Original Article

The impact of laparoscopic surgery in colorectal cancer resection with respect to the development of liver metastasis in the long-term

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ABSTRACT

Introduction: Colorectal cancer (CRC) shows high incidence and mortality worldwide, particularly in Western and developed countries. The objective of this study is to evaluate the oncologic results during a minimum follow-up of 2 years of curable CRC patients submitted to laparoscopic resection in our environment, regarding to the development of hepatic metastases.

Methods: Medical records of 189 colon and rectal patients with potentially curable adenocarcinoma who have been submitted to laparoscopic resection have been reviewed through a retrospective cohort between January 2005 and March 2012 at a single institution regarded as reference to this type of treatment. Pearson's χ^2 and Long-rank tests have been used for statistical analysis and data was analyzed by statistic package STATA version 11.0.

Results: The eligible population for the study was 146 patients, 91 women (62%), with a mean age of 61 ± 13 years. Minimum follow-up was 24 months, having an mean follow-up of 60 ± 27 months and an mean follow-up of global disease recurrence of 27 ± 11 months. Hepatic metastases occurred in 7.5% of the population, most from stage III, and the mean recurrence period was 25 ± 16 months.

Conclusions: Laparoscopic resection for potentially curable CRC in this cohort did not change the long-term incidence of hepatic metastases, considering that our results are comparable to large randomized clinical trial results. Laparoscopic resection was effective and safe for analyzed patients, regarding long-term oncologic results.

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Impacto da cirurgia videolaparoscópica em ressecções de câncer colorretal quanto ao desenvolvimento de metástases hepáticas a longo prazo

RESUMO

Palavras-chave:
Câncer colorretal
Cirurgia laparoscópica
Colectomia vídeo-assistida
Resultados a longo prazo
Metástases hepáticas

Introdução: O câncer colorretal (CCR) apresenta elevada incidência e mortalidade mundial, especialmente nos países ocidentais e desenvolvidos. O objetivo deste estudo é avaliar, durante um seguimento mínimo de 2 anos, pacientes com CCR potencialmente curável submetidos a ressecções laparoscópicas, em relação ao surgimento de metástases hepáticas.

Métodos: Através de coorte retrospectiva foram revisados os prontuários de 189 portadores de adenocarcinoma de cólon e reto potencialmente curáveis, submetidos a ressecção laparoscópica entre janeiro de 2005 e março de 2012, numa única instituição considerada de referência neste tipo de tratamento. Para análise estatística foram usados o teste χ^2 de Pearson e o teste Log-rank, e os dados foram analisados pelo pacote estatístico STATA versão 11.0.

Resultados: A população elegível do estudo foi de 146 pacientes, sendo 91 mulheres (62%), com idade média de 61 ± 13 anos. O seguimento mínimo foi de 24 meses, sendo o tempo médio de seguimento de 60 ± 27 meses, e o tempo médio de recorrência global da doença de 27 ± 11 meses. Metástases hepáticas ocorreram em 7,5% da população, a maioria proveniente do estadio III, e o tempo médio de recorrência no fígado foi de 25 ± 16 meses.

Conclusões: Para esta coorte a ressecção do CCR potencialmente curável por via laparoscópica não modificou a incidência de metástases hepáticas a longo prazo, ao comparar nossos resultados aos dos grandes ensaios clínicos randomizados. Para os pacientes analisados, a ressecção laparoscópica foi eficaz e segura em relação aos resultados oncológicos a longo prazo.

Introduction

Worldwide, colorectal cancer (CRC) is the third most common malignancy and the fourth most responsible for mortality related to cancer.[1] Its incidence is higher in industrialized and Western countries, such as those in Western Europe, USA and Australia, and is growing in Asian countries such as Japan and Hong Kong, where historically the risk of the disease was low.[2–6] Its incidence is also high in Brazil; and for the year 2014, the National Cancer Institute (INCA) estimated 32,600 new cases.[7]

Despite the medical technology and pharmaceutical industry advancements observed, surgical resection remains the main therapeutic modality for CRC, being the only considered curative.[8–11]

After initial reports of colorectal resections by laparoscopy, from the first publication in 1991 by Jacobs et al. [12] the technique has become widespread. Concerns about the quality of resection, including the status of surgical margins and the radicalism of the lymphadenectomy, and also about the long-term oncological results, prompted a series of studies and randomized prospective clinical trials, the most important being the Barcelona, COST, CLASICC and COLOR studies.[13–23] The results of these trials showed that, in experienced hands, laparoscopy has a beneficial effect on post-operative recovery, when compared to open surgery, without compromising the oncological results in the long run.

Because of numerous publications speaking in favor of the technique and the increasing ability of surgeons, there was a significant increase in the number of colorectal surgeries by laparoscopy in the last decade around the world, and also among us. As the approach had a strong penetration in the treatment of malignant disease, we believe that it is necessary to ensure that the good results obtained in randomized clinical trials are similarly occurring also outside of these contexts.

Whereas the most frequent site of colorectal metastasis is the liver,[24] and liver metastases are the main cause of mortality in these patients,[25] this study aims to verify the emergence of liver metastasis in potentially curable CRC patients operated by laparoscopy in a reference center in our midst during a minimum follow-up of 2 years.

Patients and methods

Patients

This study follows a retrospective observational model, having been submitted and approved by the Ethical Committee of the Hospital e Maternidade Municipal Nossa Senhora Monte Serrat.

The study included patients with colon and rectum adenocarcinoma in stages I, II and III by TNM classification, according to the American Joint Committee on Cancer

(AJCC) and the International Union Against Cancer (IUAC),[26] and which underwent laparoscopic surgical resection with curative intent between January 2005 and March 2012 by the same surgical team at a referral center for advanced laparoscopic colorectal surgery: Instituto Lubeck, Itu – São Paulo.

Patients operated in emergency due to intestinal obstruction or perforation, patients with synchronous liver metastases or other distant metastases (stage IV by AJCC and IUAC),[26] patients undergoing surgery without curative intent, those carriers of concomitant inflammatory bowel disease, patients in Stage 0 (carcinoma in situ), and patients whose loss of follow-up occurred before reaching two years postoperatively were excluded.

Preoperative evaluation

The standard pre-operative evaluation included laboratory tests, including carcinoembryonic antigen (CEA), radiography or chest tomography, computed tomography (CT) abdominal and pelvic (in cases of rectal tumor) and colonoscopy.

Surgical technique

Laparoscopic surgery followed current oncological patterns: high lymphovascular ligation, longitudinal and circumferential safety margins, comprehensive lymph node resection, bowel mobilization and identification of anatomical structures without tumor manipulation, protection of the site used for specimen extraction, and exploration of the abdominal and pelvic cavity. The dissection of the colon was performed on a medial-lateral direction, with total resection of the corresponding mesocolon. The resection of the rectum was held in conjunction with a total mesorectal excision, or from mesorectum to the level of rectal section. The anastomoses in the right, transverse and descending colon were extracorporeal procedures, through the incision used for specimen extraction, and made by manual or mechanical technique. Colorectal anastomoses in surgery for sigmoid colon and rectum consisted in intracorporeal and mechanical procedures (double stapling).

Complementary therapy

Patients with rectal adenocarcinoma in clinical stage T3, T4 or with positive lymph nodes underwent preoperative radiation therapy and chemotherapy, and were treated with surgical resection between 6 and 8 weeks after completion of neoadjuvant therapy.

Adjuvant chemotherapy was administered to patients with cancer of the colon or rectum in stage III, and to patients in stage II with poorer prognosis criteria, such as vascular, lymphatic and perineural tumor invasion, tumors poorly differentiated, and intestinal wall impairment of T4 grade. Patients aged over 75 years and those who rejected the treatment were not submitted to adjuvant therapy.

Therapeutic radiotherapy and chemotherapy were performed as recommended by the National Comprehensive Cancer Network (NCCN).[27]

Data collection

From chart review, the following data was recorded: date of surgery and age at the time of the procedure, tumor location and type of colorectal laparoscopic resection, pathological tests, including degree of tumor differentiation, number of lymph nodes resected and their involvement, degree of intestinal wall invasion, and tumor stage according to the TNM staging system proposed by AJCC and IUAC, status of proximal, distal and circumferential surgical margins of the surgical specimen, and postoperative mortality considered until the 30th day of surgery.

The follow-up data collected were CEA, abdominal and pelvic CT (in cases of rectal tumor), chest radiography or CT and colonoscopy. Patients without a complete colonoscopy before the treatment were examined after surgery or after adjuvant therapy. The remaining patients repeated the colonoscopy after one year of treatment; and all, from a complete examination, underwent endoscopic surveillance every 3–5 years.

Follow-up

The follow-up was considered from the date of surgery to the appearance of liver metastasis, or development of a distant metastasis in another site, locoregional recurrence, until the date of death for reasons not related to the primary tumor, or until the last medical visit.

Statistical analysis

The statistical analysis consisted in verifying the distribution and re-coding of the variables. For the descriptive analysis, the variables were expressed as mean, standard deviation, frequency distribution, confidence intervals at 95%, and percentage. We conducted comparisons of proportions among variables using Pearson's χ^2 test.

The association among exposure variables and the appearance of metastasis was evaluated by Kaplan–Meier analysis, using the log-rank test. For this purpose, behavior of the variable "response at the end of the exposure in time" was interpreted in the following presentation: (i) characterization, for each patient, of the failure situation (recurrence of cancer), interpreted by the elapsed time between the entry of the patient in the study until the occurrence of the event of interest; (ii) definition, for each patient, of the situation of censorship, interpreted when the event of interest had not occurred until the end of observation, or until the patient loss during follow-up.

P values <0.05 were considered statistically significant, and the data were analyzed using the statistical package STATA version 11.0 (Stata Corp, College Station, TX, USA).

Results

Medical records of 189 patients undergoing laparoscopic resection of colon or rectal cancer without signs of widespread disease (stages I–III), with a minimum of 2 years follow-up, operated with curative intent between January 2005 and March

Table 1 – Clinical characteristics of patients.	
Characteristics	
Female, n (%)	91 (62)
Age in years, mean ± SD	61 ± 13
Tumor location, n (%)	
Caecum	5 (4)
Ascending colon[a]	21 (14)
Transverse colon[b]	4 (3)
Descending colon	7 (5)
Sigmoid colon	56 (38)
Rectum	53 (36)
Intervention, n (%)	
Right colectomy	25 (17)
Transverse resection	4 (3)
Left colectomy	7 (5)
Rectosigmoidectomy	105 (71)
Abdominoperineal resection of the rectum[c]	4 (3)
Total colectomy	1 (1)
Lymph nodes resected, mean ± SD	24 ± 12
Extension of the primary tumor, n (%)	14 (10)
T1	42 (28)
T2	77 (53)
T3	13 (9)
T4	
Lymph node metastasis, n (%)	106 (72)
N0	26 (18)
N1	14 (10)
N2	
Stage tumor, n (%)	53 (36)
I	53 (36)
II	40 (28)
III	
Histology, n (%)	15 (10)
Well differentiated	120 (82)
Moderately differentiated	11 (8)

Sample size = 146 patients; n, number of patients; % Percentage; SD, standard deviation.
[a] Includes the hepatic angle.
[b] Includes splenic angle.
[c] Rectum amputation.

Table 2 – Tumor recurrence and mortality.	
Overall tumor recurrence, n (%)	19 (13.5)
Recurrence type, n (%)	
Liver metastasis	11 (7.5)
Pulmonary metastasis	4 (3)
Regional locus	3 (2)
Carcinomatosis	1 (1)
Recurrence time in months, mean ± SD	27 ± 11
Follow-up time in months, mean ± SD Perioperative mortality, n (%)	60 ± 27
Overall tumor recurrence, n (%)	1 (1)

Sample size = 146 patients; n, number of patients; %, percentage; SD, standard deviation.

2012, were reviewed. As the exclusion criteria, 43 patients were excluded from this sample.

The population eligible for analysis in this study was composed of 146 patients; 91 were female (62%) and the mean age was 61 ± 13 years. The most frequent tumor site was sigmoid colon (56/38%), and the more often performed intervention was a retosigmoidectomy (105/71%). The mean number of resected lymph nodes was 24 ± 12, and 3 cases had compromised their circumferential surgical margin (<2 mm disease-free margin); these were cases of rectal cancer with infiltration of the intestinal wall (T4). A patient with impaired surgical margin showed locoregional recurrence 24 months after resection of the primary tumor. There were no cases of compromised longitudinal margins. Tumor stages more incident in this population were I and II, with 53 cases each. Most tumors exhibited a moderate degree of tumor differentiation (120/82%). The characteristics of the study population are shown in Table 1.

As the minimum follow-up given in the study was two years, patients operated until March 2012 were included.

The overall tumor recurrence occurred in 19 patients, representing an incidence of 13% of the study population. Liver, lung, locoregional sites and peritoneum (carcinomatosis) were the sites of recurrence, as shown in Table 2. There was no recurrence at the site of trocars. The most frequent location of metastases was in the liver, occurring in 11 patients (7.5%). The mean time of overall disease recurrence was 27 ± 11 months, with a mean follow-up of the study population of 60 ± 27 months. The operative mortality was only one female patient with stage II, victimized by a pulmonary thromboembolism on the 12th postoperative day. Table 2 shows the types of recurrence and the follow-up time until the event.

Patients with stage III had a higher number of recurrences (10/7%) (P 0.030), and a lower mean time until its occurrence (21 months), compared to the other stages (CI 95%: 16–26) (P 0.05), a statistically significant difference, as shown in Table 3.

Of the 11 patients who developed liver metastases, the majority came from the stage III, and seven patients had primary colon tumor. Three patients with liver metastasis simultaneously presented lung metastases, and two of these patients exhibited primary neoplasm of the rectum, and one of the colon. The mean time to recurrence in the liver was 25 ± 16 months. Table 4 shows the profile of patients who developed liver metastases.

Discussion

Colorectal cancer is a public health problem worldwide, because in addition of its high incidence, this disease is associated with high mortality. The prognosis is good if the disease is diagnosed at an early stage,[1,2,28] but about 25% of patients already have liver metastases at diagnosis.[24,29] The policy of prevention with screening tests for premalignant lesions and diagnosis of the disease at an early and asymptomatic stage is still deficient in our country. Thus, we are faced with large numbers of patients eligible for surgery. The use of laparoscopy in the treatment of malignant disease of the large intestine and rectum is growing throughout the world and also in our midst. Recently, large-scale randomized studies have demonstrated the non-inferiority of laparoscopic surgery over open surgery for the treatment of CRC regarding the

Table 3 – Recurrence of disease by stage.				
Recurrence	I	II	III	Total
Number[a], n (%)	3 (2)	6 (4)	10 (7)	19 (13)
Time in months[b], Mean (CI 95%)	40 (9–71)	31 (24–38)	21 (16–26)	27 (21–33)

Sample size = 146 patients; n, number of patients; %, percentage; CI 95%, confidence interval of 95%.
[a] Pearson's χ^2 test, P 0.030.
[b] Log-rank test, P 0.05.

Table 4 – Recurrence by liver metastasis.						
	Gender	Localization	Primary tumor	Stage	Disease-free time (months)	2nd place of recurrence
1	F	Rectum	T2, N0	I	12	Pulmonary
2	M	Sigmoid	T3, N0	II	24	–
3	F	Sigmoid	T3, N0	II	6	–
4	M	Sigmoid	T3, N0	II	28	–
5	F	Rectum	T3, N0	II	42	Pulmonary
6	F	Sigmoid	T3, N1	III	36	–
7	M	Sigmoid	T2, N1	III	60	Pulmonary
8	F	Ascending	T3, N1	III	24	–
9	M	Rectum	T3, N2	III	10	–
10	M	Sigmoid	T3, N1	III	11	–
11	F	Rectum	T3, N1	III	22	–

oncological results in the long run.[30] The aim of this study was to determine whether the good results of laparoscopic colorectal surgery that abound in the current international literature,[14–23] are in fact occurring in our country, that is, outside the favorable context of randomized controlled trials.

Despite the difficulty of performing a retrospective cohort due the incomplete data storage and loss to follow up of patients, 146 patients with colon and rectal adenocarcinomas in stages I–III submitted to surgical laparoscopy with curative intent and with a minimum follow-up of 2 years were enrolled in this study. Patients treated at the institution here considered are submitted to surgery through laparoscopy, almost without exception, irrespective of exhibiting physical and/or tumor characteristics favorable to the technique. Due to the high degree of surgical team expertise, conversions to laparotomy occur only rarely, although compliance with these rates extrapolates the nature of this study. Patients with tumors at all stages, except those metastatic ones, including those with locally advanced, bulky tumors, were included. Likewise, patients with transverse colon, splenic angle and rectum malignancies, which are considered technically more labor-intensive and difficult to resect laparoscopically, participated in this study, making our sample broader, compared to that of recently published clinical trials that excluded patients with tumors in these locations.[14,18,20,22,31]

In the population studied, 62% of tumors had infiltration into the intestinal wall (T3 and T4), making up a group of patients with locally advanced tumors; and almost one third of patients (28%) was in stage III. Despite the greater technical difficulty to resect rectal tumors, taking into account that the pelvic cavity is narrow and surrounded by rigid bony structures that make it difficult the laparoscopic instrumentation, 36% of our population was operated for colorectal neoplasia.

Sixty-two percent of patients were female, differing from the world literature, which points to males having a higher incidence in most populations,[1,2,4] but according to Brazilian data, that show a higher relative risk for women in our country.[1] Regarding age, the study population had a mean age of 61 years, and this age profile matches up to current data, showing that 90% of CRC patients were over 50 years old at diagnosis.[4,6]

The study was designed for a minimum follow-up of 24 months, according to data of the American Society of Clinical Oncology (ASCO) and other studies that demonstrate the occurrence of 75–80% of relapses occurring within the first two years after resection of the primary tumor.[32,33] Considering that the mean follow-up was 60 ± 27 months for this cohort, it is likely that our records have included the majority of the recurrences, making this a relevant study for the verification of long-term oncological results.

The literature points to two major criteria related to quality of tumor resection: the status of surgical margins and the quality of lymphadenectomy.[2,33]

Regarding the surgical margins we found a rate of 5.66% of circumferential margins committed, considering only cases of rectal surgery, since this commitment was observed in 3 of 53 patients operated for rectal adenocarcinoma, and in no case of colonic tumor. The first large randomized clinical trial including patients with rectal cancer was the CLASICC study, which showed positive circumferential margins in 12% for the group laparoscopically operated versus 6% for the group of open surgery.[20] Also in comparison with COLOR II study, published more recently and with short-term results of 1044 patients with rectal cancer randomized to treatment by laparoscopy or open surgery, our rate of positive margins was lower, since COLOR II found 10% of compromised circumferential margins in both groups.[34] Just as in COLOR II

study, we considered as positivity for circumferential margin commitment the presence of tumor cells in those outermost radial 2 mm of the surgical specimen. Although some authors consider the thickness of 1 mm free of neoplastic cells as sufficient, and Nagtegaal et al. concluded that the local recurrence risk of rectal neoplasms changes from 5.8% to 16% when the circumferential surgical safety margin is greater or smaller than 2 mm, respectively.[35]

The number of lymph nodes removed during resection of colorectal malignancy is used as a quality criterion of the oncological resection.[36] The AJCC considers that at least 12 lymph nodes should be in the surgical specimen for a proper oncological staging.[2] In this study, the mean number of lymph nodes resected was 24 ± 12 which, besides demonstrating the adequacy of lymphadenectomy, exceeds the mean published by several other authors like Lacy et al., Braga et al. and Liang et al., among others.[37,38]

The overall recurrence rate of the disease was 13%, with the addition of hepatic, lung, and locoregional recurrences and of peritoneal carcinomatosis. Historically, these sites are the most affected when there is tumor dissemination.[32] The data in the literature are quite variable, with rates of relapse between 9% and almost 30%, usually observed up to 5 years after resection of the primary tumor.[16–23] Among the studies with a greater number of patients are the Barcelona,[19] Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC),[21] and the Colon Cancer Laparoscopic or Open Resection (COLOR),[23] which published overall recurrence rates of 16.98%, 23.57% and 19.66%, respectively. Considering these and other large-scale trials, we found that the overall recurrence rate found in this study is lower than the mean of contemporary studies.[37,38] We believe that the favorable results obtained here may be due, at least in part, to the high technical expertise and extensive experience in laparoscopic colorectal surgery of the surgical team, considering the criteria that qualify the oncologic resections aforementioned.

Some authors such as Braga et al., Leung et al., Liang et al., and Mirza et al. found incidences of distant metastases between 14% and 20% in the long term.[37,38]

Our goal was to identify, specifically, the incidence of liver metastases, since these are mainly responsible for the mortality associated with CRC.[25] In our study, we found liver disease recurrence in 7.5% of patients operated laparoscopically. Most patients with this relapse pattern were in stage III. In a prospective non-randomized study coordinated by Felliciotti et al. which evaluated 197 patients undergoing right or left hemicolectomy for treatment of CRC, the group treated with laparoscopy had a liver recurrence rate of 8.1% from the disease, compared to 10.7% in patients operated by laparotomy with a follow-up of three years.[39] Still taking into account the incidence of liver metastases published in the Clinical Outcomes of Surgical Therapy (COST) study[14] which analyzed 872 patients operated for colorectal adenocarcinoma (except transverse colon), and that showed 5.8% of hepatic recurrence after 5 years in the group operated by laparotomy and 5.5% in patients undergoing laparoscopy, our results are thus comparable. In a recently published Australian trial involving 601 patients with colon cancer (except transverse colon), the disease recurred in 13.7% of patients operated by laparoscopy,

with 60% of these recurrences were in the liver (8.22%), and most of them occurring in the first 2 years after surgery of the primary tumor.[31]

Our analyzes included all cases of colon and rectum neoplasms, and it is worth mentioning the fact that more than a third of patients have been operated for colorectal cancer, a location not included in most randomized clinical trials published to date. In a Japanese study evaluating only rectal and rectosigmoid transition tumors, the rate of liver metastases was only 1.5% in a follow-up of 3 years. This finding probably was related to the fact that only T1 and T2 tumors were included.[40]

In contrast, Laurenti et al., in a study which included only rectal neoplasms, with most of the locally advanced type, found disease-free survival at 5 years similar to laparoscopy and laparotomy surgery groups, with distant metastasis rate of 20, 6% and 24.9%, respectively.[41] In a meta-analysis that pooled 2095 patients with rectal cancer from 12 publications, late oncological results similar between laparoscopy and open surgery groups were found.[42] COLOR II, an ongoing clinical study, randomized 1044 patients with rectal cancer for laparoscopic resection or open surgery; soon, this study will bring more definitive oncological results in the long run, with respect to the use of laparoscopy for the treatment of rectal cancer.[34]

In our study, we found a relationship between the segmental location of the primary tumor and increased chance of liver metastasis development.

The mean time to recurrence of the disease in the liver was 27 ± 11 months, and this finding is consistent with the literature, that shows the occurrence of most relapses until the first 2.5 years after treatment of the primary tumor.[32,33]

The operative mortality occurred in a woman with a stage II tumor due to pulmonary thromboembolism on the 12th day after the surgery, despite the routine administration of anticoagulants and early ambulation in the perioperative period. Thus, the study population had 1% of operative mortality, which is comparable to data from the meta-analysis involving studies of Barcelona, COST and CLASSIC, which found a mortality of 1.6% for conventional colorectal surgery and 1.4% for laparoscopic surgery.[43]

In light of current knowledge, it is observed that the extent and quality of oncologic resection – specifically the number of lymph nodes removed, colonic or rectal length resected and corresponding mesos, as well as circumferential margins – do not differ between laparoscopy and laparotomy.[17,18,20,22] Also with respect to long-term results, a current meta-analysis that compiled data from more than 4500 patients from 12 randomized clinical trials showed no difference as to overall recurrence, local or distant recurrence, overall mortality or mortality associated with cancer, and disease-free survival at 3 and 5 years between resections by laparoscopy versus open surgery.[37,38] What is still debatable are the long-term oncological results of laparoscopic resections for CRC outside the context of randomized controlled trials.[14,19,21,34]

The contribution of this study lies in having analyzed an actual sample of the population, that is, without excluding carriers of locally advanced tumors and/or tumors in more difficult locations for laparoscopic resection.

Conclusion

We conclude that, for the population of this study, the use of laparoscopy in the resection of potentially curable CRC did not alter the incidence of liver metastases in the long term, compared to publications of international randomized clinical trials. For the patients analyzed, laparoscopic resection was considered as an effective and safe method in the treatment of CRC, concerning oncological results in the long run.

Conflict of interests

The authors declare no conflict of interests.

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