ORIGINAL ARTICLE

Colorectal cancer: immune response in laparoscopic versus open colorectal surgery

Cáncer colorrectal: comparación de la respuesta inmune entre cirugía abierta y laparoscópica

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Abstract

Introduction: *Colorectal cancer is the second most frequent cause of deaths from cancer worldwide. Enhanced recovery protocols (ERPs) were developed in 90s to improve the recovery of these patients. Within ERPs, this work aims to compare immune response between open and laparoscopic procedures to support the best surgical approach.* ***Materials and methods:*** *The immune status of 148 patients undergoing colorectal surgery (74 by laparoscopic and 74 by open surgery [OS]) was studied in three moments: before surgery (POD0) and on the 1st and 3th post-operative days (POD1 and POD3).* ***Results:*** *Comparing to the laparoscopic group, in the OS group, C-reactive protein levels were significantly higher on POD1 and POD3 ($p < 0.001$), whereas lymphocyte levels were significantly lower ($p = 0.006$) and neutrophil levels were higher ($p = 0.012$) on POD1. On the other hand, higher levels of B cells ($p = 0.023$) were observed on POD1 in the laparoscopic group. Natural killer cell levels were significantly reduced ($p = 0.034$) in this group on POD3.* ***Conclusions:*** *Within the ERP, immune response pattern in both surgery approaches appears to be similar. Nevertheless, a greater inflammatory response of the OS is observed, whereas earlier recovery of the immune levels baseline seems to be a trend in the laparoscopic surgery.*

Keywords: *Immune response after surgery. Enhanced recovery protocols. Colorectal cancer surgery. Laparoscopic and open surgery.*

Resumen

Introducción: *El cáncer colorrectal es la segunda causa más frecuente de muerte por cáncer en todo el mundo. Los protocolos de recuperación mejorados (ERP) se desarrollaron en los años 90 para mejorar la recuperación de estos pacientes. Dentro de los ERP, este trabajo tiene como objetivo comparar la respuesta inmune entre procedimientos abiertos y laparoscópicos para respaldar el mejor abordaje quirúrgico.* **Material y métodos:** *Se estudió el estado inmunológico de 148 pacientes sometidos a cirugía colorrectal (74 por vía laparoscópica y 74 por cirugía abierta) en tres momentos: antes de la cirugía (POD0) y en el 1 y 3 días postoperatorios (POD1 y POD3). Resultados: En comparación con el grupo laparoscópico, en el grupo de cirugía abierta los niveles de proteína C reactiva fueron significativamente más altos en POD1 y POD3 ($p < 0.001$), mientras que los niveles de linfocitos fueron significativamente más bajos ($p = 0.006$) y los niveles de neutrófilos fueron más altos ($p = 0.012$) en POD1. Por otro lado, se observaron niveles más altos de células B ($p = 0.023$) en POD1 en el grupo laparoscópico. Los niveles de células asesinas naturales se redujeron significativamente ($p = 0.034$) en este grupo en POD3. Conclusiones: Dentro del ERP, el patrón de respuesta inmune en ambos enfoques quirúrgicos parece ser similar. Sin embargo,*

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se observa una mayor respuesta inflamatoria de la cirugía abierta, mientras que la recuperación más temprana de los niveles inmunitarios basales parece ser una tendencia en la cirugía laparoscópica.

Palabras clave: *Respuesta inmune después de la cirugía. Protocolos de recuperación mejorados. Cirugía de cáncer colorrectal. Cirugía laparoscópica y abierta.*

Introduction

The first studies in laparoscopic surgery (LS) reported a higher tumor recurrence rate[1,2]. However, as subsequent randomized studies were conducted and surgeons overcame the learning curve inherited by a new surgical technique, numerous benefits of LS were established. Among the short-term advantages, the most outstanding ones are the faster return of intestinal motility, which leads to an earlier return to a normal diet; the reduction of post-operative pain, which translates into a lower need for analgesia; and finally, quick recovery of the patient, which results in a shorter length of stay. In the long term, identical rates of tumor recurrence and patient survival have been showed in open versus LS[3-6].

In parallel to the development of LS, the multimodal rehabilitation programs emerged. These programs are also known as Fast-track protocols, enhanced recovery after surgery (ERAS) protocols, or Enhanced Recovery Protocols (ERP)[7,8]. These protocols aim to achieve an early recovery of patients after surgery, minimizing stress and comorbidities, and reducing hospital stay, with the consequent decrease in waiting lists and hospital costs.

This study aims to understand the immune response that occurs after open and laparoscopic intervention within ERPs. Evidence-based medicine supports the use of laparoscopic approaches in colorectal cancer surgery. However, clear evidence that this surgical technique provides greater benefits than open surgery (OS) is still lacking. By studying the immune response of patients within these protocols will help to homogenize the sample, so that the patients treated for oncological pathology start from the best possible physiological conditions.

In this work, it has been hypothesized that advantages observed in LS may arise due to a better-preserved immune system in this procedure with respect to OS. Therefore, immune parameters have been collected to compare the immune response between both surgical approaches. Not only the immune response between both surgical approaches has been compared but also the evolution over time of each parameter has been analyzed.

Materials and methods

Patient selection

A prospective non-randomized study including patients diagnosed with operable colon cancer and included in an ERP was carried out. Patients underwent major abdominal surgery for a colorectal cancer process, either by laparotomy or laparoscopy, in the General and Digestive Surgery Department of the Hospital Lozano Blesa (Zaragoza, Spain). The sampling was conducted between June 1, 2013, and June 15, 2017.

A surgical team composed of surgeons, anesthetists, and nurses trained in ERP was established. The ERP established by the Spanish Multimodal Rehabilitation Group was followed.

The surgeons were trained in both laparoscopic and open colorectal surgery. Surgical technique was decided by this surgical team according the patient's clinical history to provide them the best possible treatment. Right hemicolectomy, left hemicolectomy, sigmoid colectomy, and anterior resection were the surgical procedures included in this study, being considered as the most standardized and less aggressive techniques. The same anesthetic procedure by intravenous analgesia was followed in all cases. Patients' exclusion criteria are shown in table 1.

Finally, 148 patients were included in the study, 74 undergoing OS, and 74 LS. The study was approved by the Aragon Institutional Review Board (IRB number: C.P.-C.I. PI13/0087). A written informed consent was provided by all the patients included in this study.

Blood sampling

Blood samples were collected from patients before the surgical intervention (POD0) and at 24 (POD1) and 72 h (POD3) post-surgery. C-reactive protein (CRP) parameter was performed from serum samples taken from patients by venipuncture. To this end, IMMAGE® Immunochemistry Systems (Beckman Coulter) were used.

Table 1. Exclusion criteria of patient selection

Patients classified as ASA IV
Patients with uncompensated cardiorespiratory disease
Patients with chronic and acute renal impairment
Patients with altered preoperatory parameters
Patients with chronic hepatic impairment
Patients with situations of uncorrected intraoperative hypovolemia
Patients with generalized sepsis
Patients with coagulopathies
Patients with increased intracranial pressure (ICP)
Patients with a known allergy to anesthetics
Patients with needing a perioperative transfusion
Chronic opiate users

ASA: American society of anesthesiologists.

Human physiological values are 0.02-0.61 mg/dl. Higher values indicate a systematic inflammatory response.

Hemogram was performed in a DxH 800 Hematology Analyzer (Beckman Coulter) from whole blood in EDTA anticoagulant obtained by venipuncture. Blood parameters measured were white blood cell (WBC) count (WBC, 4-11 mil/mm^3), hematocrit (HCT, 36-45%), neutrophil percent (NE, 40-75%), lymphocyte percent (LY, 20-45%), monocyte percent (MO, 2-10%), eosinophil percent (EO, 0-5%), and basophil percent (BA, 0-2%).

Serum samples were obtained by venipuncture and collected to determine immunoglobulins IGA (68-378 mg/dl), IGG (768-1632 mg/dl), and IGM (60-263 mg/dl). The nephelometry technique was carried out by IMMAGE® Immunochemistry Systems (Beckman Coulter). The nephelometer BN II System (Siemens) was used to determine IGE (0-180 mg/dl). The end-point nephelometry was carried out from serum samples obtained by venipuncture.

The determination of all the antibodies was automatically carried out in a Cytomics FC500 flow cytometer (Beckman Coulter), following the manufacturer's instructions for the treatment of the samples from the analysis of whole blood in anticoagulant heparin obtained by venipuncture. The percentage of total T lymphocytes (CD3, 65-80%), T-helper (Th) cells (CD4, 40-50%), T cytotoxic (Tc) cells (CD8, 26-30%), B lymphocytes (CD19, 10-15%), CD4/CD8 (1,5-2), and natural killer (NK) cells (CD56, 5-10%) were obtained.

Table 2. Clinical and demographic variables according to the type of surgery

	OS (n = 74)	LS (n = 74)	p-value*
Sex (male)	61 (82.43)	47 (63.51)	0.143
Age (years)	69.33 (10.42)	66.98 (10.38)	0.416
Weight (Kg)	82.23 (12.33)	76.97 (10.15)	0.140
Height (cm)	166.55 (7.49)	164.23 (7.45)	0.365
Body Mass Index	29.83 (4.03)	28.53 (2.85)	0.155
ASA			0.746
II	32 (43.24)	35 (47.30)	
III	42 (56.76)	39 (52.70)	
Cancer stage (TNM Classification)			
Stage II	34 (45.95)	30 (40.54)	0.803
Stage III	40 (54.05)	44 (59.46)	
Operation type			
Right hemicolectomy	31 (41.90)	19 (25.68)	
Left hemicolectomy	15 (20.27)	11 (14.86)	
Sigmoidectomy	4 (5.40)	35 (47.30)	
Anterior resection	24 (32.43)	9 (12.16)	
Complications	31 (41.89)	22 (29.73)	0.511
Operation time (min)	206.15 (31.11)	190.27 (22.51)	0.121

OS: open surgery, LS: laparoscopic surgery, ASA: American Society of Anesthesiologists. Data showed as n (%) for qualitative variables and as mean value (SD) for quantitative variables.

Statistical analysis

Statistical analysis was performed using the SPSS software package, with $p < 0.05$ indicating statistical significance.

The Chi-square test and Fisher test were used to show the relationship between independent qualitative variables, while the McNemar test or Crochan's Q test were applied if the variables were found to be related. The Kolmogorov–Smirnov test was used to determine whether the variables complied with normality criteria, whereas the Mann–Whitney U-test and Student's t-test were used to compare the means of independent variables. The means obtained at the different sample-processing times were collated using the Wilcoxon test when 2 times were compared, and the Friedman tests when all 3 times were compared.

Results

Clinical and demographic characteristics

No statistically significant differences ($p > 0.05$) were found between the study groups with respect to the clinical and demographic aspects studied (Table 2). More

Table 3. CRP levels (mg/dl) according to the type of surgery (mean ± SD) in the 3 different moments

	POD0	POD1	POD3	p (global)	p (POD0-POD1)	p (POD0-POD3)	p (POD1-POD3)
CRP							
OS	1.40 (1.99)	10.63 (4.5)	13.77 (9.31)	< 0.001	< 0.001	< 0.001	0.395
LS	0.84 (0.91)	5.28 (1.60)	7.20 (5.73)	< 0.001	< 0.001	< 0.001	0.291
p	0.132	< 0.001	< 0.001				

POD0: day if intervention; POD1: post-operative day 1; POD3: post-operative day 3, CRP: C-reactive protein.

complications were not observed in OS and although not significantly, operation time and length of stay were longer in the OS group. In addition, a statistically significant difference ($p < 0.005$) was observed in the meantime of patients who remained in hospital, with those suffering complications being hospitalized for longer (32.29 days; SD = 28.09) than those who did not (7.83 days; SD = 3.98), irrespective of the intervention group.

Pro-inflammatory marker

Higher CRP significantly levels were obtained on POD1 and POD3 in the OS group compared to LS group, 10.63 (SD = 4.5) and 13.77 (SD = 9.31) compared to 5.28 (SD = 1.60) and 7.20 (SD = 5.73), respectively (Table 3). CRP followed the same evolution in both groups, increasing significantly their values over time, remaining in all the post-operative days higher in OS than in LS.

Immune parameters

Hematocrit and WBCs

The evaluation of blood parameters according to the type of surgery (Fig. 1) depicted significant differences when comparing OS and LS on POD1. In the OS group, the percentage of lymphocytes was lower (9.61% vs. 13.53%, p = 0.005), while the percentage of neutrophils was higher (81.59% vs. 77.43%, p = 0.011).

It can be observed in the graphs how the levels of the hematocrit, lymphocytes, monocytes, eosinophils, and basophils are higher in the case of LS according the time, whereas the values of WBC and neutrophils remain lower, indicating a less aggressive innate immune response of the laparoscopic approach to the surgical act. In fact, the percentage variation was used to compare the evolution of the parameters between the two intervention groups. No statistically significant differences between them were obtained, but a trend toward restoring baseline levels of the following parameters in LS group with respect to OS group on POD3-POD0 was observed: hematocrit (−7.48% vs. −8.8%), lymphocytes (−29.99% vs. −37.06%), monocytes (0.38% vs. −3.5%), eosinophils (63.38% vs. 196.64%), and basophils (−4.7% vs. −20.78%).

Immunoglobulins

The comparison between the two groups did not show any significant difference in the immunoglobulin levels for the periods studied (Fig. 2). There were no statistically significant differences in the evolution of immunoglobulins according to the type of surgical intervention. Besides, most of levels of immunoglobulins remained within the biological reference interval, pointing to a preserved humoral immunity in both cases.

Lymphocyte profile

As it is shown in figure 3, when comparing LS versus OS, a statistically significant higher percentage of B-lymphocytes was found in LS (14.12% vs. 11.05%, p = 0.023) on POD1, but a lower percentage of NK cells (10.58% vs. 14.33%, p = 0.034) on POD3.

Analyzing the evolution of the parameters over time, a significant difference in the case of the NK cells on POD3-POD0 (p = 0.026) was found. An increase of almost 30% was observed in the OS group, while there was a decrease of 10.51% in the LS group. It was also observed that the percent variation on the interval POD3-POD0 for all parameters (except CD3) - while not significant - was lower in the LS group compared to the OS group. This suggests that the immune global change produced in the lymphocyte populations after laparoscopy surgery is inferior to that produced by OS.

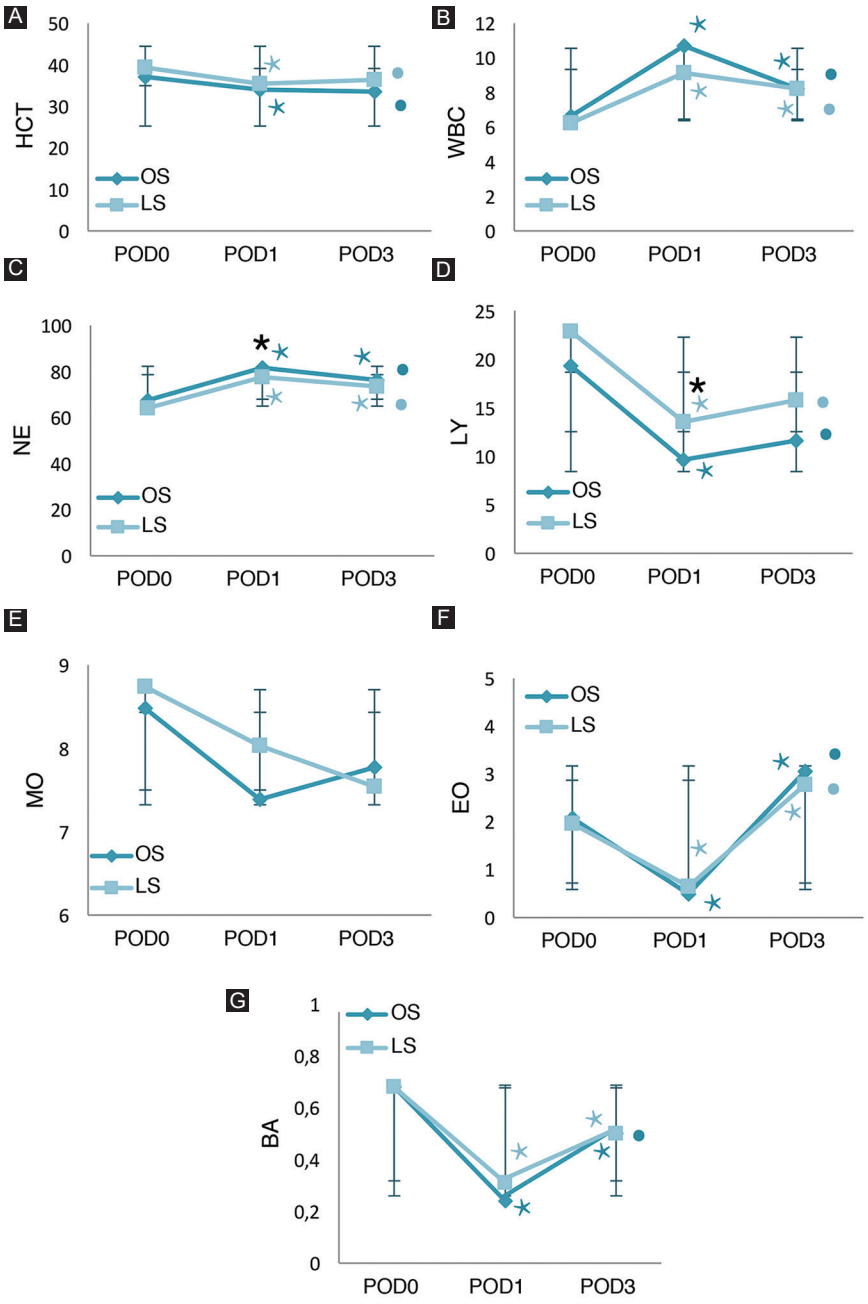

Figure 1. *Evolution of hematocrit and white blood cells according to the type of surgery (mean0 ± SD).* **A:** *hematocrit levels.* **B:** *white blood cells levels.* **C:** *neutrophils levels.* **D:** *lymphocyte levels.* **E:** *monocytes levels.* **F:** *eosinophil levels.* **G:** *basophils levels. *Statistical significance (p < 0.05) between groups (OS: open surgery; LS: laparoscopic surgery). *Statistical significance (p < 0.05) between a POD and the previous (within LS). *Statistical significance (p < 0.05) between a POD and the previous (within OS). ●Statistical significance (p < 0.05) between POD3 and the POD0 (within LS). ●Statistical significance (p < 0.05) between POD3 and the POD0 (within OS).*

Discussion

In this study, we compared immune response due to open and LS in oncological patients undergoing colorectal surgery. All patients were included within the same ERP to optimize their physical, physiological, and psychological conditions. This fact allows attributing the effects obtained in changes in the immune response mainly to the surgical approach, and not to other individual characteristics factors. Indeed, no significant demographic or clinical differences were obtained in the comparison groups (open vs. laparoscopy).

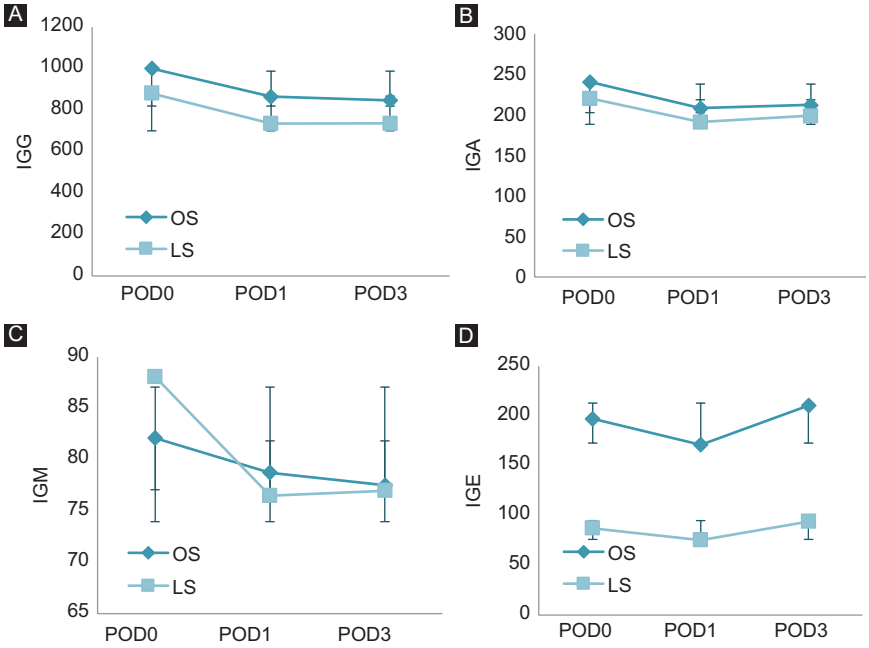

Figure 2. *Evolution of immunoglobulins according to the type of surgery (mean ± SD).* **A:** *immunoglobulin G levels.* **B:** *immunoglobulin A levels.* **C:** *immunoglobulin M levels.* **D:** *immunoglobulin E levels.*

Many works[9-11] have focused on the study of the systemic inflammation response produced by the surgical act. Pro-inflammatory markers such as CRP or interleukin (IL)-6 as well as different acute phase proteins have been studied, concluding that LS produces a lower innate response than OS, especially in the first post-operative hours. In this work, the systemic inflammation marker CRP was analyzed. CRP levels were significantly increased over time (p global < 0.001) in both OS and LS, suggesting that an inflammatory response occurs in both cases. However, CRP levels were significantly higher in OS, not only on POD1 but also on POD3, indicating a more aggressive inflammatory response.

In this work, hematocrit levels were used to evaluate intraoperative bleeding. A significant reduction was observed in both surgical groups, without statistically significant differences among them. However, it was observed higher hematocrit levels in the LS group, which could suggest a lower risk of surgical and post-operative hemorrhages, as it was also observed in the Evans et al. study[12].

The results obtained regarding leukocyte levels and their populations partially agree with the ones reported by Huang et al.[13] and Fujii et al.[14] An increase in leukocytes and neutrophils levels as well as a reduction in lymphocyte levels in both groups was also observed. However, the authors observed greater lymphocyte levels in the LS group on POD4, while, in this study, these values have arisen on POD1. Fujii et al.[14] also observed an increase in leukocytes and a decrease in the lymphocyte levels on POD1, without finding differences between groups except for the case of leukocytes (higher in OS vs. LS). However, they studied more post-operative days, verifying that the leukocyte levels returned to their baseline levels on POD7 in both groups. In our study, the maximum post-operative time studied was 72 h (POD3). Thus, this tendency to recover leukocytes or neutrophils baseline levels could not be observed. Nevertheless, a certain trend to recover earlier baseline levels of the rest of lymphocyte populations has been observed. Furthermore, it seems that LS group recovers earlier baseline levels than OS group. These findings pointed to an immune system suppression caused by surgery. The higher lymphocytes levels found in LS versus OS indicate that this immune system suppression is less pronounced in LS, since the reduction in lymphocytes is lower compared to OS. This fact would support studies that have reported preserved cell-mediated immunity in LS[15-17].

In addition, the highest neutrophil and CRP levels observed in OS would support a greater inflammatory response produced by this surgical technique, especially in the short-term (on POD1), as Ramanathan et al.[18], Gustafsson et al.[19], and among others[20-22] have reported.

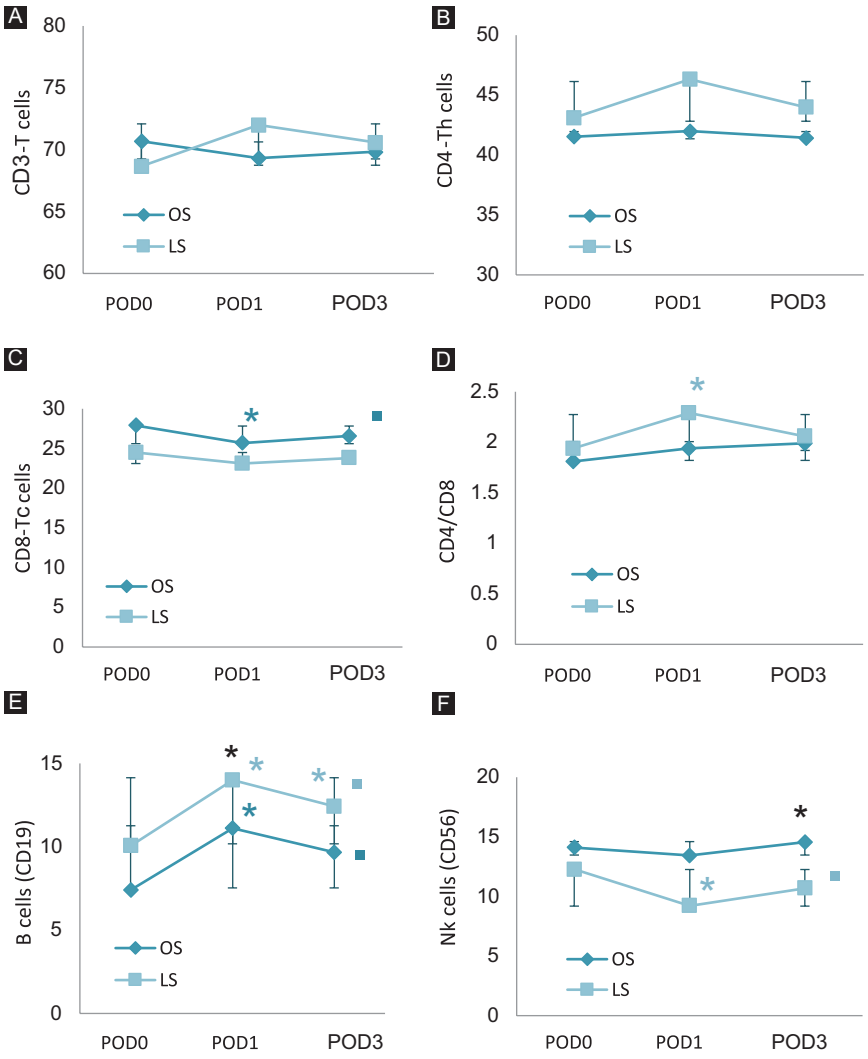

Figure 3. *Lymphocyte profile according to the type of surgery (mean ± SD).* **A:** *T cells levels.* **B:** *T-helper cells levels.* **C:** *T cytotoxic levels.* **D:** *CD4/CD8 ratio.* **E:** *B cells levels.* **F:** *NK cell levels.*
*Statistical significance (p < 0.05) between groups (OS: open surgery; LS: laparoscopic surgery). *Statistical significance (p < 0.05) between a POD and the previous (within LS). *Statistical significance (p < 0.05) between a POD and the previous (within OS). ■Statistical significance (p < 0.05) between a POD and the POD0 (within LS). ■Statistical significance (p < 0.05) between POD3 and the POD0 (within LS). Statistical significance (p < 0.05) between POD3 and the POD0 (within OS).*

The analysis of NK cells showed significantly lower levels in LS on POD3. This fact could suggest a lower anti-tumor capacity of the laparoscopic approach. Studies that have included NKs[23] did not observe significant differences between OS and LS. However, Huang et al.[13] reported a pronounced post-operative decrease of NK cells in OS. Nevertheless, data did not show significantly statistically differences. Furthermore, NK cells recovered their baseline levels on POD7 in both surgical approaches. Within ERP, Wichmann et al.[24] also observed a NK cell suppression after surgery. However, they did not compare OS versus LS, but conventional care versus ERP. Long-term patient survival data should be collected to assess this effect more accurately.

In the case of Tc lymphocytes, when studying evolution over time, a significant reduction was observed in OS group on POD1-POD0 and POD3-POD0. This may suggest a major immunosuppression in OS. Nevertheless, CD4/CD8 ratio did not show significant variations. Thus, immunosuppression does not seem to have any influence. On the other hand, although there are no differences in the evolution of Th and Tc lymphocytes in LS, the CD4/CD8 ratio showed a significant increase on POD1, what could indicate a greater preservation of cellular immunity in the LS recent post-operative period.

With respect to humoral immunity, lower B lymphocyte levels on POD1 were observed in OS versus LS. This fact could suggest a major immunosuppression in

OS, as other studies have been suggested[25,26]. Despite of this, no difference in the immunoglobulins levels between groups was observed. Therefore, a suppression of the humoral response in OS cannot be reported.

Conclusions

As a synthesis of all the immune parameters analyzed, it has not been possible to establish a different pattern of immune response between OS and LS. However, a greater organic aggression and inflammatory response in OS has been observed, especially in the short-term period. In addition, the evolution of the immune parameters studied over time has shown a trend toward recovering earlier their pre-operative levels, as well as minor immune changes in the laparoscopic approach. This fact points to a better-preserved immune system in LS. However, further studies should be designed, to assess this hypothesis.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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 and 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.

References

1. Berends FJ, Kazemier G, Bonjer HJ, Lange JF. Subcutaneous metastases after laparoscopic colectomy. Lancet. 1994;344:58.
2. Vukasin P, Ortega AE, Greene FL, Steele GD, Simons AJ, Anthone GJ, et al. Wound recurrence following laparoscopic colon cancer resection. Results of the American Society of Colon and Rectal Surgeons Laparoscopic Registry. Dis Colon Rectum. 1996;39:S20-3.
3. Braga M, Vignali A, Gianotti L, Zuliani W, Radaelli G, Gruarin P, et al. Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome. Ann Surg. 2002;236:759-66.
4. Bärlehner E, Benhidjeb T, Anders S, Schicke B. Laparoscopic surgery for colon and rectal cancer. Surg Technol Int. 2004;13:93-9.
5. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr., et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg. 2007;246:655-62.
6. Clinical Outcomes of Surgical Therapy Study Group; Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004;350:2050-9.
7. Kehlet H, Slim K. The future of fast-track surgery. Br J Surg. 2012;99:1025-6.
8. Kehlet H. Fast track surgery: the facts and the challenges. Cir Esp. 2006; 80:187-8. [doi: 10.1016/S0009-739X(06)70955-1].
9. Dunker MS, Ten Hove T, Bemelman WA, Slors JF, Gouma DJ, Van Deventer SJ. Interleukin-6, C-reactive protein, and expression of human leukocyte antigen-DR on peripheral blood mononuclear cells in patients after laparoscopic vs. conventional bowel resection: a randomized study. Dis Colon Rectum. 2003;46:1238-44.
10. Tsimogiannis KE, Telis K, Tselepis A, Pappas-Gogos GK, Tsimoyiannis EC, Basdanis G. A-defensin expression of inflammatory response in open and laparoscopic colectomy for colorectal cancer. World J Surg. 2011;35:1911-7.
11. Ozawa A, Konishi F, Nagai H, Okada M, Kanazawa K. Cytokine and hormonal responses in laparoscopic-assisted colectomy and conventional open colectomy. Surg Today. 2000;30:107-11.
12. Evans C, Galustian C, Kumar D, Hagger R, Melville DM, Bodman-Smith M, et al. Impact of surgery on immunologic function: comparison between minimally invasive techniques and conventional laparotomy for surgical resection of colorectal tumors. Am J Surg. 2009;197:238-45.
13. Huang C, Huang R, Jiang T, Huang K, Cao J, Qiu Z. Laparoscopic and open resection for colorectal cancer: an evaluation of cellular immunity. BMC Gastroenterol. 2010;10:127.
14. Fujii K, Sonoda K, Izumi K, Shiraishi N, Adachi Y, Kitano S. T lymphocyte subsets and Th1/Th2 balance after laparoscopy-assisted distal gastrectomy. Surg Endosc. 2003;17:1440-4.
15. Gitzelmann CA, Mendoza-Sagaon M, Talamini MA, Ahmad SA, Pegoli W Jr., Paidas CN. Cell-mediated immune response is better preserved by laparoscopy than laparotomy. Surgery. 2000;127:65-71.
16. Wang H, Wang Y, Xing H, Zhou Y, Zhao J, Jiang J, et al. Laparoscopic surgery within an enhanced recovery after surgery (ERAS) protocol reduced postoperative ileus by increasing postoperative treg levels in patients with right-side colon carcinoma. Med Sci Monit. 2018;24:7231-7.
17. Cui M, Gong C, Jiang B, Yao Z, Chen L, Di J, et al. Evaluation of immune responses of gastric cancer patients treated by laparoscopic and open gastrectomy. Med Oncol. 2015;32:253.
18. Ramanathan ML, MacKay G, Platt J, Horgan PG, McMillan DC. The impact of open versus laparoscopic resection for colon cancer on C-reactive protein concentrations as a predictor of postoperative infective complications. Ann Surg Oncol. 2015;22:938-43.
19. Gustafsson UO, Tiefenthal M, Thorell A, Ljungqvist O, Nygrens J. Laparoscopic-assisted and open high anterior resection within an ERAS protocol. World J Surg. 2012;36:1154-61.
20. Braga M, Vignali A, Zuliani W, Radaelli G, Gianotti L, Martani C, et al. Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. Dis Colon Rectum. 2002;45:1070-7.
21. Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. J Gastrointest Surg. 2012;16:1379-88.
22. Glatz T, Lederer AK, Kulemann B, Seifert G, Holzner PA, Hopt UT, et al. The degree of local inflammatory response after colonic resection depends on the surgical approach: an observational study in 61 patients. BMC Surg. 2015;15:108.
23. Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, et al. Suppression of cellular immunity by surgical stress. Surgery. 2000;127:329-36.
24. Wichmann MW, Eben R, Angele MK, Brandenburg F, Goetz AE, Jauch KW. Fast-track rehabilitation in elective colorectal surgery patients: a prospective clinical and immunological single-centre study. ANZ J Surg. 2007;77:502-7.
25. Sammour T, Kahokehr A, Chan S, Booth RJ, Hill AG. The humoral response after laparoscopic versus open colorectal surgery: a meta-analysis. J Surg Res. 2010;164:28-37.
26. Marik PE, Flemmer M. The immune response to surgery and trauma: implications for treatment. J Trauma Acute Care Surg. 2012;73:801-8.