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Navid Mokarram Dorri, Mathilde Del, Francesco Cannone, Manon Lefebvre, Cecile Loaec, et al.. Is minimally invasive surgical approach a reasonable option in apparent early stage epithelial ovarian cancer restaging? Results from a multicentric retrospective study. EJSO - European Journal of Surgical Oncology, 2024, 50 (3), pp.107976. 10.1016/j.ejso.2024.107976 . hal-04593742

HAL Id: hal-04593742 https://amu.hal.science/hal-04593742v1

Submitted on 21 Jan 2025 $\,$

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Is minimally invasive surgical approach a reasonable option in apparent early stage epithelial ovarian cancer restaging? Results from a multicentric retrospective study

Navid Mokarram Dorri ^{a,*}, Mathilde Del^b, Francesco Cannone^c, Manon Lefebvre^d, Cecile Loaec^e, Laura Sabiani^a, Camille Jauffret^a, Guillaume Blache^a, Gilles Houvenaeghel^{a,g}, Xavier Carcopino^f, Jean-Marc Classe^e, Fabrice Narducci^d, Alejandra Martinez^b, Eric Lambaudie^{a,g}

^a Department of Surgical Oncology, Institut Paoli-Calmettes, Marseille, France

^b Department of Surgical Oncology, Institut Claudius Regaud - Institut Universitaire du Cancer de Toulouse - Oncopole, Toulouse, France

^c Department of Obstetrics and Gynecology, Azienda di Rilievo Nazionale e Alta Specializzazione (ARNAS) Garibaldi, Catania, Italy

^d Department of Surgical Oncology, Oscar Lambret Cancer Centre, Lille, Hauts-de-France, France

^e Department of Surgery, Institut de Cancerologie de l'Ouest, Boulevard Professor Monod, 44805, Saint Herblain, France

^f Department of Obstetrics and Gynaecology, Hôpital Nord, APHM, Aix-Marseille University (AMU), University Avignon, CNRS, IRD, IMBE, UMR 7263, Marseille,

France France Science (NDC) Leavier Dedit Coloration (CDCM) Air Marville University Angloit, Chiversity Avignoit, Chives and Chives a

^g Inserm, CNRS, Institut Paoli Calmettes, CRCM, Aix Marseille Univ, Marseille, France

ABSTRACT

Early stage ovarian cancer Laparoscopy Robotic surgery Minimally invasive surgery Surgical staging	<i>Introduction:</i> To perform surgical staging of early stage ovarian cancer (EOC), conventional laparoscopy (LS) and robot-assisted laparoscopy (RLS) appear to be reliable procedures compared to open surgery. But oncologicals results with long-term follow up are limited in the literature. The objective of this study is to evaluate the surgical and long-term survival for patients managed by minimally invasive surgery (MIS). <i>Materials and methods:</i> We conducted a multicentric retrospective study in 6 institutions. All patients referred for epithelial EOC (apparent stage I-IIa) managed with LS and RLS were involved. <i>Results:</i> From December 2008 to December 2017, 140 patients were included (109 in LS group and 31 in RLS group). A total of 27 (19.2 %) patients were upstaged to an advanced ovarian cancer (FIGO stage > IIA), and 73 % of patients received chemotherapy. Mean operative time was $265,8 \pm 88,4$ min and significantly longer in RLS group (LS = $254,5 \pm 86,8$; RLS = $305,6 \pm 85,5$; p = $0,008$). Rate of severe post-operative complications (grade 3) was $5,7$ %. Thirteen conversion to laparotomy occurred, including one per-operative hemorrhaege. After a mean follow-up of $60,7$ months, $29 (20.7 \%)$ patients recurred, with a time to recurrence was >24 months in $51,7$ % of cases. Overall survival (OS) was 88.6 % and disease-free survival (DFS) was 79.3 %. Oncologic outcomes were similar between LS and RLS group (OS: p = $0,504$ and DFS: p = $0,213$). <i>Conclusion:</i> Surgical staging of EOC by LS or RLS approach has long-term equivalent surgical and oncological approach. These results seem to be equivalent to open surgery according to literature review.

1. Introduction

In 2020, ovarian cancer is still a fatal disease responsible for more than 200 000 death worldwide; it is the thirteenth cause of cancer death, regardless of age or gender. The overall survival rate is around 43 % five years after the diagnosis [1]. High-grade serous carcinoma is the most common type accounting for approximately 75 % of epithelial ovarian

cancers, they are biologically aggressive tumors from their outset with a propensity for metastasis [2]. Early stage ovarian cancer (EOC) is defined by FIGO international classification as a tumor limited to the ovaries which corresponds to stage I. It represents only 13,5 % of cases. The 5-years survival rate of FIGO stage I is over 83 % whereas it's over 65.5 % in stage II [3,4]. Circumstances of diagnosis are generally fortuitously after a systematic sonographic exam or after the

anatomopathological analysis of an adnexectomy for apparent benign cyst. The number of asymptomatic ovarian masses has increased with the use of prenatal sonography, 5 % of tumors that complicate pregnancies are malignant [5].

If an early stage ovarian cancer is confirmed, it is recommended to perform a surgical restaging including colpo-hysterectomy, bilateral adnexectomy, total omentectomy, lymphadectomy from the pelvis and para-aortic regions, cytologic washings and peritoneal biopsies performed by xypho-pubian laparotomy [6]. Surgery, in stage I like in advanced stages, has to be complete. Indeed, it will directly have an impact on the administration of adjuvant treatments as well as the risk of recurrence. In the literature, from 7,3 %–13 % of presumed early stage cancer are upstaged to FIGO IIIA1 stage by lymph node dissections [7–9].

As an alternative to open surgery, the interest of conventional laparoscopy (LS) has been published in respect to oncological outcomes. Minimally invasive surgery (MIS) offers obvious advantages compared to laparotomy: smaller incisions, reduced blood loss/tranfusion, less post-operative infections, reduction of pain, better intraoperative visualization of the anatomical structures, shorter hospitalization stay or time to recovery and faster access to chemotherapy. These benefits are also demonstrated during robot-assisted laparoscopy (RALS) procedure that provides additionally high-resolution of three dimensional view, higher accuracy of robotic arms and an apparent favourable learning curve [10-14]. Feasibility and safety of such intervention were already reported in several retrospective cohorts; complications rate, disease-free survival and overall survival were comparable when MIS were performed [15-29]. Nonetheless, most of these data concern small sized monocentric cohort with a short follow-up and heterogeneous population. Lee et al. [22] suggest a remarkable long-term prognosis during a follow-up period of 31,5 months thanks to an overall survival of 95 % in this indication.

The main objective of our study is to confirm upstaging rate after MIS restaging, in an homogenous retrospective cohort of patients managed by LS or RALS, for an apparent early stage epithelial ovarian cancer. Secondary objectives include surgicals characteristics and oncologicals outcomes.

2. Materials and methods

This study is a multicentric retrospective study of apparent EOC cancer treated by MIS (LS and RLS) from december 2008 to december 2017 in 4 Comprehensive cancer centers (Paoli-Calmettes Institute, IUCT Oncopole, Oscar-Lambert center, ICO institute) and 2 university hospital (APHM, Garibaldi Nesima Hospital of Catania (Italy)).

Inclusions criteria concerned patients with Stage I-IIA EOC diagnosed after initial adnexectomy for suspected cysts on sonography or pelvic MRI. They were secondly scheduled for comprehensive surgical restaging.

Exclusions criteria were, non-epithelial ovarian cancer, borderline tumors and patients with suspicious peritoneal localization on body CT scan before restaging.

Investigationnal Review Board of each center approved the study design (ref: COPS-IPC 2020-054). Detailed oral information were delivered about the surgical procedure to each patient; they signed a consent for the use of personal data for medical research.

2.1. Surgical procedure

All patients included had undergone prior oophorectomy for a suspected ovarian mass (no suspected adenopathy or carcinosis). This initial surgery was performed by laparoscopy or laparotomy depending on the size of the tumour. The operative report of patients referred from another centre was always available. In our study, the apparent FIGO stage corresponds to the definitive histological report and the operative findings. For surgical restaging, the choice of the laparoscopic approach (LS or RALS) was done according to surgeon's experience and preference. Comprehensive surgical staging included total hysterectomy, adnexectomy, pelvic and aortic lymphadenectomy, infracolic omentectomy, appendectomy, peritoneal biopsies and cytology. Fertility-sparing surgery was discussed for women younger than 40 years-old and nulligest patients with low grade EOC. Concerning peri operative care, enhanced recovery after surgery protocols were systematically associated [30].

2.2. Post-operative follow-up

Adjuvant treatment was decided in a systematic post-operative multidisciplinary tumor board. Chemotherapy regimen was chosen in accordance to age, grade and definitive FIGO stage.

Post-operative consultation occurred one month after surgery then follow up was organized every three or six months, in relation with adjuvant treatment.

2.3. Data collection and statistical analyses

We collected demographic data (age, BMI, smoking status), tumoral characteristics (histological type, grade and apparent FIGO stage). Perioperative data included operative time, hospital stay, complication rate according to clavien-dindo classification, lymph node count and FIGO stage.

Upstaging rate is defined in two ways. Firstly, by the ratio of postoperative FIGO stages to apparent FIGO stages, all cases combined. Secondly, we distinguish upstaging rate to an advanced ovarian cancer (> FIGO IIA).

Overall survival was calculated from the date of the MIS until the death for any cause or the last medical visit. Disease-free survival was calculated from the date of the MIS until recurrence or the last medical visit. Statistical analyses were performed by using the SPSS (SPSS Inc., Chicago, IL, USA) statistical software package for windows. Categorical variables were compared between LS and RLS group by using the 2-tailed chi-square and in case of small sized sample we used Fisher test. Continuous variables were compared by using the Student t-test. Survival analyses were conducted by using the Kaplan-Meier method, and surviving patients were censored at the date of last follow-up. A p-value of <0.05 was considered statistically significant.

3. Results

One hundred and fourty patients underwent MIS for presumed FIGO stage I-II EOC, 109 were performed by LS and 31 by RALS. Patients and tumors characteristics are summarized in Table 1. The mean age was $53,4\pm12,7$ years and the mean body mass index was $24,5\pm5,5$ kg/m2. No difference was observed concerning ASA score. The leading histologic group was high-grade serous type (n = 60). The pre operative FIGO stage was IA for 96 of the patients (68,6%). Only 5 patientes with FIGO Stage II were included. There was no significative differences concerning age, BMI, smoking status, histotype or CA 125 level.

Peri-operative data are described in Table 2. Mean operative time was $265,8 \pm 88,4$ min and significantly longer in RLS group (LS = $254,5 \pm 86,8$; RLS = $305,6 \pm 85,5$; p = 0,008). Only one per operative haemorrhage (blood loss >500 ml) has been reported justifying conversion to open surgery. Thirteen laparoconversion (9,3 %) were necessary. Difficulty of exposure was mainly in cause, seven of them had obesity (BMI >30 kg/m2).

Monitoring in intensive care unit after surgery concerned ten patients. The rate of grade 1/2 complications was 22,1 % including fever (LS: 5,5 %; RLS: 6,4 %; p = 0,84) and lymphocele (LS: 8,3 %; RLS: 16,2 %; p = 0,19) without difference between MIS approaches. Grade 3 complications were observed in 8 patients with two cases of hemoperitoneum and 4 wound dehiscence, that justified re-intervention, without difference between LS and RLS. Mean hospital stay was $4 \pm 2,6$ days

Table 1

Patients and tumors' characteristics.

Characteristic	All patients (n = 140)	LS (n = 109)	RLS (n = 31)	р	
Age (years; mean \pm SD)	$\textbf{53,4} \pm \textbf{12,7}$	$\begin{array}{c} 53,5 \pm \\ 12,6 \end{array}$	$\begin{array}{c} 53,1 \\ 13,4 \end{array}$	0,88	
BMI ((kg/m2; mean \pm SD)	$\textbf{24,5} \pm \textbf{5,5}$	24,3 ± 4,8	25,1 ± 7,3	0,56	
Smoke	25 (17,9 %)	20 (18,3 %)	5 (16,1 %)	0,77	
ASA Score $= 1$	69 (49,3,%)	56 (51,4 %)	13 (41,9 %)		
ASA Score $= 2$	66 (47,1 %)	48 (44 %)	18 (58,1 %)		
ASA Score = 3	5 (3,6 %)	5 (4,6 %)	-	0,28	
Ca-125 > 35 U/mL	79 (56,4 %)	57 (52,3 %)	22 (70,9 %)	0,06	
Histological type					
LG Serous	11 (7,8 %)	9 (8,3 %)	2 (6,4 %)		
HG Serous	60 (42,9 %)	48 (44,1	12 (38,7		
		%)	%)		
Endometrioid	28 (20 %)	20 (18,3 %)	8 (22,6 %)		
Clear cells	15 (10,7 %)	11 (10,1 %)	4 (9,7 %)		
Mucinous	19 (13,6 %)	16 (14,7 %)	3 (9,7 %)		
Mixed	7 (5 %)	5 (4,6 %)	2 (3,2 %)	0,88	
Apparent FIGO					
IA	96 (68,6 %)	75 (68,8 %)	21 (67,7 %)		
IB	19 (13,6 %)	14 (12,9 %)	5 (16,1 %)		
IC	20 (14,3 %)	18 (16,5 %)	2 (6,5 %)		
IIA	5 (3,6 %)	2 (1,8 %)	3 (9,7 %)	0,20	

Data are expressed as mean \pm standard deviation, or as n (%). LS laparoscopy, RLS Robotic-Assisted laparoscopy.

without difference between the 2 approaches.

Concerning restaging results: median lymph node count was 5 by pelvic side and 12 for aortic area, without any significative difference between LS and RALS (Table 3). There was no significative difference in final FIGO stage and positive peritoneal cytology between LS and RLS. Fourty-five patients were upstaged (Table 4). Amongst these patients, 27 (19,2 %) were upstaged to an advanced ovarian cancer (FIGO stage \geq IIB). In LS group, 37 (33,9 %) patients were upstaged, 8 (25,8 %) patients were upstaged in RLS group (p = 0,51) when all situations are considered.

Ten patients underwent fertility sparing surgery, eight were in LS group (7,3 %) and two in RLS group (6,5 %) (Table 5). Ninety two patients (73,7 %) were referred to adjuvant chemotherapy. In RLS group, the rate was significantly higher (RLS: 24 = 77,4 % vs LS: 68 = 63,4 %, p = 0,04). The mean time of Return To Intended Oncological Treatment (RIOT) of the entire cohorte was $38,2 \pm 15,3$ days without significative difference (p = 0,24) between LS group ($37,1 \pm 16,3$ days) and RLS group ($41,6 \pm 11,2$ days). The mean follow-up period was $60,7 \pm 28,5$ months, it was longer in LS group ($63,2 \pm 28,6$ months vs $52,1 \pm 26,9$ months) but without significative difference with RLS group (p = 0,052). We observed 29 recurrences (20,7 %), the median onset was $25,9 \pm 21$ months.

In 51,7 % of cases, time to recurrence was more than 24 months (Table 6). There was no difference between both groups according to the period when occurred the recurrence (p = 0,62). The Figo stage at diagnosis was similar between both group (0,94). The recurrence

Table 2

Intraoperative and post-operative data.

	All patients (n = 140)	LS (n = 109)	RLS (n = 31)	р
Operating time (min; mean \pm SD)	$\textbf{265,8} \pm \textbf{88,4}$	$\begin{array}{c}\textbf{254,5} \pm \\ \textbf{86,8} \end{array}$	305,6 ± 85,5	0,008
Intensive care unit admission, n (%)	10 (7,1 %)	8 (7,3 %)	2 (6,4 %)	0,86
Intraoperative complications				
Hemorraghe, n (%)	1 (0,7 %)	1 (0,9 %)	_	
Conversion to laparotomy, n (%)	13 (9,3 %)	11 (10,1 %)	2 (6,4 %)	0,59
Post-op. Complications gr 1 et 2 ^a , n (%)	31 (22,1 %)	22 (20,2 %)	9 (29,0 %)	0,73
Fever	8 (5,7 %)	6 (5,5 %)	2 (6,4 %)	0,84
Lymphocele	14 (10 %)	9 (8,3 %)	5 (16,2 %)	0,19
Post-op. Complications gr 3 ^a , n (%)	8 (5.7 %)	7 (8,3 %)	1 (3,2 %)	0,68
Hemoperitoneum	2 (1,4 %)	2 (1,8 %)	_	
Wound dehiscence	4 (2,9 %)	3 (2,7 %)	1 (3,2 %)	0,88
Urinary tract infection	2 (1.4 %)	2 (1.8 %)	-	
Hospital stay, days, median \pm SD	$4\pm2\text{,}6$	4 ± 2,7	$4\pm1{,}7$	0,06

Data are expressed as mean \pm standard deviation, or as n (%). LS laparoscopy, RLS Robotic-Assisted Laparoscopy.

^a according to Clavien-Dindo Classification.

Table 5	
Definitive	pathology.

Table 2

Characteristic	All patients (n = 140)	LS (n = 109)	RLS (n = 31)	р
Left pelvic nodes, median (range)	5 (3–18)	5 (3–18)	5 (3–15)	0,21
Right pelvic lymph nodes, median (range)	5 (2–21)	5 (2–21)	5 (2–12)	0,54
Para-aortic lymph nodes, median (range)	12 (3–38)	12 (4–38)	9 (3–21)	0,61
Final FIGO stage				
IA	65 (46,3 %)	51 (46,8 %)	14 (45,2 %)	
IB	16 (11,4 %)	11 (10,1 %)	5 (16,1 %)	
IC	25 (17,9 %)	20 (18,3 %)	5 (16,1 %)	
IIA	7 (5 %)	4 (3,6 %)	3 (9,7 %)	
IIB	2(1,4 %)	2 (1,8 %)	-	
IIIA	5 (3,6 %)	4 (3,7 %)	1 (3,2 %)	
IIIB	8 (5,7 %)	8 (11,1 %)	-	
IIIC	12 (8,6 %)	9 (5,6 %)	3 (9,7 %)	0,60
Positive Cytology	18 (12,9 %)	14 (12,8 %)	4 (12,9 %)	0,99

Data are expressed as mean \pm standard deviation, or as n (%). LS laparoscopy, RLS Robotic-Assisted Laparoscopy.

concerned upstaged EOC as often as advanced stage at diagnosis; 13 reccurences (44,8 %) concerned patient with FIGO stage at diagnosis \geq IIA. The serous and clear cell histotype were dominant (75,9 %). Sites of relapse mostly took the form of peritoneal carcinosis (75,9 %), they were equally distributed between both groups (p = 0,88).

Overall survival (OS) was 79,3 % and disease-free survival (DFS) of 88,6 %. In LS group, OS was 89 % with a DFS of 78.9 %, in RLS group OS was 80.6 % with DFS of 87,1 %. Survival analyses in Figs. 1 and 2 do not

Table 4

Pre-operative and post-operative concordance table.

Filial FIGO									
Apparent FIGO	IA	Ib	Ic	IIa	IIb	IIIa	IIIb	IIIc	upstage
IA = 96	65 (67,7 %)	4	9	4		3	6	5	31
IB = 19		12 (63,2 %)	1		1	1	1	3	7
IC = 20			15 (75 %)				1	4	5
IIA = 5				3 (60 %)	1	1			2
Total	65	16	25	7	2	5	8	12	45 (32,3 %)
Upstage	≤ IIA = 18 (12,9	9 %)			> IIA =	= 27 (19,2 %)			

Apparent FIGO stage = Pre-operative FIGO stage, Final FIGO stage = Post-operative FIGO stage.

Table 5

Treatment method and survival outcomes.

	All patients (n = 140)	LS (n = 109)	RLS (n = 31)	р
Surgical procedure				
Comprehensive staging	130 (92,9 %)	101	29 (93,5	
surgery		(92,7 %)	%)	
Fertility sparing surgery	10 (7,1 %)	8 (7,3 %)	2 (6,5 %)	0,86
Treatment				
Surgery only	48 (34,3 %)	41 (37,6	5 (22,6	
		%)	%)	
Surgery + adjuvant	92 (73,7 %)	68 (62,4	24 (77,4	0,04
chemotherapy		%)	%)	
Upstage	45 (32.1 %)	37 (33.9	9 (25.8	0.51
- <u>r</u> - 0		%)	%)	- , -
RIOT (days; mean \pm SD)	$\textbf{38,2} \pm \textbf{15,3}$	37,1 \pm	41,6 ±	0,24
		16,3	11,2	
Follow-up period (month;	$60{,}7\pm28{,}5$	63,2 \pm	52,1 \pm	0,052
mean \pm SD)		28,6	26,9	
Recurrence	29 (20,7 %)	21 (19,2	8 (25,8	0,45
		%)	%)	
Time to recurrence (month;	$\textbf{25,9} \pm \textbf{21}$	28,9 \pm	17,8 \pm	0,11
mean \pm SD)		22,9	12,7	
Current status				
No evidence of diseade	111 (79,3 %)	86 (78,9	25 (80,6	
		%)	%)	
Alive with disease	13 (9,3 %)	11 (10,1	2 (6,5)	
		%)		
Dead of disease	16 (11,4 %)	12 (11,0	4 (12,9	0,81
		%)	%)	

Data are expressed as mean \pm standard deviation, or as n (%). LS laparoscopy, RLS Robotic-Assisted Laparoscopy.

show significative difference between LS and RLS groups, for OS (p = 0,504) and DFS (p = 0,213).

4. Discussion

Our study is one of the largest of the literature, including restaged EOC. Surgical restaging of apparent EOC cancer is a key component of curative management to define the most adapted treatment limiting downstaging's risk.

4.1. MIS approach and comparison with open surgery

Table 7 includes main cohorts of surgical staging by LS or RALS since 2004. We notice that RLS is negligible compared with LS, there were only three comparative studies [12,26,27] and a fourth one that sets them apart [29]. Intra operative complications rate and operating time were often similar. RLS was gradually introduced in the various centers participating to our study during the 2010s. Consequently, there was a

	All patients	LS	RLS	р
Recurrence	29 (20,7 %)	21 (19,2 %)	8 (25,8 %)	0,45
Time to recurrence (months; mean \pm SD)	25,9 ± 21	28,9 ± 22,9	17,8 ± 12,7	0,11
<12 months	9 (31,1 %)	6 (28,6 %)	3 (37,5 %)	
12-24 months	5 (17,2 %)	3 (14,3 %)	2 (25 %)	
>24 months	15 (51,7 %)	12 (57,1 %)	3 (37,5 %)	0,62
FIGO stage at diagnosis				
IA/IB	12 (41,4 %)	9 (42,9 %)	3 (37,5 %)	
IC	4 (13,8 %)	3 (14,2 %)	1 (12,5 %)	
\geq IIA	13 (44,8 %)	9 (42,9 %)	4 (50 %)	0,94
Histological type				
Serous/Clear cell	22 (75,9 %)	18 (85,7 %)	4 (50 %)	
Others	7 (24,1 %)	3 (14,3 %)	4 (50 %)	0,06
Site of relapse				
Pelvic	2 (6,9 %)	2 (9,5 %)	-	
Peritoneal carcinosis	22 (75,9 %)	16 (76,2 %)	6 (75 %)	
Lymphadenopathy	3 (10,3 %)	2 (9,5 %)	1 (12,5 %)	
Metastatic	2 (6,9 %)	1 (4,8 %)	1 (12,5	0,88

Data are expressed as mean \pm standard deviation, or as n (%). LS laparoscopy, RLS Robotic-assisted Laparoscopy.

significant difference in experience between surgeons, which led to significantly longer operating times in RLS group (305,6 \pm 85,5 min vs 254,5 \pm 86,8 min, p = 0,008) compared to LS group. Only Facer et al. [27] described a higher rate of conversion to laparotomy in RLS (7.2 % vs 17.9 %, P < 0.001). This can potentially be explained by the absence of BMI-adjusted statistical analyses.

We observe divergence between the authors about post-operative complication rates, notably Koo et al. [18], because of systematic identification of retroperitoneal lymphocele. These variable rates are correlated with lymph node counts and follow-up duration.

Comparative studies with laparotomy are summed up in Table 8. They showed a constant decrease of hospital stay. These findings match with ours; all the cohorts of patients treated by laparotomy were discharged, on average, beyond 4 days.

Analysis of operating time is conflicting between the authors. Mini

Table 6Recurrences characteristics.



Fig. 1. Overall survival of laparoscopy (LS) vs robot-assisted laparoscopy (RLS).



Fig. 2. Disease-Free survival of laparoscopy (LS) vs robot-assisted laparoscopy (RLS).

Table 7

Clinical data in mini-invasive management of early ovarian cancer.

invasive procedure was frequently considered at least faster than open surgery [12,16,18,23] whereas Ditto et al. [20] study shows a significant increase of operating time (207.2 (71.6) minutes vs. 180.7 (47.0) minutes; p = 0.04). Several factors led to these discordant results. The first and most obvious is heterogeneity of experience and skills of practitioner from each surgical teams. Secondly, recent innovations and improvements of surgical devices of LS and RLS simplify surgical interventions.

Lymph nodes count also varies between studies but remains roughly equivalent for each method. As a result, we deduce each author could proceed lymph node dissection with same efficiency by open or MIS. As mentioned previously, complications were not defined samely in the respective protocols. Nevertheless, the minimally invasive approach produced results that were at least equivalent, if not beneficial. Furthermore, the major intraoperative incidents leading to laparoconversion are sporadic.

4.2. Upstaging

Upstaging rate reflects the performance of the procedure. Its knowledge is crucial taking into account the possibility to add to conventional chemotherapy, bevacizumab and parp inhibitor in FIGO stage III. It is the reason why we distinguished upstaging up to FIGO IIA (12.9%) and above (19,2%). Regardless of the surgical approach used (LS or RLS), results are broadly equivalent in the literature, with a reported rate of upstaging scaled between 10,8 and 25.6% (Table 9). The main criticism of the mini-invasive approach is the supposed lack of exhaustiveness of abdominal cavity exploration; various anatomicals areas, such as Morrison's space, the posterior part of the diaphragmatic dome, the root of the mesentery or the entire small bowel, cannot always be explored. Nonetheless, comparative studies (Table 8) with laparotomy also show no difference in performance.

4.3. Survival data

While the results of our retrospective study seem to confirm the data of the literature concerning the feasibility, safety of LS or RLS, and upstaging rate in the management of EOC, it is important to assess the oncological outcomes of these patients managed with a MIS approach compared to open surgery.

The present study suggests less favourable long-term outcomes (Table 9) than a previous one [26] published in our centre. It was a

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Author, year	n	Epithelial	Operating time,	Hospital stay,	Group P N		PN AON		complications (%)	
		Tumor	min	days	LS	RLS			Intraop.	Post-op.
Leblanc, 2004	42	34 (80,9 %)	238	3,1	100 %	-	14 (4–27)	20 (7–40)	7,5	NR
Nezhat, 2008	36	20 (55,5 %)	195	2,4	100 %	-	14,8 (0-45)	12.2(0-53)	0	11,1
Ghezzi, 2012	82	73 (89 %)	263	4	100 %	-	23 (3–39)	13 (3–34)	1,2	15,8
Brockbank, 2013	35	33 (94,2 %)	210	2	100 %	-	6 (1–32)	5,6 (1–19)	11,4	2,8
Bogani, 2014	35	31 (88,6 %)	335	4	100 %	-	22 ± 5.9	10 ± 7	0	2,8
Koo, 2014	24	20 (83,3 %)	192	13	100 %	-	$\textbf{26.8} \pm \textbf{8.5}$	17.7 \pm	0	54,1
								10.1		
Chen, 2015	65	51 (78,4 %)	LS 232 RLS 176	LS 5,5 RLS 3,5	67 %	33 %	NR	NR	LS 4,8 RLS 2,3	0
Melamed 2016	1096	1096 (100 %)	NR	3	100 %	-	NR	NR	NR	NR
Minig, 2016	50	50 (100 %)	225	2	100 %	-	15 (10–21)	10 (4–15)	6	28
Lu, 2016	42	42 (100 %)	200	3	100 %	-	20 (10-35)	8 (4–17)	0	7,1
Ditto, 2017	50	50 (100 %)	207	4	100 %	-	16.6 ± 7.9	16.7 ± 6.6	0	2
Ye, 2017	19	NR	LS 233 RLS 251	LS 11 RLS 15	53 %	47 %	NR	NR	LS 0 RLS 0	LS 10 RLS 0
Lee, 2018	24	24 (100 %)	306	8	100 %	-	20 (5-42)	4 (3–8)	4,1	4,1
Facer, 2019	1901	1901 (100 %)	NR	LS 3						
RLS 1	66 %	44 %	NR	NR	NR	NR				
Gallotta, 2021	254	254 (100 %)	NR	NR	74 %	26 %	NR	NR	NR	NR
Present study	140	100 %	LS 254,5 RLS 305,6	$4\pm2,\!6$	77,9 %	22,1 %	$10\pm3{,}1$	$12\pm \textbf{7,7}$	10	29,3

Op. = Operative PN= Pelvic Nodes, AoN = Para-Aortic Nodes, LS = Laparoscpy, RLS = Robotic-Assisted Laparoscopy, NR = Not Rapported.

Table 8

Comparative data with laparotomy in early ovarian cancer management.

Author, year n		Operating time,	Hostpital stay,	P N	Ao N	Complica	Complications (%)		Recurrence rate	Overall Survival
		min	days	Intra		Intraop.	Post op.	(%)	(%)	(%)
Bogani, 2014	32	230	6	15	6	0	28	46,8	28,1	NR
Koo, 2014	53	224.1	13.1	$\begin{array}{c} \textbf{27.8} \pm \\ \textbf{13.2} \end{array}$	$\begin{array}{c} 21.2 \pm \\ 11.2 \end{array}$	5	56,6	NR	3,8	94,7 (3 years)
Chen, 2015	73	232.3	9,7	NR	NR	4,8	0	NR	NR	95,8
Melamed 2016	1030	NR	4	NR	NR	NR	NR	19,2	NR	88,5 (4 years)
Minig, 2016	58	220	5	13,5	10	34,4	38	14	12	95
Lu, 2016	50	240	7	22	7	2	6	20	13	90
Ditto, 2017	50	180,7	6,1	19.5 ± 9.3	$\textbf{18.4} \pm \textbf{9.2}$	2	4	26		NR
Present Study	38	265,8	4 ± 2,6	$10 \pm 3{,}1$	$12 \pm \textbf{7,7}$	10	29,3	19,2	20,7	88,6

Op. = . Operative, PN= Pelvic Nodes, AoN = Para-Aortic Nodes, LS = Laparoscpy, RLS = Robotic-Assisted Laparoscopy, NR = Not Rapported.

Table 9

Survival outcome in mini-invasive management of early ovarian cancer.

Author, year	n	Upstage (%)	Follow-up, months	Recurrence (%)	Disease-Free Survival (%)	Overall Survival (%)
Leblanc, 2004	42	19	54	7,1	90,5	97,6
Nezhat, 2008	36	19,4	55,9	8,3	83,3	100
Ghezzi, 2012	82	25,6	28,5	7,3	95,1	98,8
Brockbank, 2013	35	23	18	5,7	94	100
Bogani, 2014	35	43	64	11,4	89	NR
Koo, 2014	24	NR	31	8,3	96,2	86,1 (3 years)
Chen, 2015	65	NR	LS 29,6 RLS 13,1	NR	LS 95,2	LS 100
					RLS 97,2	RLS 100
Melamed 2016	1096	12,2	28,7	NR	NR	91,5 (4 years)
Minig, 2016	50	24	26	12	98	98
Lu, 2016	42	21,4	82	11,9	NR	92,9
Ditto, 2017	50	20	49,5	14	NR	NR
Ye, 2017	19	NR	24	0	NR	NR
Lee, 2018	24	17,9	31.5	8,3	83	95
Facer, 2019	1901	11,5 LS	LS 37,5	NR	NR	NR
		10,8 RLS	RLS 37,8			
Gallotta, 2021	254	18,1	61	15,3	84 (5 years)	92,5 (5 years)
Present study	140	19,2	60,7	20,7	79,3	88,6

LS = Laparoscopy, RLS Robotic-Assisted Laparoscopy, NR = Not Rapported.

retrospective cohort of 39 cases of EOC managed by MIS between 2006 and 2014. It reported overall survival of 97,4 % after approximately two years. Three historical cohorts [15–17] similarly-sized followed patients more than fifty months, overall survival was 97,6 % in Leblanc et al. [16] and 100 % according to Nezhat et al. [15]. This difference maybe in relation with inclusions criteria of non-epithelial ovarian mass well-known as good prognosis tumors. However, Lu et al. [17] and Gallota et al. [29] led the two longest follow-up of exclusive epithelial EOC; they obtained respectively 92.9 % and 92,5 % of 5-years OS which are closer to our results but still more favourable.

Such a selection bias also affect the recurrence rates. It was indeed higher than 10 % in long-term follow up of cohorts with small proportion of non-epithelial tumors. In our study, one third of recurrences occurred before 12 months and mostly developed in the form of peritoneal carcinomatosis. Peritoneal involvement must have been underestimated when early relapse were experienced, especially in one case reported after only 4 months. Minig et al. [23] indicated reccurrence rate of 12 % in LS, the first one was a lymph node recurrence which occurred after 13 months. Gallota et al. [29] identified 45 % of relapses between 1 and 2 years; in multivariate analysis, grade 3 was the only independent factor which influenced negatively DFS.

In our literature review (Table 9), recurrence rate increases with duration of follow-up until reaching 28,1 % for open surgery vs 11,4 % for LS according Bogani et al. [24]. The largest comparative cohort study published by Melamed et al. [25] didn't find differences on 4 years survival analyses: 91.5 % for LS vs 86.3 % for laparotomy. A recent meta-analysis [31] also concludes there were no significant difference in

terms of risk of reccurence (HR = 0.93, 95 % [CI], 0,80 to 1,09) and mortality (HR = 0,85, 95 % [CI], 0,63 à 1,14). However, they demonstrate that upstaging rate \geq FIGO stage II was significatively higher in the open surgery group (RR = 0.70, 95 % [CI] 0.57–0.87; p = 0.009).

4.4. General considerations and prospects

Laparoscopy have lately been a controversial issue in oncologic surgery. Since the publication of the randomized prospective trial entitled LACC [32] which reports a decrease of disease-free survival at 4,5 years (86 % vs vs 96,5 %; -10,6, 95 % [CI] -16.4 to -4.7) and a lower rate of overall survival (3 years, 93.8 % vs. 99.0 %; HR = 6,00, 95 % [CI], 1.77 to 20.30) of early cervical cancer managed by LS or RALS, the place of LS or RLS is debated. These findings were tempered by other studies that underlined the role of unprotected tumor manipulation issue [33]. If we focus on patients with uterus-confined endometrial cancer (FIGO I-II), we notice that survival analyses are equivalent; that's why mini-invasive surgery is nowadays first-choice procedure [34]. In EOC, 2 risks are associated with an apparent benign ovarian cyst manipulation: cyst rupture with peritoneal tumor spillage and a limited exploration of peritoneal cavity. The Lochness study [35] has demonstrated that a tumor size >30 mm and adherence in ovarian fossa were associated with a higher risk of tumor spillage and decreased DFS.

Main limitation of our study is its retrospective and observational design. No prospective trial was conducted so far according to the literature. A systematic Cochrane review has not found good-quality evidence to help quantify the risks and benefits of laparoscopy for the management of EOC as routine clinical practice [36]. Secondly, there is a lack of data about a supposed intra-peritonal tumoral rupture that could have happened during the first surgery. We presume that unprotected extraction of ovarian mass have a negative impact on survival outcomes. In an observational study of 7884 cases of early ovarian cancer with intra-operative capsule rupture [37], the clear cells type was associated with a higher rate of 5-years mortality (HR = 1.99, 95 % [IC], 1.45 à 2.75). In another cohort of more than 8000 patients, we observed higher death rate when capsule rupture occurred in mini-invasive surgery group compared with open surgery [38]. It is therefore highly recommended to practice systematic protected extraction of all suspected ovarian mass.

The other challenge involved in introducing these approaches was to reduce the time interval between surgery and adjuvant therapy. Two of the comparative studies [23,24] failed to show any benefit for the MIS, despite respectively good performance (LS: 31 days vs. Laparotomy: 38 days and LS: 22 days vs. Laparotomy: 30 days). In our study, patients received their first course of chemotherapy after an average of 38,2 \pm 15,3days, despite a relatively low complication rate. In a recent published study by our team concerning ERAS programs for patients undergoing laparotomy for advanced ovarian cancer, the RIOT was also 44.2 \pm 18.7 days [39]. The minimally invasive approach alone seems not to reduce RIOT in our experience; it is coordination with medical oncology teams and the scheduling of care that must be improved as a matter of priority.

5. Conclusion

Our study confirms the place of MIS in the initial management of EOC as an option for surgical restaging. Overall survival and long-term recurrence risk are similar to open surgery according to our literature review. LS and RLS offer both similar performances. Thus, patient management remains oncologically optimal as long as quality surgical criteria are followed, while offering the advantages of minimally invasive surgery (reduced hospitalization time and lower complication rates). Despite these encouraging results, our data are not analyzed prospectively in comparison with a control group of patients (laparotomy), which must constitute the next step of our task.

Authors contribution

Navid Mokarram Dorri: Conceptualization, Investigation, Formal analysis, Writing - Original Draft. Mathilde Del: Investigation. Francesco Cannone: Investigation. Manon Lefebvre: Investigation. Cecile Loaec: Investigation. Laura Sabiani: Visualization. Camille Jauffret: Data curation, Validation. Guillaume Blache: Validation. Gilles Houvenaeghel: Validation. Xavier Carcopino: Project administration. Jean Marc Classe: Project administration. Fabrice Narducci: Project administration. Alejandra Martinez: Project administration. Eric Lambaudie: Conceptualization, Supervision, Writing - Review & Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Navid Mokarram Dorri reports administrative support was provided by Paoli-Calmettes Institute.

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