Original Article

Comparison of Laparoscopy and Laparotomy in the Management of Early-stage Ovarian Cancer

Nuria Ginjaume Garcia*, Cristina Soler Moreno, Natalia Teixeira, Pia Español Lloret, Rocío Luna Guibourg, Ramon Rovira Negre

Department of Gynecologic Oncology, Hospital De La Santa Creu I De Sant Pau, Barcelona, Spain

Abstract

Objectives: The objective of this study was to assess the feasibility of minimally invasive surgery for early-stage ovarian cancer (EOC) by comparing the surgical and survival outcomes between laparoscopy and laparotomy.

Materials and Methods: This was a retrospective, single-center observational study that included all patients who underwent surgical staging for EOC by laparoscopy or laparotomy between 2010 and 2019.

Results: Forty-nine patients were included; of which 20 underwent laparoscopy, 26 laparotomy, and three conversion from laparoscopy to laparotomy. No significant differences were observed between the two groups regarding operative time, number of lymph nodes dissected, or intraoperative tumor rupture rate, while estimated blood loss and transfusion requirements were lower in the laparoscopy group. The complication rate tended to be higher in the laparotomy group. Patients in the laparoscopy group had a faster recovery, with earlier urinary catheter and abdominal drain removal, shorter hospital stay, and a trend toward earlier tolerance of oral diet and mobilization. At a mean follow-up of 45.7 months, 14 patients had disease recurrence, with no differences in the mean progression-free survival between the two groups (36 months for laparoscopy vs. 35.5 months for laparotomy, $P = 0.22$).

Conclusion: Laparoscopic surgery performed by a trained gynecological oncologist is a safe and effective surgical approach for comprehensive staging of EOC, with the additional benefits of a faster recovery compared to laparotomy.

Keywords: Comprehensive surgical staging, early-stage ovarian cancer, laparoscopy, laparotomy

Introduction

Ovarian cancer (OC) represents the fourth-most common gynecologic malignancy and is a leading cause of death due to cancer in women, as approximately 80% of patients are diagnosed at an advanced stage.[1] According to the Spanish Association of Oncology, about 3500 cases of OC/year are diagnosed in Spain.[2]

Nevertheless, the prognosis of early-stage OC (EOC), corresponding to 20% of the total diagnoses, is favorable. The 5-year survival rate ranges from 80% to 95%.[3] Consequently, focusing on early detection and management of early-stage disease is a key point for research.

Optimal surgical staging is the first step in the treatment of EOC. The purpose of surgical staging is to confirm the diagnosis, determine the extent of the disease, and remove as much disease as possible. In addition, the pathology findings determine the need for adjuvant therapy, making comprehensive surgical staging of EOC particularly important.[4,5] According to the International Federation of Gynecology and Obstetrics (FIGO), the optimal procedure includes total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies, diaphragmatic scrapings, and bilateral pelvic and para-aortic lymph node dissection.[6,7]

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Address for correspondence: Dr. Nuria Ginjaume Garcia, Santa Creu I Sant Pau Hospital, C/sant Quintí 89, Barcelona 08041, Spain.
E-mail: nuriag544@gmail.com

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The laparoscopic surgical approach performed by an experienced gynecological oncologist confers several benefits, including pain reduction, a more rapid recovery, shorter hospitalization, and decreased morbidity. However, its feasibility and safety should also be considered. Despite the cited benefits, and perhaps due to the lack of patient data, there are concerns regarding issues such as risk of tumor rupture, inadequacy of staging, tumor spillage in the abdominal cavity, and port-site metastases in the laparoscopic approach.

Many studies have attempted to demonstrate the advantages of laparoscopy over laparotomy in EOC surgery.[8-12] However, the studies have major limitations, and no high-quality evidence has been provided to date.[13]

This study was designed to assess the feasibility and survival outcomes of laparoscopic versus open surgery for EOC.

Patients and Methods

Study design and patient selection

This was a retrospective, single-center observational study including all patients who underwent primary surgical management for EOC either by laparoscopy or laparotomy at our hospital between January 2010 and November 2019. Pathological examination was performed for all tumors, and all histologic types of OC were included. EOC was defined as Stage I or II disease according to the FIGO classification after comprehensive surgical staging. Patients with borderline tumors and advanced OC (FIGO Stage III or IV) were excluded from the study. Participation did not imply any change to standard care.

Before surgery, patients were evaluated using ultrasound and tumor marker levels (Ca-125, Ca-19.9, and HE4), as well as computed tomography in most cases. Decision on surgical approach was made by a multidisciplinary committee of experts, based on patient and tumor characteristics, and patients who were selected for laparoscopic approach were always informed of the possibility of conversion to laparotomy.

Electronic clinical charts of all included patients were reviewed, and information was collected on demographic and clinical characteristics, preoperative assessment, surgery description (duration, blood loss, tumor rupture, and intraoperative complications), postoperative complications and their timing, time to tolerance of oral diet and mobilization, and length of hospital stay. Data on disease recurrence and survival were also collected.

Ethical approval

This study was approved by the Institutional Ethics Committee, and written informed consent was obtained from patients before surgery.

Surgical technique

Surgery was always performed by the same two experienced gynecologic-oncologist surgeons and their surgical team. Single-dose prophylactic antibiotics (cefazolin 2 g) were administered intravenously before surgery.

Laparoscopy

Depending on the tumor size and previous surgeries, two different techniques were used to access the abdominal cavity and create the pneumoperitoneum (Veress technique at Palmer's point or direct entry with an 11-mm trocar in the umbilicus). Once intra-abdominal pressure reached 12–15 mmHg, accessory trocars were inserted. Two 5-mm trocars were placed in both the lower and lateral abdominal quadrants, and one 5-mm trocar was placed in the infraumbilical area. Initially, the abdominal cavity, including all parietal and visceral peritoneal surfaces and organs, was carefully explored. Peritoneal washing and aspiration of liquid for cytologic examination were always performed. After initial assessment, suspicious adnexa were removed and sent for pathology. In all procedures, tumor extraction was carefully performed through the umbilical trocar, retrieving the tumor with an endobag to avoid contact with the port sites. For large tumors, puncture and aspiration of material were carried out within the bag. The integrity of the endobag was always verified.

After the diagnosis of ovarian tumor malignancy in the perioperative pathological assessment, comprehensive surgical staging was performed. This consisted of multiple peritoneal biopsies, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy up to the left renal vein, and a total infra- and supracolic omentectomy. Contralateral adnexectomy and total hysterectomy were also performed. The appendix was only resected in mucinous tumors. To perform the para-aortic lymphadenectomy and the omentectomy, an extra 10-mm suprapubic trocar was placed. All surgical specimens were extracted individually using endobags during the procedure, except the uterus and the adnexa, which were extracted through the vagina. In terms of the energy source, the laparoscopic procedures were performed with bipolar, monopolar, and advanced bipolar or ultrasonic devices, especially for lymphadenectomy.

After reinspection and washing of the abdominal cavity and checking hemostasis, the vaginal cuff was closed with simple extracorporeal knots of an absorbable suture. Trocars were also withdrawn under vision, and the fascia and skin layers of the 10 mm incisions were sutured. All surgical specimens were sent for pathological study.

Laparotomy

Laparotomy was performed through midline longitudinal incision in all cases. In accordance with our institutional

protocols, comprehensive surgical staging was performed similarly to the laparoscopic procedure. After the diagnosis of ovarian tumor malignancy, the staging consisted of peritoneal washing, peritoneal biopsy, para-aortic and bilateral pelvic lymphadenectomy, omentectomy, hysterectomy, and adnexectomy of the contralateral adnexa. The fascia was closed with 2/0 Monocryl with a small-bite technique. Finally, the wound was washed with a povidone-iodine solution, and the skin was closed with staples.

Postoperative management was similar in both groups in terms of diet resumption, pain, and complication management. Early mobilization was encouraged for all patients. After hospital discharge, patients were followed up at regular intervals, while receiving adjuvant therapies as indicated. The standard treatment was six cycles of adjuvant carboplatin-paclitaxel in both groups. Exceptionally, a minority of patients underwent three or four cycles due to treatment toxicity.

Statistical analysis

Both groups were initially compared regarding age, body mass index (BMI), presenting symptoms, abdominal examination findings, and tumor marker elevation at time of diagnosis, as well as tumor size, FIGO stage, and histological type.

The surgical outcomes comprised operative time, intraoperative blood loss and transfusion requirements, peritoneal cytology, intraoperative tumor rupture, complication rate, and number of pelvic and para-aortic lymph nodes retrieved. Postoperative outcomes included duration of hospital stay, duration of abdominal drainage, recovery indicators (time to tolerate oral diet, mobilization, urinary catheter removal, and time to start chemotherapy), postoperative complications, disease recurrence, and death.

Complications were classified as "early" when occurring within 1 month of surgery, and "late" when after 1 month; severity of complications was classified according to Clavien–Dindo score. Women were considered to have disease recurrence if they had persistent tumor marker elevation and/or new findings on imaging.

Survival outcomes were calculated with the start of follow-up taken to be the date of the final treatment of primary disease (surgery or end of adjuvant chemotherapy). For progression-free survival (PFS) assessment, patients were censored at the date of recurrence, last visit, or death. For overall survival analysis, patients were censored at the last visit or death.

Distribution of data was visually assessed for all continuous variables to determine whether it was sampled from a Gaussian distribution. For descriptive analysis, continuous variables were presented as mean (standard deviation) or median (minimum-maximum). The Student's *t*-test was performed to compare continuous normally distributed data, while the Mann–Whitney *U*-test was used for data that did not follow a normal distribution. Categorical variables were presented as percentages, and differences between groups were analyzed using two-tailed Chi-square test or Fisher's exact test when appropriate. Survival analysis was performed with Kaplan–Meier curves as well as log-rank tests. Statistical analysis was performed with SPSS version 26.0 (SPSS Inc., Chicago, IL, USA), statistical software package. Differences between groups were considered significant when $P < 0.05$.

Results

Forty-nine patients were included in this study. The most common presenting symptom was abdominal pain (34.7% of patients). Other symptoms such as pre- or postmenopausal uterine bleeding, abdominal mass or distension, constitutional symptoms, or bowel obstruction were less frequent (between 2% and 14.3%).

Laparoscopic staging surgery was performed in 20 patients and laparotomy in 26. In three patients, laparoscopy was initially performed, with conversion to laparotomy at the surgeon's discretion due to technical difficulties: in one case due to severe adhesions, and in two others because tumor size was larger than expected based on preoperative imaging. These patients were included in the laparotomy group.

The patients' characteristics are described in Table 1. No differences were observed between the two groups regarding demographic characteristics (age and BMI). Patients who underwent laparotomy were more likely to have a tumor mass on abdominal examination before surgery (83% vs. 20%, $P < 0.01$) and elevation of Ca-125 (86% vs. 40%, $P < 0.01$), while no differences were observed between the two groups regarding the tumor marker level range (In the laparoscopy group, Ca-125 ranged from 4.4 to 2602.8, 8kUI/L, while in the laparotomy group, it ranged from 11.9 to 1189.4kUI/L).

Table 1: Basal characteristics of patients included in the study, according to surgical approach

	Laparoscopy ($n=20$), n (%)	Laparotomy ($n=29$), n (%)	P
Age (years)	56.0±18.1	55.1±20.8	0.87
BMI (kg/m^2)	24.8±4.9	25.7±5.2	0.57
Abdominal examination			
Normal	16 (80)	5 (17)	<0.01
Tumor mass	4 (20)	24 (83)	
Tumor marker elevation			
Ca-125	8 (40)	25 (86)	<0.01
Ca-19.9	2 (10)	10 (34)	0.25
HE4	5 (25)	12 (41)	0.08

BMI: Body mass index

No differences were observed regarding elevation of other tumor markers.

Tumors were significantly larger in the laparotomy group (16.2 cm vs. 5.2 cm in the laparoscopic group, $P < 0.001$) [Table 2]. No significant differences were observed between the two groups regarding histologic classification, grade, positive cytology, or FIGO stage. Most were epithelial tumors, serous being the most frequent histological type (32.7%), followed by clear-cell (20.4%), endometrioid (14.3%), and mucinous (12.2%) types, although 20.3% were nonepithelial tumors (granulosa cell, yolk sac, dysgerminoma, carcinoid, and Mullerian seromucinous). The majority of cases were Grade III and FIGO Stage IA or IC; there were no patients with stage IB disease.

The main surgical outcomes of both groups are presented in Table 3. No significant differences were found between the two groups regarding operative time, number of lymph nodes dissected, or intraoperative tumor rupture rate. Patients who underwent laparoscopy had a significantly lower intraoperative blood loss (182 ml vs. 476.5 ml, $P < 0.01$) and required blood transfusion less frequently than patients who had laparotomy (0 vs. 6 patients, $P = 0.03$).

Complication rate tended to be lower among patients in the laparoscopy group. In this group, 3 (15%) patients had complications, either intra- or postoperatively (only one of them classified as Clavien–Dindo III or IV, which was a vascular lesion during surgery), compared to 10 (35%) patients in the laparotomy group (five being classified as Clavien–Dindo III or IV; two vascular lesions, one urologic lesion during surgery, one postoperative hemorrhage, and one eventration), although these differences did not reach statistical significance. There was no evidence of trocar-site metastasis in any patient.

Table 2: Comparison of pathological findings and surgical staging according to surgical approach

	Laparoscopy ($n=20$), *n* (%)	Laparotomy ($n=29$), *n* (%)	*P*
Tumor size (cm)	5.2±3.2	16.2±7.0	<0.01
Histology			
Serous	9 (45)	7 (24)	0.51
Mucinous	1 (5)	5 (17)	
Clear cell	3 (15)	7 (24)	
Endometrioid	3 (15)	4 (14)	
Others	4 (20)	6 (21)	
Grade			0.63
I	1 (6)	2 (11)	
II	2 (12)	4 (22)	
III	14 (82)	12 (67)	
Positive cytology	2 (15)	4 (22)	1.00
FIGO stage			
IA	9 (45)	12 (43)	0.48
IB	-	-	
IC	9 (45)	12 (43)	
IIA	2 (10)	1 (4)	
IIB	-	3 (11)	

FIGO: Federation of Gynecology and Obstetrics

In the laparoscopy group, a complete cytoreduction (i.e., no macroscopical residual tumor) was achieved in 90% of the patients, whereas the other 10% received an optimal cytoreduction (i.e., macroscopical residual tumor <1 cm). In comparison, in the laparotomy group, 76% of the patients received complete cytoreduction, and 24% an optimal one. There was no statistical significance between the two groups ($P = 0.21$).

Among patients who underwent laparoscopy, a nonsignificant trend toward an earlier start of oral diet and mobilization was observed.

A lower proportion of patients in the laparoscopic group had late urinary catheter removal (>24 h; 33% vs. 61%, $P = 0.04$).

Finally, patients in the laparoscopy group had a significantly shorter duration of abdominal drainage (3.4 vs. 6.1 days, $P < 0.01$) and a shorter hospital stay (4.9 vs. 8.7 days, $P < 0.01$) than patients in the laparotomy group. Despite these differences, a laparoscopic approach did not imply an earlier start on adjuvant treatment, as time to start chemotherapy was similar in both groups.

Over a mean follow-up period of 45.7 months, 14 patients had disease recurrence: four in the laparoscopy group and 10 in the laparotomy group. Six patients with recurrence presented serous tumors, two mucinous, one clear cell, two endometrioid, and three other histological types. In these patients, tumor size ranged from 1 to 32 cm and none of them had intraoperative tumor rupture. Five of these patients received chemotherapy. Pelvic-confined recurrence accounted for 42% of the recurrences. Nodal recurrence was observed in 33% of the cases; all of them affecting pelvic lymph nodes, and only half of these affecting para-aortic lymph nodes. Thirty-three percent of patients developed peritoneal carcinomatosis. None of the patients recurred with distant metastasis.

The mean PFS time was comparable in both groups (36 months for patients who underwent laparoscopy vs. 35.5 months for laparotomy). Kaplan–Meier survival analysis and log-rank testing revealed no significant differences on PFS between the two groups ($P = 0.22$) [Figure 1].

Five patients died due to OC during the follow-up period; two in the laparoscopy group and three in the laparotomy group. There were insufficient cases to analyze overall survival in this cohort.

Table 3: Comparison of perioperative surgical outcomes and recovery indicators according to surgical approach

	Laparoscopy (*n*=20), *n* (%)	Laparotomy (*n*=29), *n* (%)	*P*
Operative time (min), mean±SD	224.7±89.0	214.7±74.8	0.70
Blood loss (mL), mean±SD	182.0±120.0	476.5±391.4	<0.01
Need for blood transfusion, *n* (%)	0	6 (25)	0.03
Tumor rupture, *n* (%)	4 (20)	7 (25)	0.74
Pelvic lymph nodes removed*	11.5 (0-20)	13.5 (0-36)	0.54
Para-aortic lymph nodes removed*	7.5 (0-19)	8.5 (0-34)	0.86
Total patients with complications	3 (15)	10 (35)	0.19
Intraoperative	2 (10)	3 (11)	1.00
Early postoperative (<1 month)	1 (5)	6 (21)	0.22
Late postoperative (>1 month)	1 (5)	2 (7)	1.00
Serious postoperative (Clavien–Dindo III–IV)	1 (5)	5 (17)	0.38
Time to oral diet tolerance (h)			
<12	15 (83)	18 (64)	0.10
12–24	3 (17)	4 (14)	
>24	0	6 (22)	
Time to mobilization (h)			
<12	8 (45)	5 (19)	0.15
12–24	6 (33)	10 (37)	
>24	4 (22)	12 (44)	
Time to urinary catheter removal (h)			
<12	3 (17)	0	0.04
12–24	9 (50)	11 (39)	
>24	6 (33)	17 (61)	
Time to abdominal drain removal (days)	3.4±1.6	6.1±3.7	<0.01
Hospital stay (days)	4.9±3.2	8.7±3.5	<0.01
Time to start chemotherapy (days)	44.5±23.5	41.9±35.7	0.83

*median (min-max). SD: Standard deviation

Discussion

The use of minimally invasive surgical techniques has been increasing in the recent years in most surgical specialties, including oncology. The recent publications show the feasibility of the laparoscopic approach in the treatment of EOC.[10-12,14] Nevertheless, several concerns have been raised in the literature regarding the use of a laparoscopic approach, in particular concerning operative time, tumor rupture, accuracy of surgical staging, occurrence of port-site metastasis, disease recurrence, and survival rate.[12,14-18]

The results of this study suggest there are no significant differences in these outcomes between laparoscopic versus open approach, while laparoscopy provides the advantages of minimally invasive surgery, with a trend toward a faster recovery and lower complication rate. Moreover, there were no differences in PFS between patients having laparoscopy or laparotomy. These results are mostly in line with previous reports.[10,12,19]

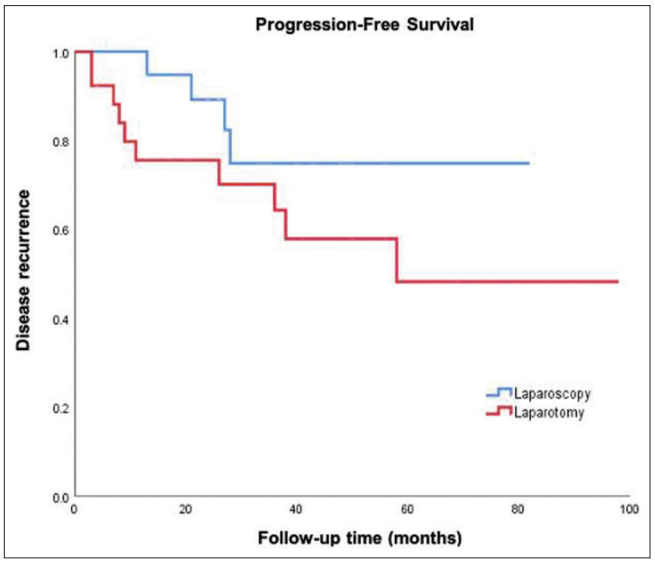

Figure 1: Kaplan–Meier analysis of PFS of patients with EOC who underwent laparoscopic or laparotomic staging surgery. Kaplan–Meier curve shows no differences between the two approaches ($P = 0.22$). PFS: Progression-free survival, EOC: Early-stage ovarian cancer

The first debated issue concerning the use of laparoscopic surgery for staging of OC is the accuracy of the technique. It has been suggested that the laparoscopic approach lacks tactile sensation and does not allow for a meticulous inspection of the abdominal cavity, particularly in certain areas such as the posterior surface of the liver and the higher part of the left diaphragm.[12] However, the optical magnification provided by laparoscopy allows for a better visualization of intra-abdominal surfaces and optimal performance in tumor resection.[20]

A surrogate for the completeness of surgical staging could be the number of lymph nodes removed in lymphadenectomy. It has been suggested that optimal lymphadenectomy may be more difficult to achieve on laparoscopy, yet all the available evidence as well as our findings show no difference in the number of pelvic and para-aortic lymph nodes retrieved.[8,9,11] In some cases, lymphadenectomy was not performed due to finding of OC in the definitive pathological result and decision of nonreintervention due to patients' age and/or comorbidities, and no evidence of pathological lymph nodes in postsurgery imaging tests.

Regarding operative time, Ghezzi *et al.* reported a significantly longer operative time with laparoscopy than

with laparotomy.[12] However, the systematic reviews by Lu *et al*. and Bogani *et al*. found no differences in operative time, consistent with the findings of the present study.[9,21] The discrepancy could be explained by an improvement in the skills required for the laparoscopic technique over the recent years.

Another of the major concerns regarding the use of laparoscopy in oncologic surgery is the possibility of intraoperative tumor rupture, as this results in upstaging and is an independent predictor of disease-free survival.[22] The role of the surgeon's experience in performing the laparoscopic technique is, therefore, of great importance. However, neither the most recent systematic review nor the results of this study found differences in the intraoperative tumor rupture rate between laparoscopic versus open approaches.[21]

The use of laparoscopy for oncologic surgery also raises concern about the possibility of port-site metastasis. Large series of patients undergoing laparoscopic surgery for malignant disease reported in the literature indicate that port-site implantation is rare, occurring in 1%–2% of cases,[11,14,23,24] and is comparable with the incidence of wound recurrence rate after laparotomy.[18] Furthermore, it occurs mostly in the setting of advanced stage disease, ascites, carcinomatosis, or primary peritoneal cancer.[17,25] In this study, there were no cases of port-site metastasis, supporting the evidence available in the literature.

Corroborating the accuracy and safety of laparoscopy for surgical staging of EOC, previous studies report no differences in overall survival or PFS rates between patients who had laparoscopy or laparotomy, although these parameters are difficult to evaluate since the follow-up time in the different studies is very heterogeneous.[19,21,26-28] The present study observed no differences in PFS between the two groups, supporting the observations reported in the literature.

The results of the present study indicate that the laparoscopic approach offers many advantages over laparotomy: less blood loss and transfusion requirements, a trend toward lower complication rate, a shorter hospital stay, and earlier removal of abdominal drains and urinary catheters. These results are in line with previous reports in the literature.[15,19,21,28-31]

Bogani *et al*. reported that time to chemotherapy was shorter in laparoscopic staging.[21] It is possible that this study did not find similar results due to the lack of an appropriate fast track for early starting of chemotherapy in our hospital since our Medical Oncology Department recommends start of chemotherapy 30–40 days after surgery. Thanks to the assessment of the results of this study our team is creating a working group with the Medical Oncology Department for improving the timing to start of chemotherapy.

The strengths of this study are the consistency and high standard of the surgical procedure, always performed by the same team of experienced gynecologic surgeons. Moreover, the exclusion of borderline tumors and fertility-sparing surgery has provided us with a highly homogeneous study population.

Nonetheless, it is important to recognize the limitations of this study. First, it is a nonrandomized retrospective analysis. Second, our sample size might be insufficient to observe significant differences between groups for some outcomes. Furthermore, the survival outcomes are limited by our follow-up period of 46 months, which may not be long enough for this purpose.

Conclusion

According to our findings, we can conclude that laparoscopic staging surgery performed by a trained gynecological oncologist is a safe and effective approach for comprehensive staging of EOC, with the additional benefits of a faster recovery and shorter hospital stay.

Nonetheless, multicenter prospective randomized trials with a longer follow-up time are necessary to confirm these results and support the wider use of laparoscopy in the management of EOC.

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Conflicts of interest

There are no conflicts of interest.

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