 0.25 or greater, lymphovascular invasion, grade B AL and no administration or delay in CT were independent predictors of survival.

Discussion

AL is a major surgical complication after AR for rectal cancer, that has adverse effects on morbidity, short-term mortality and quality of life [1-5]. Several studies have addressed the oncologic impact of AL on survival in rectal cancer patients, with some reporting adverse outcomes [19,20] while others did not find significant differences [21,22]. A systematic review and metanalysis recently published by Wang et al. [6] has shown that AL is associated with high LR rates and poor OS and DFS. However, a word of caution is needed when interpreting these findings, since different oncologic protocols may have been used among the studies considered, the length of follow-up was variable, some studies included patients operated in the pre-TME era, only a few studies addressed the rate of DM, and, most importantly, different definitions of AL have been used throughout the studies.

In 2010, the ISREC proposed a definition and a clinical grading system of AL after AR, aiming at standardizing the reports of the studies and at helping to improve the outcomes of patients experiencing AL after AR [8]. Since then, several studies [9-12] have validated the clinical relevance of the ISREC AL grading system, showing that short-term outcomes vary according to the AL severity. However, there is very limited evidence about the impact of AL severity according to the ISREC AL on long-term survival. To date, only two studies have been conducted aiming at evaluating the association between AL severity and oncologic outcomes, reporting conflicting results [13,14]. For instance, Takahashi et al. [14] retrospectively reviewed 615 patients undergoing curative resection for colon or rectal cancer. Since the number of patients experiencing grade A AL was too small (N=7) for a proper analysis, the authors defined two groups of AL patients: patients conservatively treated and patients surgically treated. After a median follow-up of 64.6 months, patients with AL that required a surgical treatment had a significantly worse disease-specific survival than patients with no AL or grade A/B leak; grade C AL was also found to be an independent predictors of poorer survival. However, the interpretation of these findings is limited by the fact that both colon and rectum (only 226 patients, one third of the whole series) cancer

patients were considered and only a few confounder variables have been used in the multivariate analysis. On the contrary, Kulu et al. [13] analyzed the outcomes of 570 rectal cancer patients (51 patients with AL). With a mean follow-up of 4.7 years, no significant correlation between AL severity and oncologic outcomes was found.

Some mechanisms have been proposed to explain the poorer oncologic outcomes in rectal cancer patients with AL after AR. First, the inflammatory reaction in response to peritoneal infection seems to lead to an increase in expression of proinflammatory and proangiogenic factors, including interleukin-6 and vascular endothelial growth factor, that might enhance the growth of residual cancer cells [23]. In addition, the postoperative inflammation might act directly on cancer cells, increasing their capacity of proliferation, invasiveness and migration, thus leading to increased risk of LR and DM [24]. A few studies have been focused on the prognostic value of both preoperative [25] and postoperative [26,27] CRP levels as marker of sustained systemic inflammation. For instance, Katoh et al. [27] analyzed 207 colorectal cancer patients (76 with rectal cancer) and found that increased CRP levels at two weeks after surgery were significantly associated with poorer 5-year DFS. Similar results were previously obtained by McMillan et al. [26] in a series of 174 colorectal cancer patients (53 with rectal cancer). We have analyzed the possible oncologic impact of persistently raised postoperative CRP levels in patients who experienced a postoperative AL. Patients with tumor recurrence had significantly higher postoperative CRP levels than patients who remained disease-free during the entire follow-up period (P=0.011). In addition, sustained higher CRP levels were observed among grade B than grade C AL patients (P=0.006). When patients were analyzed according to the AL treatment received, those who had undergone a Hartmann procedure had significantly lower CRP levels (P=0.046). These patients had also both slightly better OS and DFS than the 32 patients with AL who received a radiological/endoscopic treatment, or a diverting loop stoma and peritoneal lavage, even though the difference was not statistically significant. These findings might reflect the fact that performing a Hartmann procedure allows to resect the leaked anastomosis and effectively drain the pelvic collections, thus removing

possible exfoliated tumor viable cells [28,29] and limiting the inflammatory environment, with the consequent reduced activation of proinflammatory and proangiogenic factors. On the other side, other treatments that are less invasive, such as radiological or surgical drain of the collections, fashioning a diverting stoma or the endoscopic vacuum therapy, may not achieve the same results, thus resulting in prolonged intraabdominal and systemic inflammation and eventually in poorer oncologic outcomes.

Adjuvant CT has been demonstrated to provide clear benefits in terms of risk of death and cancer recurrence in patients undergoing rectal resection for non-metastatic rectal cancer [30]. Time-to-CT is key to maximize the oncologic outcomes, with a delay of 8 weeks or more that is associated with worse OS and DFS [31-33]. Postoperative complications are one of the main factors that are associated with delay in initiation of CT more than 8 weeks after rectal resection [34]. In our series of patients with indication for adjuvant CT, CT was more likely not administered or delayed more than 8 weeks in case of AL (60.6% vs. 35.9%, P=0.010). We found that the occurrence of grade B AL independently affected the administration of adjuvant CT. Interestingly, grade C AL and other grade ≥3 complications were not independent factors affecting the administration of CT.

The treatment of AL depends on several factors, including the size of the anastomotic defect, the site of the anastomosis and the presence of localized or generalized peritonitis [35,36]. There are some reasons linked to the management of the AL that might explain the higher rate of administration of adjuvant CT within 8 weeks in grade C than grade B AL patients. First, a Hartmann procedure, that is usually performed in case of major anastomotic defect with generalized peritonitis, minimizes the risk of further septic anastomotic-related complications occurring during adjuvant CT, since the leaked anastomosis is taken down and an end colostomy is fashioned. Second, patients who undergo a less invasive surgical treatment for AL (proximal diversion with or without primary defect repair and drain, or drain alone) have more likely a small leak with localized peritonitis. This approach appears to be safe and effective, with a rate higher than 90% of healing,

thus allowing patients to start adjuvant CT within 8 weeks [37]. During the last 10 years, a novel approach to selected patients with large extraperitoneal AL with no generalized peritonitis in the presence of a diverting stoma has been proposed: the endoscopic vacuum therapy [38]. There is increasing evidence that it is safe, with an overall success rate of about 80% [39-41]. However, median duration of the treatment is 40 days; as a consequence most patients treated with this approach are not submitted to adjuvant CT within 8 weeks after surgery.

The open approach, along with age and CCI >2 independently affected the use of adjuvant CT (OR 2.06, 95% CI 1.26-3.37, P=0.004). This finding is consistent with that reported by Strouch et al. [42] in a series of 150 patients who underwent low anterior resection for rectal cancer and postoperative CT. They showed that the laparoscopic approach is associated with a quicker postoperative recovery, less complications and, as a consequence, a shorter time to initiation of postoperative CT.

We acknowledge that this study has some limitations that are inherent to its retrospective nature. However, electronic medical charts were reviewed in detail~~s~~ when patient's characteristics or postoperative data were missing in the database. In addition, this study was conducted at a single institution; as a consequence, the results might not be generalized. Nevertheless, this is the first study that aimed at assessing the impact of AL severity on oncologic outcomes during a very long follow-up period (median, 80 months), investigating possible mechanisms by which it may affect survival. Lastly, we were not able to calculate for all patients the neutrophil-to-lymphocyte ratio that has been indicated as a predictor of survival in colorectal cancer patients [43].

In conclusion, the results of this study show that grade B AL might be a predictor of poor survival in rectal cancer patients and an independent factor affecting the use of postoperative CT. Delaying more than 8 weeks after surgery or no administrating adjuvant CT seems to play a major role in determining the oncologic outcomes in these patients. Our findings also suggest that postoperative systemic inflammation might be more sustained in grade B than grade C AL patients, with possible adverse impact on long-term survival. Further studies are warranted to better elucidate

the effects of chronic inflammation, thus possibly leading to a more tailored multimodal oncologic approach to patients with AL.

Disclosures

Marco Ettore Allaix, Fabrizio Rebecchi, Federico Famiglietti, Simone Arolfo, Alberto Arezzo, and Mario Morino have no conflicts of interest or financial ties to disclose.

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LEGENDS FOR FIGURES

Figure 1

A. Overall survival. No leak vs. Grade B: $P<0.001$ (Log rank test); No leak vs. Grade C: $P=0.041$ (Log rank test); Grade B vs. Grade C: $P=0.232$ (Log rank test).

B. Disease-free survival. No leak vs. Grade B: $P<0.001$ (Log rank test); No leak vs. Grade C: $P=0.004$ (Log rank test); Grade B vs. Grade C: $P=0.126$ (Log rank test).

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