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Editorial

Anastomotic leak in colorectal cancer surgery: Short term outcomes have long term consequences

La dehiscencia anastomótica en la cirugía del cáncer colorrectal: los resultados a corto plazo tienen consecuencias a largo plazo

Anastomotic leak is one of the most serious complications in colorectal surgery ranging from 1 to 20%.[1] This complication is associated with considerable morbidity and mortality and may affect the quality of life and the surgeon-patient relationship. Several studies have shown that anastomotic leak and subsequent postoperative intraabdominal infection are also associated with higher rates of tumor recurrence and cancer-specific mortality.[2–4] A recent meta-analysis including 43 studies with a total of 154,981 patients who underwent colorectal cancer surgery found that postoperative surgical site infection and anastomotic leakage had a significant negative impact on disease-free survival, local recurrence and overall recurrence.[5] This association has also been reported after resection of liver metastases and other gastrointestinal malignancies.[6] Moreover, the severity of the postoperative infection has also been correlated with the increased risk of recurrence.[7]

However, this effect has not been found in other studies.[8–10] The development of anastomotic leakage did not affect the risk of local recurrence, overall recurrence, overall survival or cancer-specific survival in a multicentre observational study using prospectively collected data from 1181 consecutive patients with rectal cancer in 22 hospitals included in the Spanish Rectal Cancer Project.[10] These results were consistent with the data reported by national colorectal cancer registries such as those of Denmark[8] and Sweden[9] among others. Therefore, the question of whether AL contributes to disease recurrence remains controversial and requires further investigation.

In this issue of Cirugía Española, Brito da Silva et al.[11] investigated the influence of anastomotic leakage on long-term survival of patients undergoing curative colon cancer resection. The authors performed a single-center retrospective cohort study throughout a 10-year period including patients with a first-time diagnosis of colon cancer, undergoing planned R0 colonic resection without rectal involvement, and having primary anastomosis without a protective stoma. A total of 686 patients were included. Anastomotic leakage occurred in 57 patients (8.3%) and was associated with higher postoperative morbidity and mortality, length of stay and early readmissions. Short-term and long-term overall survival was inferior in the leakage group. Risk factors independently associated with reduced overall survival included anastomotic leakage occurrence, higher ASA classification and delayed/missed adjuvant chemotherapy. However, anastomotic leakage did not impact local and distant recurrence.

The present study has some limitations, mainly the limited number of patients and the small number of events compared with other larger studies, which may have prevented achieving significant differences in the long-term oncological outcome between patients with and without anastomotic leakage. In this sense, this study does not contribute to clarifying the controversy. We cannot stress enough the importance of elucidating this relationship, given that postoperative complications, particularly surgical site infection and anastomotic leakage, are potentially preventable. If shown to impact on long-term oncological results, these complications could serve not only as measures of quality and safety but also predictors of long-term outcomes and may identify potential points of intervention and remediation to improve colorectal surgical results.[7]

Despite the limitations, the study by Brito da Silva et al. agrees with others that have not been able to demonstrate the effect of anastomotic leak on the oncological outcome.[8–10,12]

The heterogeneity in the quality of the studies carried out, ranging from single-center retrospectives to population-based or propensity-matched cohort studies, may explain, in part, the opposite conclusions reached. Other reasons that can explain the contradictory results are the differences in the definition of anastomotic leakage and surgical site infection, differences in the follow-up periods and differences in the oncological outcomes evaluated.

Beyond the methodological drawbacks of the different studies, both those that support and those that reject the association between anastomotic leak and tumor recurrence, the investigation of the mechanisms responsible for this association can provide insight that explains the variability of the observed results. It has been proposed that soluble factors released during the infection-induced inflammatory response could stimulate viable residual tumor cells present in the surgical field and in venous blood, as well as dormant micrometastases, favoring their survival and the subsequent development of a recurrence.[11] Experimental models and clinical studies suggest that a combination of mechanisms (amplification of angiogenesis, induction of epithelial-mesenchymal transition, stimulation of migration and invasiveness, evasion of the immune response, and others yet to be identified) act in combination favoring tumor recurrence in selected patients after surgery with curative intent. Moreover, changes in the intestinal microbiome in the context of an anastomotic leak might be associated with not only worse short-term outcomes and higher mortality but also with worse long-term outcomes. In this sense, several studies have shown that *Fusobacterium nucleatum* abundance in tumor samples increases in higher pT stages of cancer and correlates with worse outcomes in terms of overall survival, disease-free survival, or cancer-specific survival. This unfavorable prognosis could also be linked to the fact that *F. nucleatum* helps to activate autophagy-related pathways in colorectal cancer patients, promoting chemoresistance to oxaliplatin and 5-FU. The potential interactions between different bacterial species and the oncological outcome in colorectal cancer patients warrants further investigation.[13,14]

Interestingly, Cox-regression analysis in the study by Brito da Silva et al. showed that anastomotic leakage was associated with lower long-term overall survival and the underlying reason for this association, in the absence of increased tumor recurrence, remains also to be established. Reasons mentioned by the authors must be considered including unresolved inflammation that can lead to frailty and decompensation of previous comorbidities. In this sense, long-term survival in patients who suffer severe postoperative complications is directly related to the hospital's ability to implement surgical quality improvement initiatives that are focused not only on perioperative care but also on intermediate and longer-term care. The long-term sequelae of a hospitalization for sepsis is a good example for this change in the care model that should include timely source control, post discharge rehabilitation, screening for new chronic medical conditions, adequate medication reconciliation, and assurance of adequate support systems. Patients treated at hospitals with poor failure to rescue performance demonstrate not only higher perioperative mortality rates but also worse longer-term survival.[15]

In conclusion, all possible efforts should be made to avoid anastomotic leak after colorectal resection for cancer not only to elude short-term associated morbidity but also long-term consequences.

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