ORIGINAL ARTICLE

Influence of surgical site infection on oncological prognosis after curative resection for colorectal cancer: An observational single-institution study

Influencia de la infección del sitio quirúrgico en el pronóstico oncológico tras resección con intención curativa del cáncer colorrectal

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Abstract

Background: *An exacerbated inflammatory response to post-operative infection could favor an environment in which residual viable tumor cells present in the surgical bed, bloodstream, or occult micrometastases can survive and progress to produce local or distant recurrence. In this regard, a surgical site infection (SSI) could be an important risk factor for disease progression. This study aimed to investigate the impact of SSI on long-term survival and recurrence of colorectal cancer.* **Methods:** *Patients who underwent curative-intent resection for colorectal carcinoma between 2011 and 2013 were retrospectively analyzed. Overall and disease-free survival (DFS) and local recurrence rate for patients with and without SSI were analyzed.* **Results:** *One hundred and thirty-eight patients were included in the study. Fifty-one (37%) patients showed SSI but revealed no differences in recurrence rate and overall survival compared with non-infected patients. However, the stratified analysis revealed that patients with an intra-abdominal abscess or an organ-space-infection showed a higher recurrence rate and a decreased 5-year overall and DFS.* **Conclusions:** *SSI may have an influence on the oncological prognosis and, therefore, could be considered a recurrence factor. Further multi-institutional studies are necessary to conclude a causal association.*

Key words: *Surgical site infection. Colorectal cancer. Oncological prognosis.*

Resumen

Antecedentes: *Una respuesta inflamatoria exacerbada por una infección postoperatoria podría favorecer un entorno en el que células tumorales residuales viables presentes en el lecho quirúrgico, torrente sanguíneo o micrometástasis ocultas puedan sobrevivir y progresar para producir una recurrencia local o a distancia. En este sentido, una infección del sitio quirúrgico (ISQ) podría ser un factor de riesgo de progresión de la enfermedad. Este estudio tuvo como objetivo investigar el impacto de la ISQ en la supervivencia y recurrencia del cáncer colorrectal.* **Método:** *Todos los pacientes con carcinoma colorrectal sometidos a resección con intención curativa entre 2011 y 2013 fueron analizados retrospectivamente. Se analizó supervivencia global y libre de enfermedad y la tasa de recurrencia local en pacientes con cáncer colorrectal con y sin ISQ.* **Resultados:** *Se incluyeron 138 pacientes. 51 (37%) sufrieron ISQ pero no mostraron diferencias en la tasa de recurrencia y supervivencia*

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global respecto a los pacientes no infectados. Sin embargo, el análisis estratificado reveló que los pacientes con un absceso intraabdominal o una infección órgano-espacio mostraron una tasa de recurrencia más alta y una disminución en la supervivencia global y libre de enfermedad. **Conclusiones:** *La ISQ, en función de la gravedad y la respuesta inflamatoria que genera, puede influir en el pronóstico oncológico y, por lo tanto, podría considerarse un factor de recurrencia. Futuros estudios multicéntricos son necesarios para demostrar una posible asociación.*

Palabras clave: *Infección de sitio quirúrgico. Cáncer colorrectal. Pronóstico oncológico.*

Introduction

Colorectal carcinoma (CRC) is the most common malignant tumor regardless of gender and the leading cause of cancer death in both sexes in developed countries[1]. The main determinant of survival in patients after curative resection is recurrence, with an incidence of 30-40%. In this regard, surgical site infection (SSI) has become a very important issue in recent years since some studies have pointed out a likely relation with a worse oncological prognosis. It is thought that the amplification of the inflammatory and angiogenic response induced by SSI could favor an environment in which residual viable tumor cells present in the surgical bed, bloodstream, or occult micrometastases can survive and progress to produce local or distant recurrence[2-4].

We designed a study to analyze whether SSI is related to oncological prognosis in patients undergoing curative resection of CRC.

Materials and Methods

Study population and patient management

We conducted a retrospective study of a prospective collected database with all consecutive patients diagnosed of colon or rectal carcinoma at our institution from January 1, 2011, to December 31, 2013. Only patients who underwent curative-intent resection and anastomosis, with or without protective stoma or abdominoperineal resection, were included in the study. A personal history of histological diagnosis of any type of cancer, different from CRC, was considered exclusion criteria. Patients who died within the first 90 days after surgery were also excluded from the study.

All patients underwent pre-operative staging with chest and abdominal computed tomography followed by pelvic magnetic resonance imaging if a rectal cancer was diagnosed. Pre-operative and post-operative staging was made according to the 7th edition of tumor-node-metastasis staging system[5]. Patients at stage IV after pre-operative or intraoperative evaluation were excluded from the study.

All patients at stage III and those at stage II that presented a high risk of recurrence higher recurrence risk (inadequate nodes sampling, T4 lesions, poorly differentiated histology, lymphovascular invasion, or tumor perforation or obstruction) were selected to receive post-operative adjuvant chemotherapy with a XELOX or FOLFOX regimen. Patients affected with rectal cancer suspected to be T3-T4 and/or N1 at the pre-operative imaging tests received neoadjuvant therapy with induction chemotherapy with XELOX followed by concomitant radiotherapy. Post-operative adjuvant chemotherapy with XELOX was also administered in these cases. Patients who did not receive neoadjuvant treatment were scheduled for adjuvant FOLFOX and radiotherapy if lymph node invasion was confirmed in the specimen. Otherwise, adjuvant chemotherapy with 5-Fluorouracil or capecitabine was administrated for patients with a pT3 wall invasion or greater and negative lymph node were demonstrated.

Definitions

SSI was defined as the development of surgical wound infection or organ-space infection (anastomotic leak [AL] or intra-abdominal abscess) adopting the modified CDC Definitions for SSI Surveillance by Horan et al.[6].

The diagnosis of AL was initially established by clinical criteria and subsequently confirmed by radiological tests (demonstration of extravasation of contrast medium at the level of anastomosis or presence of an abscessed collection close to it), by the leakage of intestinal content throughout a surgical drain or wound or during a surgical re-exploration. Intra-abdominal abscess was defined as the presence of an intraperitoneal abscessed collection unrelated or distant to the anastomosis. Patients with simultaneous surgical

wound and organ-space infection were registered in the latter group only.

Concerning definition of recurrent disease, local recurrence was defined as the histologic or radiologic evidence of recurrent disease at or close to the anastomosis or tumor bed. Distant recurrence was defined as intraperitoneal dissemination or liver, lung, bone, or brain metastases confirmed by diagnostic imaging or surgery.

Study variables

Demographic characteristics (age and gender), diabetes mellitus, American Society of Anesthesiologists risk scale level, tobacco use, pre-operative serum carcinoembryonic antigen level, surgical approach (open or laparoscopic), UICC disease stage[5], anatomical location of the tumor, number of harvested lymph nodes, existence of lymphovascular invasion, and adjuvant chemotherapy administration were analyzed in both groups searching for statistical difference. The primary endpoint of the study was recurrence development. Secondary endpoint was overall and disease-free survival (DFS).

Statistical analysis

All quantitative values were expressed as mean ± the standard deviation. Categorical variables were presented as values and percentages. Homogeneity was assessed by using Chi-square test with Fisher's exact test and the Mann–Whitney U test as appropriate. The influence of SSI on cancer recurrence was analyzed using also the Chi-square and the Mann–Whitney U test on univariate analysis.

For long-term outcomes, the Kaplan–Meier method was used to estimate the probability of survival and the log-rank test to evaluate the statistical significance of differences between survival distributions among the study groups. $p < 0.05$ were considered statistically significant. Statistical analysis was performed using the SPSS statistical software package for MAC v.22 (SPSS Inc., Chicago. IL. EEUU).

Results

From 177 patients, 138 patients fulfilled inclusion criteria and were included in the study (Fig. 1). SSI was diagnosed in 51 (37%) patients divided in 21 patients with wound infection and 30 patients with organ-space infection. Patients who developed an SSI were younger (average 65 years; range 44-87 years vs. 69 years, range 28-83; $p = 0.01$) and had a lower oncological disease stage at surgery (UICC stage I of 45.1% in the SSI group versus 19.5% in the non-infected group, $p = 0.001$). Relationship between patient and tumor characteristics and SSI is listed in table 1.

Table 1. Relationship between patient and tumor characteristics and surgical site infection in patient undergoing potentially curative resection for colorectal cancer

	SSI n = 51 (37%)	No SSI n = 87 (63%)	P values¶
Age (years)	65 ± 11	69 ± 11	0.01
Gender			
Female	13 (25.5%)	27 (31%)	0.48
Male	38 (74.5%)	60 (69%)	
Diabetes	13 (25.5%)	27 (31%)	0.48
Smoker	21 (41.2%)	37 (42.5%)	0.87
Previous abdominal surgery	18 (35.3%)	26 (29.9%)	0.51
ASA score* N: 103	N: 38	N: 65	
I	3 (7.9%)	6 (9.2%)	0.56
II	20 (52.6%)	34 (52.3%)	
III	14 (36.8%)	19 (29.2%)	
IV	1 (2.6%)	6 (9.2%)	
Pre-operative CEA (ng/ml)	7.49 ± 12.02	6,17 ± 10.53	0.06
Tumor site			
Colon	32 (62.7%)	47 (54%)	0.31
Rectum	19 (37.3%)	40 (46%)	
Tumor Stage§			
UICC I	23 (45.1%)	17 (19.5%)	0.001
UICC II	10 (19.6%)	39 (44.8%)	
UICC III	18 (35.3%)	31 (35.6%)	
Surgical approach			
Open	27 (52.9%)	37 (42.5%)	0.23
Laparoscopic	24 (47.1%)	50 (57.5%)	
Surgical priority			
Emergency	1 (2%)	1 (1.1%)	0.70
Elective	50 (98%)	86 (98.9%)	
Lymph nodes	22 ± 13	21 ± 12	0.60
Adjuvant chemotherapy	23 (45.1%)	49 (56.3%)	0.20
Lymphovascular invasion	13 (25.5%)	14 (16.1%)	0.17

Data are number of patients with percentage in parentheses or mean T standard deviation. ¶Significant at the $p < 0.05$ level

*American Society of Anesthesiologists risk scale level

§7th edition of the tumor-node-metastasis (TNM) cancer staging system by the American Joint Committee on Cancer and the International Union for Cancer Control (5).

Table 2. Association of recurrence and SSI and its different forms of presentation

	SSI			Wound infection			Organ/space infection		
Recurrence	Present (n = 51)	Absent (n = 87)	p value	Present (n = 21)	Absent (n = 117)	p value	Present (n = 30)	Absent (n = 108)	p value
Yes	13 (25.5%)	17 (19.5%)	0.41	3 (14.3%)	27 (23.1%)	0.36	10 (33.3%)	20 (18.5%)	0.08
No	38 (74.5%)	70 (80.5%)		22 (85.7%)	90 (76.9%)		20 (66.7%)	88 (81.5%)	

	Anastomotic leak			Intra-abdominal abscess		
Recurrence	Present (n = 17)	Absent (n = 121)	p value	Present (n = 13)	Absent (n = 125)	p value
Yes	4 (23.5%)	26 (21.5%)	0.84	6 (46.2%)	24 (19.2%)	0.02
No	13 (76.5%)	95 (78.5%)		7 (53.8%)	101 (80.8%)	

Recurrence, OS, and actuarial 5-year DFS

The median follow-up was 61 months (range 3-85 months; 75% over 69 months). During this period, recurrence of colorectal cancer was detected in 30 patients (local recurrence, n = 1; metachronous metastasis, n = 14; and both, n = 15). Recurrence rate was slightly higher in SSI group compared with patients without infection (25.5% vs. 19.5%, p = 0.41) but not statistically significant. However, patients with an intra-abdominal abscess compared with them without showed a higher recurrence rate (46.2% vs. 19.2%, p = 0.02) (Table 2).

The Kaplan–Meier analysis revealed an estimated overall survival (OS) of 70 months (95% confidence interval [CI], 63-77 months) for patients with SSI and 71 months (95% CI, 67-75 months) for the patients without SSI (log-rank p = 0.50). In addition, there was a DFS estimation of 68 months (95% CI, 59-75 months) for the patients with SSI and 69 months (95% CI, 63-74 months) for all the patients without SSI (log-rank p = 0.33) (Fig. 2). Stratified analysis showed significant differences in DFS in patients who suffered organ-space infection when compared with those who were non-infected patients (62% vs. 81%, p = 0.04). Furthermore, patients who developed an intra-abdominal abscess also showed worse OS (58% vs. 82%, p = 0.05) and DFS (53% vs. 80%, p = 0.02) (Figs. 2-6).

Discussion

A growing interest has risen in recent years about a potential relationship between AL and its subsequent inflammatory process and worse oncological outcomes[4]. An amplified and perpetuated inflammatory response induced by infection may contribute to the process of carcinogenesis and tumor progression by supplying different molecules to the tumor microenvironment that facilitate angiogenesis, invasion, and metastasis[3,7-10]. This mechanism has been observed after resection of liver metastases[11-14], hepatocarcinomas or intrahepatic cholangiocarcinomas[15], and also after esophageal carcinoma surgery[16]. To date, global SSI has not been studied as an independent factor for poor oncological prognosis after CRC surgery. Most studies only analyze some of the types of post-operative infection that enter the definition of SSI. In addition, only a few studies have investigated the isolated effect of organ-space infection (AL plus intra-abdominal abscess) on oncological outcomes. In this regard, Eberhardt et al.[17] observed a worse prognosis in patients with rectal cancer in terms of recurrence and overall and specific survival after suffering an organ-space infection. However, the inclusion of stage IV patients in this study along with the high rate of local recurrence (11%) and mortality of 14.5% during the 1st year for those patients who suffered an AL might have influenced the results. Kressner et al.[18] in 2002 analyzed organ-space and perineal wound infection after abdominoperineal amputation, observing a significant association between the latter and the rate of local recurrences. The influence of AL and intra-abdominal abscess development in stage II colorectal cancer patients was also recently analyzed by Sánchez-Velazquez et al.[19] They detected that post-operative organ-space infection was a negative predictor of DFS and cancer-specific survival.

The specific influence of AL on cancer recurrence and disease progression has been extensively

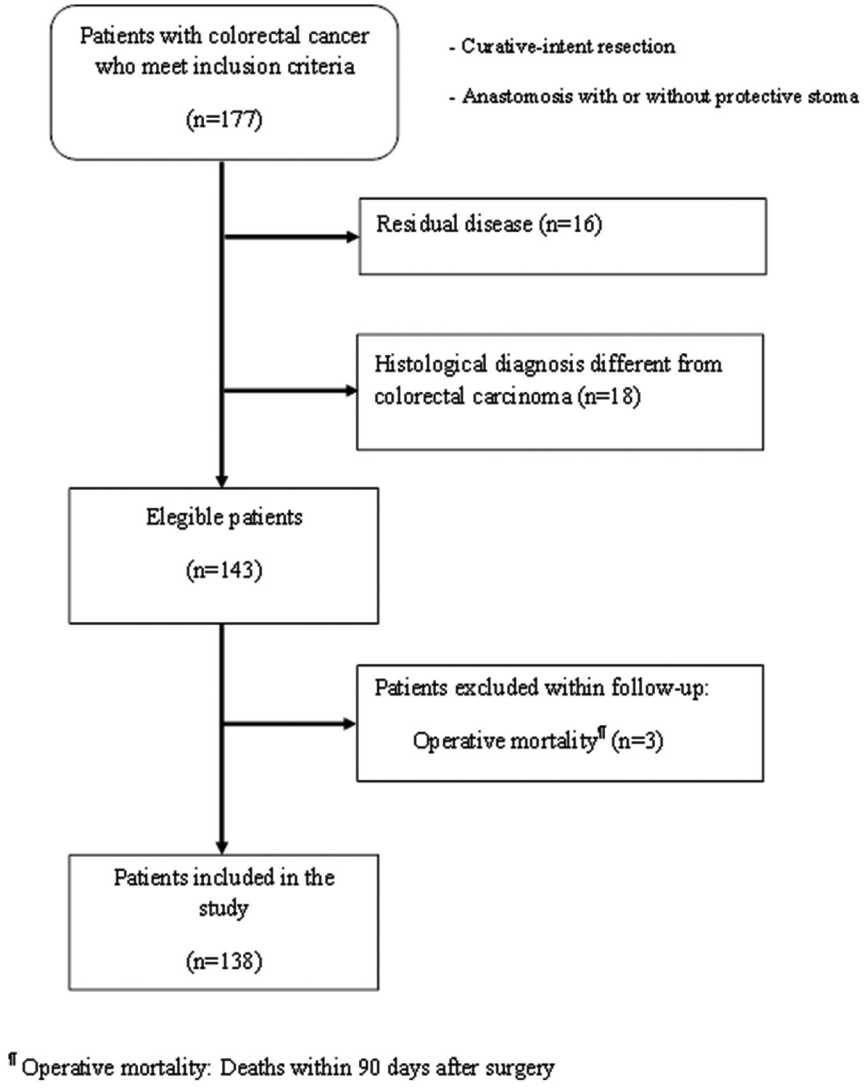

Figure 1. *Flow diagram for selected and excluded patients.*

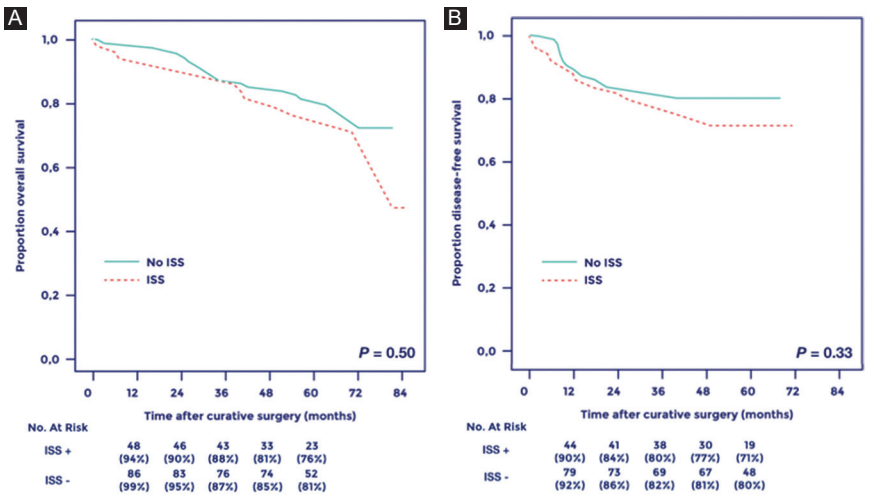

Figure 2. *Kaplan–Meier plots illustrating* **A:** *OS and* **B:** *DFS for patients with and patients without SSI.*

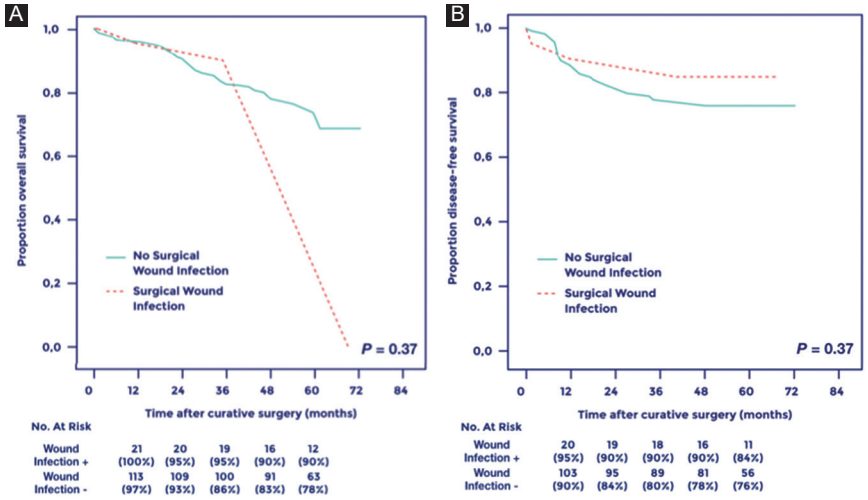

Figure 3. *Kaplan–Meier plots illustrating* **A:** *OS and* **B:** *DFS for patients with and patients without surgical wound infection.*

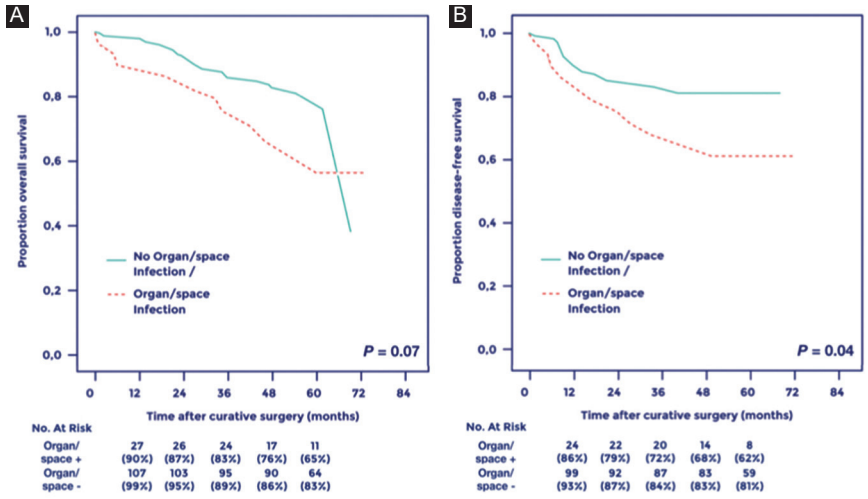

Figure 4. *Kaplan–Meier plots illustrating.* **A:** *OS.* **B:** *DFS for patients with and patients without organ/space infection.*

investigated. A meta-analysis that included 21,902 patients from 21 studies revealed that AL had a statistically significant negative impact on local recurrence rates after rectal cancer resection and was also associated to a significant reduction in long-term survival[20]. In addition, a greater number of metastases development was observed after AL occurrence, although the differences were not statistically significant. Similar results were reported by Lu et al. in their recent meta-analysis, which included 13,655 patients from 11 studies[21].

Although not statistically significant, our study showed that patients who suffered an SSI developed an increased cancer recurrence rate, whereas OS and 5-year DFS did not worsen. Nevertheless, according to the analysis by type of infection, the intra-abdominal abscess confirmed a statistically significant negative effect with an increased risk of recurrence and a lower DFS in the univariate analysis.

It has been suggested that the risk of tumor recurrence could be influenced not only by the inflammatory process secondary to the infection but also through the severity of this inflammation[22]. This hypothesis, proposed by Markar et al.[16], could explain our findings because organ-space infection and, above all, intra-abdominal abscess presence represent higher infectious aggression and could therefore explain a higher tumor recurrence rate and a lower

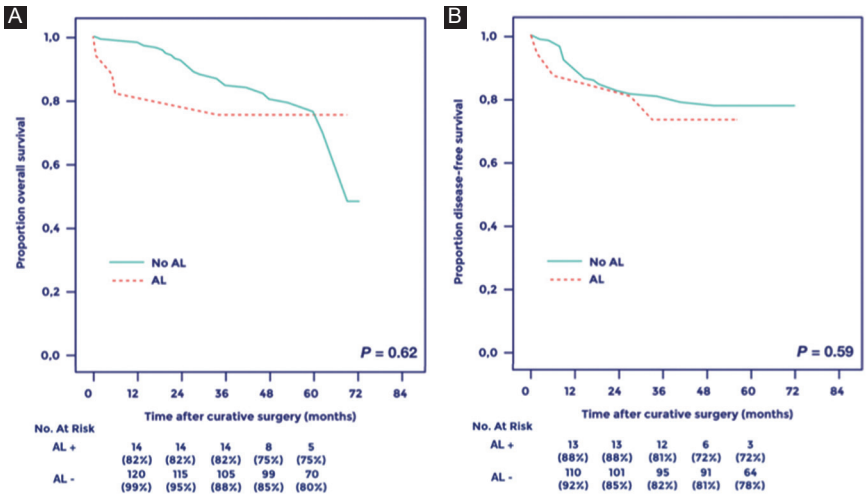

Figure 5. *Kaplan–Meier plot illustrating* **A:** *OS.* **B:** *DFS for patients with and patients without anastomotic leak.*

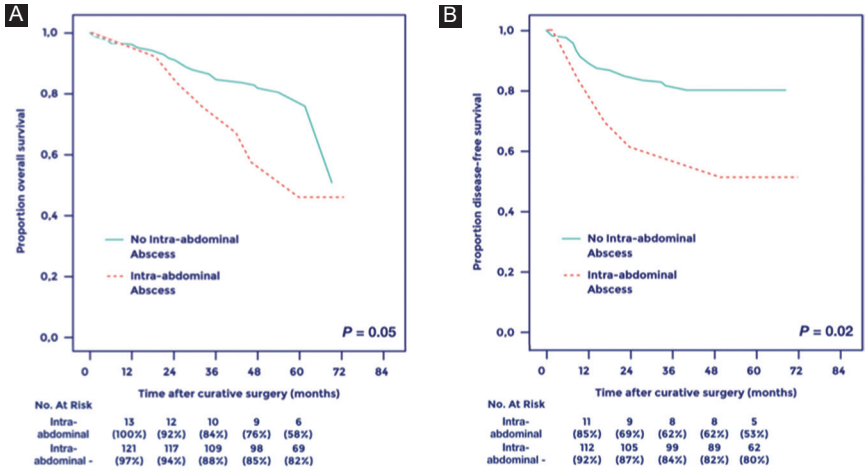

Figure 6. *Kaplan–Meier plot illustrating* **A:** *OS and* **B:** *DFS for patients with and patients without intra-abdominal abscess.*

DFS in these patients. We believe that developing SSI is not enough to negatively affect the oncological prognosis and that the presence of an associated major inflammatory process is essential in carcinogenesis. The inclusion of patients with surgical wound infection in our primary analysis that usually only generates a local minor inflammatory reaction could influence the obtained results. Furthermore, it could be assumed that the presence of an AL should be sufficient to induce a severe inflammatory response, but this hypothesis seems not to be evident according to our data. Conversely, in our study, AL led to reoperation in some patients that experienced diffuse peritonitis, whereas only percutaneous drainage and antibiotic coverage were required in other cases that developed a lower inflammatory response, revealing a non-homogeneous process in all patients.

Although our cohort was obtained consecutively during the recruitment period, we observed that the distribution by tumor stage in patients with and without SSI differed significantly, finding a higher percentage of stage I in patients with SSI. Thus, a lower cancer recurrence risk could have been expected in the SSI group. However, the recurrence rate was higher, which reinforces, even more, the idea of the negative impact of post-surgical infection on the oncological prognosis. Furthermore, it is evident that patients suffering from SSI, especially those with greater severity that require reoperation, will suffer a

delay, suspension, or incomplete administration of adjuvant chemotherapy. This fact may be considered, a confounding factor, or, depending on the point of view, just one of the ways in which SSI influences oncological prognosis.

Although our study has not been able to demonstrate that SSI represents globally an independent risk factor for poor oncological prognosis, it is clear that some relationship between infection and cancer progression may exist and that it is probably influenced by the severity of the infection. In our opinion, we may have been underpowered, and a larger sample size could therefore allow stratifying the study groups by severity of infection. We suggest that patients that suffered a post-operative SSI with a major inflammatory response should be classified as having a high-risk factor for recurrence, similar to those who develop a perforated CCR tumor and considered for adjuvant treatment in regardless of their tumor stage.

Future research should focus on the prediction, prevention, and early detection of SSI in an effort to reduce the clinical impact of SSI on oncological outcomes in CRC patients.

Conclusion

In our cohort of patients with colorectal cancer, those who developed SSI revealed a higher recurrences rate despite having significantly lower tumor stages. Although this increase did not reach statistical significance, the fact that intra-abdominal abscess development was significantly associated with tumor recurrence in the univariate analysis and DFS was significantly decreased after organ-space infection, or intra-abdominal abscess occurrence may suggest a role for SSI in oncological prognosis. Further multi-institutional studies are necessary to conclude a causal association.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals in this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy an informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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