ANTICANCER RESEARCH *41*: 955-965 (2021)
doi:10.21873/anticanres.14849

Relevance of Laparoscopic Surgery for Ovarian Cancer in Well-selected Patients: A Propensity-matched Comparison With Laparotomy

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Abstract. *Background/Aim: This study aimed to evaluate the relevance of laparoscopy in comparison with laparotomy in the management of ovarian cancer in well-selected patients. Patients and Methods: Data of consecutive ovarian cancer patients treated by laparoscopy were matched 1:1 to a cohort of patients operated by laparotomy using a propensity score matching. The inclusion criteria included patients who underwent a complete staging procedure in the early stages and optimal upfront or interval debulking surgery for advanced ovarian cancer. Results: In total, 153 patients were included. Propensity score matching led to the analysis of 41 well-balanced pairs of patients. For a median follow-up of 34.0 [19.0-64.0] months and 38.0 [24.5-75.0] months, respectively, no difference was found between the two groups in regards to overall survival (p=0.28) and disease-free survival (p=0.89). Conclusion: In well-selected patients, laparoscopic surgery may be a safe and effective alternative to laparotomy.*

Surgery, together with chemotherapy are the pillars of the management of ovarian cancer. The objective of surgery differs according to the stage. The main objective in the early stage is to establish the stage of the disease with the purpose to confirm the indication of adjuvant chemotherapy. In the advanced stages, the aim of surgery is different, since the ultimate goal is the complete cytoreduction without any residual tumor. Whenever this final result is unachievable at upfront surgery, neoadjuvant chemotherapy and interval debulking surgery are accepted as a valid alternative (1).

Classically, the surgery for gynaecological malignancies was carried out by laparotomy. Since a couple of decades, laparoscopic surgery has been increasing used in the management of gynaecological malignancies (2, 3). Thereby, in ovarian cancer, minimally invasive surgery was validated as a valid option for diagnosis, staging in early stages, and preoperative evaluation of the resectability of the disease in advanced stages (4-6). Recently, indications for laparoscopy tend to expand into the therapeutic field (7-9). Recent studies have shown that in selected patients laparoscopic cytoreduction appears to have similar survival rates to the open approach (10, 11).

Despite this, there is still some reluctance about the use of laparoscopy in ovarian cancer. In 2018, a prospective randomized trial found that patients who underwent minimally invasive radical hysterectomy for early-stage cervical cancer had lower rates of disease-free survival and overall survival, but a higher rate of locoregional recurrence than patients who underwent open abdominal radical hysterectomy (12). One of the explanations given by the authors to explain this lower oncologic outcome in the minimally invasive group has been the effect of the insufflation gas (CO_2) on tumor cell growth or spread. Even if questionable, this argument could be particularly audible in the management of ovarian cancer where the use of CO_2 pneumoperitoneum (13) and the potential peritoneal dissemination (14) are major issues.

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Key Words: Ovarian cancer, laparoscopy, minimally invasive surgery.

The aim of this retrospective propensity-matched study was to evaluate the relevance of minimally invasive surgery in comparison with conventional open surgery in the management of epithelial ovarian cancer in well-selected patients in a tertiary referral centre.

Patients and Methods

Study design and patients. This retrospective study includes all consecutive patients who had undergone histologically proven epithelial ovarian cancer surgery from January 2010 to December 2018 at Strasbourg University Hospital, France.

In our institution, the rule is to operate ovarian cancer by laparotomy. We started, however, to realise laparoscopic surgery since 2007 in some cases. The decision to realise laparoscopic surgery was surgeon dependent.

The inclusion criteria for our study included all patients who underwent a complete staging procedure in the early stages, and optimal upfront or interval debulking surgery for advanced ovarian cancer. In case of neoadjuvant chemotherapy before debulking surgery, the specific inclusion criteria were: presumed absence of residual tumors at the supra-mesocolic level and at the level of small bowel on the CT scan and laparoscopic evaluation.

Patients were excluded if they had low malignant or borderline tumor, and if they had been treated either with hyperthermic intraperitoneal chemotherapy or fertility conservative surgery. This study was approved by the Institutional Review Board (IRB).

Laparoscopic surgical technique. The first step of the procedure was a laparoscopic exploration to evaluate resectability. This was realised under general anesthesia; the patient was placed in the supine lithotomy position. The entire abdominal cavity was carefully inspected. Patients were only submitted to laparoscopic cytoreduction if they were predicted to achieve optimal debulking by laparoscopy. Otherwise, conversion to open surgery was perfomed.

After initial peritoneal exploration, laparoscopic surgery was applied to collect peritoneal washings or ascites for cytologic examination and for total hysterectomy, bilateral salpingo-oophorectomy, total infragastric omentectomy, pelvic and para-aortic lymphadenectomy and appendicectomy, as well as removal of all visible tumors. Bowel resection or other digestive or urological procedures were performed if needed. In the absence of peritoneal carcinomatous, systematic blind peritoneal biopsies were performed.

Laparotomic cytoreduction technique. Laparotomy was performed via a midline longitudinal xypho-pubic incision and exposure facilitated by an Omnitract-type spacer. The same cytoreductive procedures as described above were performed after a complete exploration.

Data collection and outcomes. Demographics and baseline oncologic characteristics were collected from the patients' medical records: age, body mass index (BMI), surgical history, clinicopathological FIGO stage, histological subtype, grade and CA 125 level at diagnosis. Staging system and architectural grade were reported in accord to the International Federation of Obstetrics and Gynecologists (FIGO) guidelines. The histological classification of ovarian tumors by the World Health Organization (WHO) was used to classify histologic subtypes.

Complexity of the surgery was assessed by measuring the validated "Surgical Complexity Score" (15). Operating time (from the skin incision to the end of the surgical procedure), blood transfusion, and intraoperative complications were also evaluated.

Postoperative morbidity was evaluated by hospital stay (defined as the duration from the date of surgery up to when the patient was discharged from hospital), rate and type of short-term complications (within 30 days of surgery) and rate and type of long-term complications (after 30 days) according to the Clavien Dindo classification (16). For the study purpose, we reported only complication grade III or worse.

Survival data was estimated by overall survival (defined by the time from initial diagnosis to date of death or last follow-up) and disease-free survival (defined by the time between initial diagnosis and date of first recurrence or last follow-up). All patients were followed up to January 30th, 2020, death, or lost to follow-up.

Adjuvant treatments were limited to patients considered at high risk of recurrence (FIGO I with grade 3, FIGO IC, II and III). Generally, it consisted in 6 cycles of platinum-based chemotherapy. The patients were routinely followed up on completion of the treatment according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO). Recurrences were confirmed by histological or imaging evaluation.

Statistical analysis. To reduce the potential biases arising from the retrospective comparison of the two groups, we performed propensity score matching. We estimated the propensity to undergo planned laparoscopic staging with a logistic regression model with variables selected a priori based on their potential to influence the likelihood of a subject undergoing laparoscopic surgery. The independent variables included age, BMI, surgical history, histological subtype, FIGO stage, grade, CA-125 levels at diagnosis, and neoadjuvant chemotherapy. Cases were matched to controls at a 1:1 ratio, using calipers of width ≤0.2 of the standard deviation of the logit of the estimated propensity score (17). To improve the quality of our propensity score analysis, we followed the guidelines for propensity score matching (18). The patients with missing data were not included in the analysis. To assess the comparability of the baseline characteristics between matched groups, a love plot was created which graphically displays the absolute standardized differences in means and variance ratio before and after matching for all the covariates (19).

Categorical data are presented as frequencies and proportions and were compared by the Chi-square test or Fisher's exact test. Continuous data are presented as mean±standard deviation or median, and the Student's *t*-test or nonparametric test were used to compare differences between groups. The Kaplan-Meier analysis was used to analyse overall (OS) and disease-free survival (DFS), and the Log-rank test was used to compare differences between groups. A stratification by FIGO stages was realized: early stages (FIGO I and II) and advanced stages (FIGO III and IV). A two-sided *p*-value <0.05 was considered statistically significant in all analyses. All analyses were performed with software R, version 3.6.2.

Results

Baseline characteristics. During the study period, we identified 153 patients meeting the inclusion criteria: 70 (46%) had undergone laparoscopic surgery and 83 (54%) conventional laparotomy. Of the 83 patients who had been

Table I. *Baseline characteristics. *Fischer exact text; **Mann-Whitney test.*

	Before matching				After matching			
	All patients n=153	Laparoscopy n=70 (46%)	Laparotomy n=83 (54%)	*p*-Value	All patients n=82	Laparoscopy n=41 (50%)	Laparotomy n=41 (50%)	*p*-Value
Age, years (mean± sd)	60.5±11.4	58.5±11.7	62.2±11.0	0.04	61.3±10.6	61.8±10.2	60.9±11.1	0.68
BMI, kg/m^2 (mean±sd)	25.3±5.1	24.8±4.4	25.7±5.7	0.26	25.7±5.1	26.0±4.3	25.5±5.9	0.72
Surgical history	88 (58%)	46 (52%)	42 (54%)	0.06	53 (65%)	27 (66%)	26 (63%)	0.82
Histological subtype				0.94*				0.87*
Serous	107 (70%)	50 (71%)	57 (69%)		63 (77%)	30 (73%)	33 (80%)	
Endometrioid	20 (13%)	9 (13%)	11 (13%)		10 (12%)	6 (15%)	4 (10%)	
Clear cells	14 (9%)	5 (7%)	9 (11%)		4 (5%)	3 (7%)	1 (2%)	
Mucinous	9 (6%)	5 (7%)	4 (5%)		2 (2%)	1 (2%)	1 (2%)	
Transitional cells	1 (1%)	0 (0%)	1 (2%)		1 (1%)	0 (0%)	1 (2%)	
Other	2 (1%)	1 (1%)	1 (1%)		2 (2%)	1 (2%)	1 (2%)	
FIGO stage at diagnosis				0.02				0.11*
I	31 (20%)	22 (31%)	9 (11%)		14 (17%)	9 (22%)	5 (12%)	
II	21 (14%)	8 (11%)	13 (16%)		11 (13%)	5 (12%)	6 (15%)	
III	86 (56%)	33 (47%)	53 (64%)		50 (61%)	21 (51%)	29 (70%)	
IV	15 (10%)	7 (10%)	8 (10%)		7 (9%)	6 (15%)	1 (2%)	
Grade				0.56*				0.50*
1	10 (7%)	4 (6%)	6 (8%)		6 (7%)	4 (10%)	2 (5%)	
2	21 (15%)	7 (11%)	14 (18%)		13 (16%)	5 (12%)	8 (20%)	
3	112 (78%)	52 (83%)	60 (75%)		63 (77%)	32 (78%)	21 (76%)	
CA 125 level at diagnosis (median [range])	344.0 [111.0-1000.0]	124.0 [40.0-564.0]	563.0 [245.0-1406.8]	<0.01	335.0 [114.3-891.8]	224.0 [80.0-888.0]	350.0 [89.0-242.0]	0.05**
Neo-adjuvant chemotherapy	72 (47%)	31 (44%)	41 (49%)	0.53	45 (55%)	22 (54%)	23 (56%)	0.82
Follow-up, months (median [range])	34.0 [19.0-64.0]	38.0 [24.5-75.0]	28.5 [14.5-46.0]	<0.01	32.0 [19.0-57.8]	31.0 [16.0-52.0]	32.0 [23.0-61.0]	0.25**

operated by laparotomy, 18 (22%) had initially undergone diagnostic laparoscopy. The baseline characteristics of the patients are summarized in Table I.

After applying the propensity score algorithm, we included in our study 41 propensity-matched patient pairs (82 patients in total). Demographics and baseline oncologic characteristics were well balanced between groups, as verified in Figure 1.

Surgery-related data. Table II presents the intraoperative details. We observed that patients undergoing laparoscopic surgery needed less transfusion with 9 patients (23%) *versus* 27 (69%) in the laparotomy group ($p<0.01$). In our study, no differences were found for the operating time (323.0±94.6 minutes *versus* 304.7±105.7 with $p=0.43$).

In the laparoscopic group, four patients experienced intraoperative complications (one bladder injury, one transverse colon injury, one vascular injury, and one obturator nerve injury) *versus* three in the laparotomy group (one sigmoid injury, one ureteral injury and one renal vein injury). All were resolved laparoscopically, without the need of conversion to open surgery.

Surgical complexity score was significantly higher in the open surgery group ($p<0.01$), principally due to the need of an extended peritonectomy and a larger number of bowel resections.

Postoperative morbidity. Table III provides details of the postoperative parameters. Length of hospital stay were significantly shorter in the laparoscopy group (5.2±3.0 days *versus* 10.1±3.7, $p<0.05$), as the length of intensive care [0 *versus* 1.0 (0-1.5) with $p<0.01$].

There were no differences for early postoperative complications between the two groups ($p=0.56$). In the laparoscopic group, two patients experienced vaginal scar disunion, while in the laparotomy group one patient developed a press syndrome due to malignant arterial hypertension with the need for intensive care.

No significant differences were also found for the number of late complications between the two groups ($p=0.24$), even if three patients in the laparotomy group experienced grade III complications: two pelvic symptomatic lymphoceles (required drainage) and one eventration (required new intervention).

The average time from debulking to initiation of adjuvant chemotherapy was shorter in the laparoscopy group, but not significantly (30.0±13.4 days *versus* 35.1±4.0 days, $p=0.30$). In the laparoscopic group, 33 patients (85%) received adjuvant chemotherapy compared to 34 (83%) in the laparotomy group ($p=0.84$).

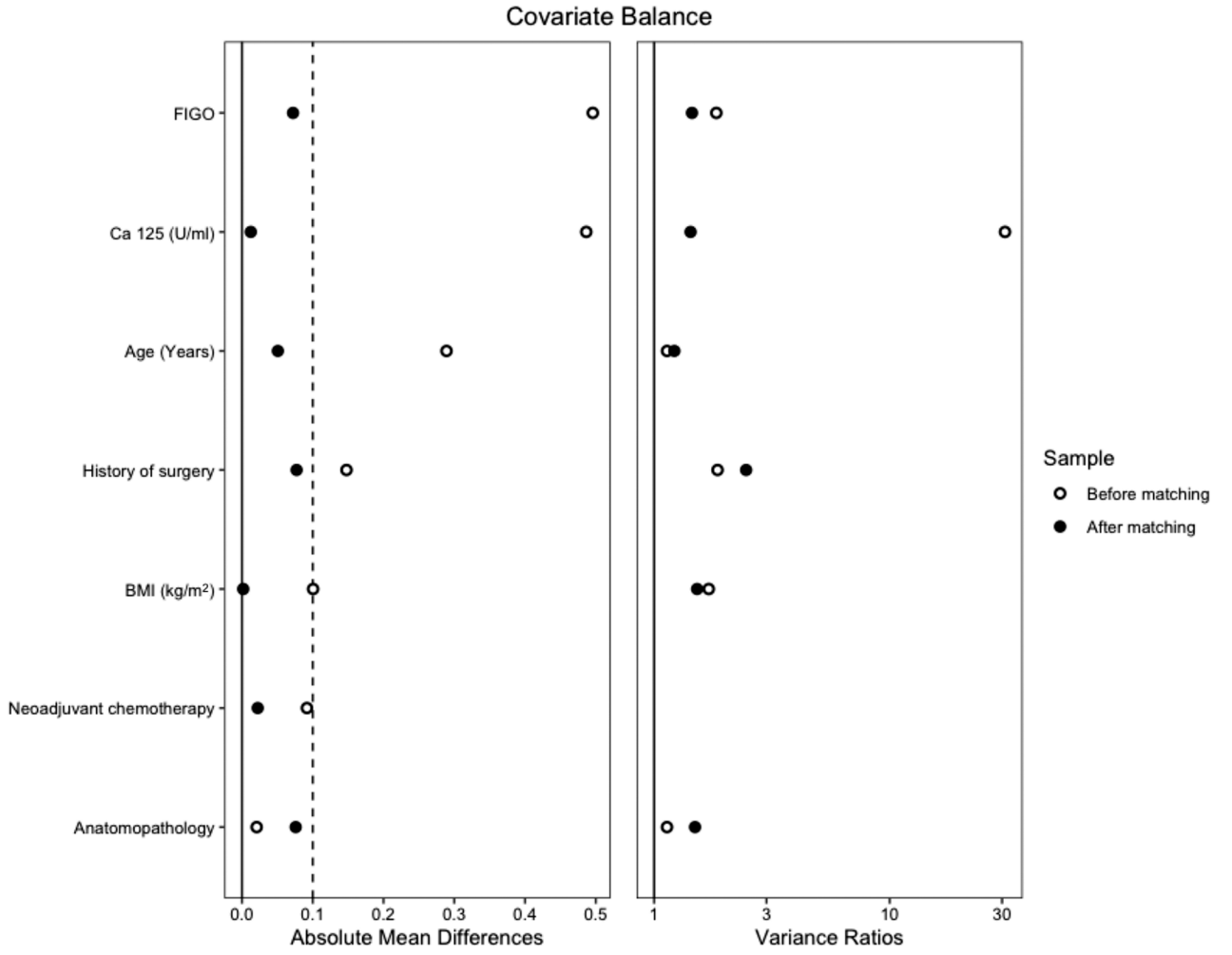

Figure 1. *Love plot*.

Survival data. No difference in survival data was noticed with a *p*-value at 0.28 for the overall survival (Figure 2). A median follow-up of 34.0 [19.0-64.0] months and 38.0 [24.5-75.0] were observed in the laparoscopic and open surgery groups, respectively. No significant difference for overall survival was observed in early stages ($p=1$) and advanced stages strata ($p=0.23$).

As regards to disease-free survival, no difference between groups was again noticed with a *p*-value at 0.89 (Figure 3). No significant difference was observed in early stages ($p=0.38$) and advanced stages strata ($p=0.85$). The recurrence rate was 47% in the laparoscopic group *versus* 51% in the laparotomy group.

Discussion

Surgery for gynaecological cancer has historically been performed by laparotomy. But due to its minimally invasive approach, laparoscopy has been shown over the years to be a proper alternative (2, 3). In this retrospective propensity-matched study, we investigated the use and effectiveness of laparoscopic surgery in women with complete staging and complete resection debulking surgery for epithelial ovarian cancer. Our study showed that, in selected cases, minimally invasive surgery for ovarian cancer was associated with reduced hospital stay, reduced intensive care unit admission, and decreased need for transfusion, without any alteration of survival. These findings are consistent with data reported by several other studies (10, 20). Other advantages of laparoscopy have already been cited in the literature, such as reduction in the need for postoperative analgesics (21), earlier initiation of adjuvant therapy (22, 23), image magnification or improved dissection in critic areas (24).

Despite this marked decrease in morbidity, several oncologic concerns have limited the widespread use of

Table II. *Surgery-related data*.

	Laparoscopy n=41 (50%)	Laparotomy n=41 (50%)	*p*-Value
Surgical procedures			
Total hysterectomy	36 (88%)	38 (93%)	0.71*
Salpingo oophorectomy	25 (61%)	33 (80%)	0.05
Infragastric omentectomy	41 (100%)	39 (95%)	0.49*
Appendicectomy	24 (59%)	21 (53%)	0.66
Pelvic lymphadenectomy	29 (71%)	29 (78%)	0.44
Para-aortic lymphadenectomy	28 (68%)	30 (73%)	0.63
Abdominal peritonectomy	6 (15%)	16 (39%)	0.01
Diaphragmatic peritonectomy	2 (5%)	10 (24%)	0.01
Bowel resection	2 (5%)	6 (15%)	0.14*
Surgical complexity score			<0.01*
Low	22 (55%)	11 (28%)	
Intermediate	18 (45%)	22 (57%)	
High	0 (0%)	6 (15%)	
Lymph nodes (mean±sd)	29.6±10.5	34.6±14.3	0.14
Operative time, min (mean±sd)	323.0±94.6	304.7±105.7	0.43
Transfusion	9 (23%)	27 (69%)	<0.01
Intra-operative complications	4 (10%)	3 (7%)	0.72

*Fischer exact test.

Table III. *Postoperative morbidity*.

	Laparoscopy n=41 (50%)	Laparotomy n=41 (50%)	*p*-Value
Hospital stay, days (mean±sd)	5.2±3.0	10.1±3.7	<0.01
Intensive care unit stay, days [median (range)]	0	1.0 [0-1.5]	<0.01
Use of morphinics, days [median (range)]	1.0 [1.0-1.0]	2.0 [2.0-3.0]	0.05
Lengh of perfusion, days [median (range)]	2.0 [1.0-3.0]	6.0 [5.0-8.0]	<0.01
Time to bowel movement, days [median (range)]	1.0 [1.0-1.0]	3.0 [2.0-4.0]	<0.01
Short term complications	2 (5%)	1 (2%)	0.56
Grade III	2 (5%)	0 (0%)	
Grade IV	0 (0%)	1 (2%)	
Late complications	0 (0%)	3 (7%)	0.24*
Grade III	0 (0%)	3 (7%)	
Grade IV	0 (0%)	0 (0%)	
Readmissions	3 (7%)	4 (10%)	0.71*
Time to initiation of chemotherapy, days (mean±sd)	30.0±13.4	35.1±24.0	0.30

*Fischer exact test.

laparoscopy, especially in ovarian cancer surgery. One of the notable features of this study is the inclusion of both early and advanced stages of epithelial ovarian cancer. Although this may have some limitations, it allowed us to investigate the global feasibility of laparoscopy for the management of epithelial ovarian cancer. To investigate more precisely the potential limitations of laparoscopy, its potential roles in ovarian cancer surgery must be divided into two categories according to the clinical stage of the disease. In apparent early stage, the goal is to properly diagnose, evaluate, and perform a complete staging (1). Our results taken together with other published data concerning the feasibility, safety and efficacy of minimally invasive surgery in accomplishing all steps of surgical staging (23, 25, 26). The combination of the results of the latest studies with our own in a meta-analysis suggests the likely effectiveness of minimally invasive surgery in selected cases of ovarian cancer, even in advanced stages (27).

As for advanced ovarian cancer, several studies have evaluated the value of laparoscopy (11, 28, 29), but many

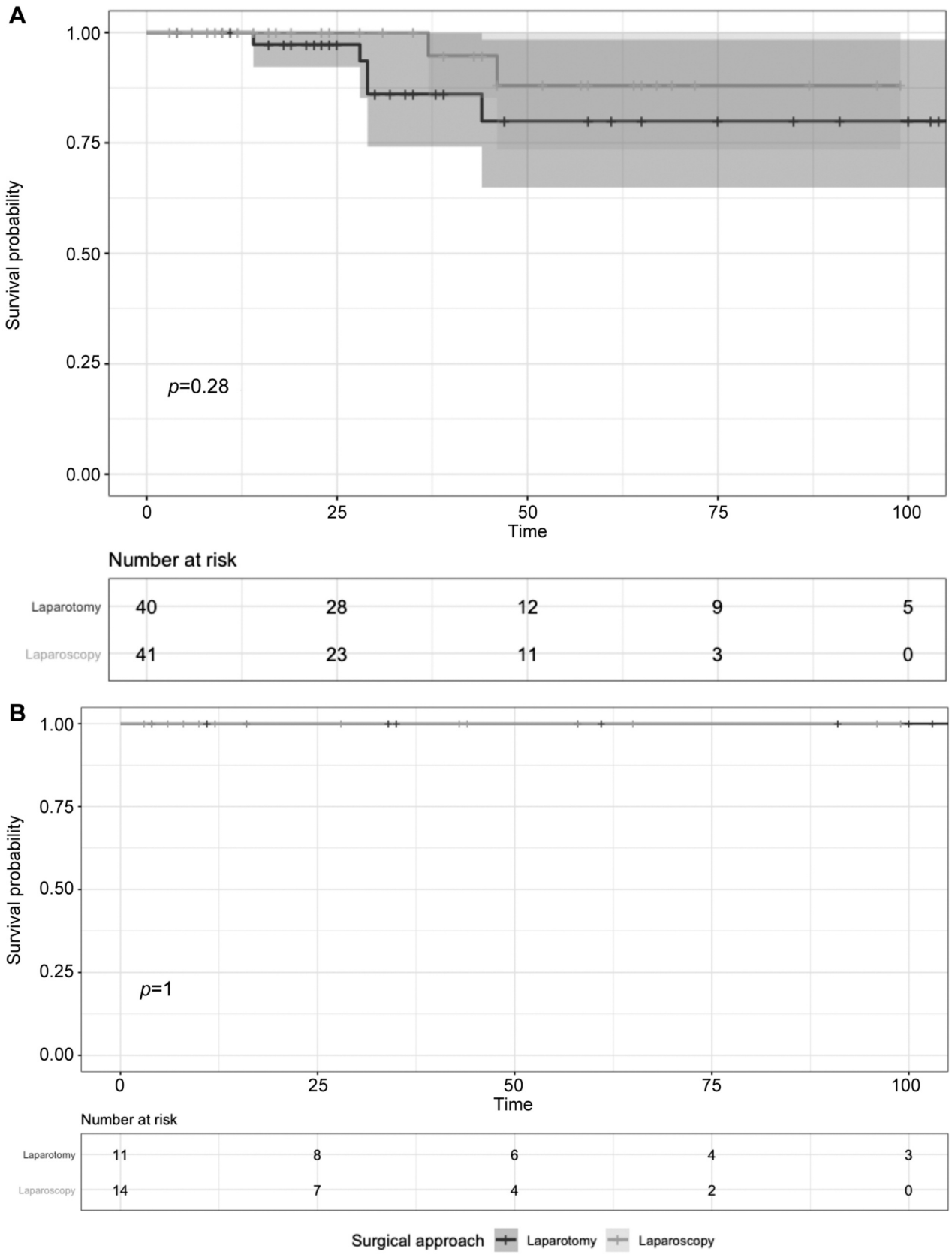

Figure 2. *Continued*

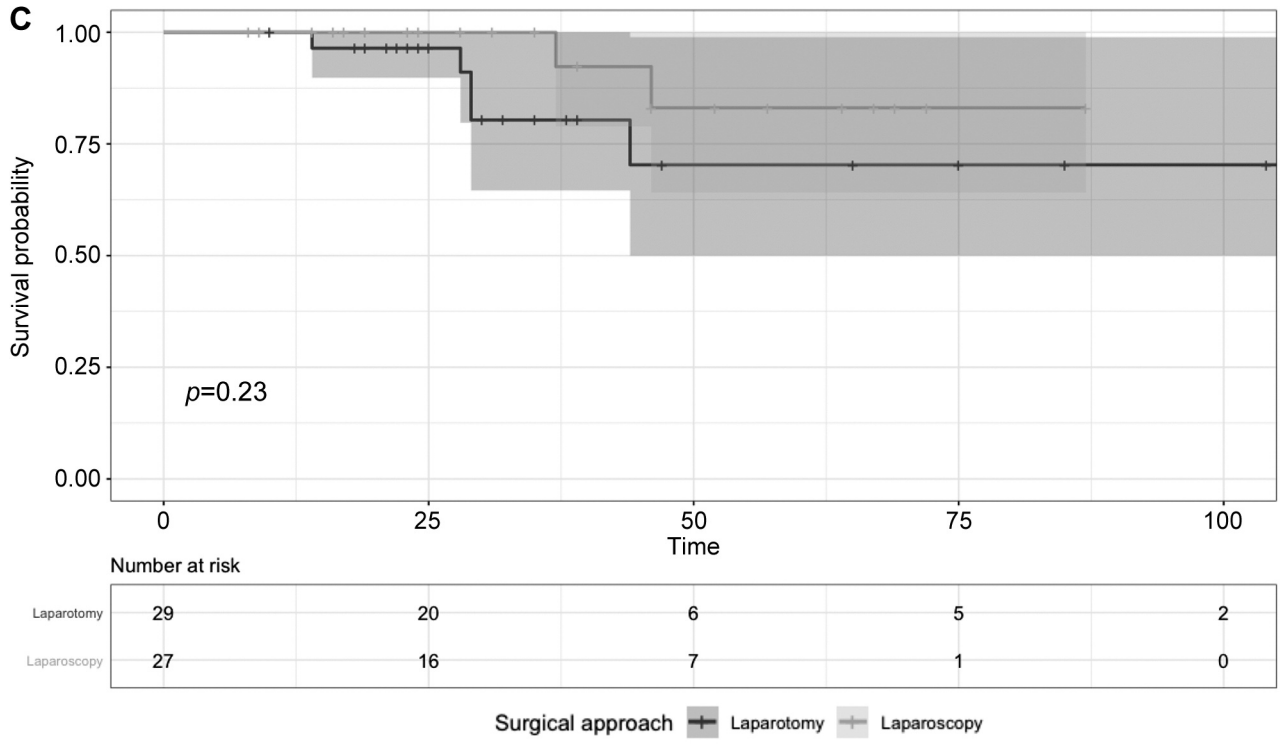

Figure 2. *Overall survival in all stages (A), early stages (B) and advanced stages (C).*

limitations have been described (30). One limitation that should be noted in our study, but also in others evaluating the utility of laparoscopy in performing cytoreductive surgery (28), is the fact that more complex surgical procedures were realised by laparotomy. This is probably an indirect expression of the higher burden of disease in the laparatomy group. In our study, to override this bias, we made the decision to include only patients who had no residual disease at the end of the surgery. In advanced ovarian cancer, the absence of residual tumor is the main prognostic factor, exceeding the burden of disease at diagnosis and the distribution of peritoneal carcinomatosis, although these may be directly related. It does, however, imply that it is necessary to have first carefully select patients who can benefit from laparoscopic debulking surgery. The use of minimally invasive surgery should be reserved only in centers that might guarantee the possibility of complete cytoreduction when judged to be feasible. One criticism that has been made in the study by Melamed et al. is the lack of information on the type and amount of neoadjuvant chemotherapy (28, 31). The choice of surgical route may be influenced by the response to chemotherapy. We were also unable to collect this information in our study. However, the aim of our study was not to define criteria for selecting patients who might benefit from laparoscopic debulking surgery.

Another point to highlight is the possible difficulty of exploration by laparoscopy. Patients affected by stage III and IV ovarian cancer are likely to have macroscopic disease located in areas not easily visible via minimally invasive surgery. From a technical point of view, the access to the retrohepatic and subhepatic regions, as well as the exploration of the hepatic and splenic hilum, could be difficult and might be a real issue in case of a minimally invasive approach. In our study, we have chosen to limit the laparoscopic approach to cases where preoperative CT scan has not shown any residual tumor after neoadjuvant chemotherapy. A very meticulous exploration of the abdominal cavity, with a special effort to confirm the absence of any residual tumor not accessible by laparoscopy was realised in every case before continuing laparoscopic surgery. This combined strategy has been used in many published studies (29, 32). In our study, 18 (22%) of the 83 patients finally operated by laparotomy had initially undergone diagnostic laparoscopy. It was, however, impossible to verify in this retrospective study whether the conversion to laparotomy was initially planned, or whether it was decided because of the exploration showing the impossibility to realise an optimal resection by laparoscopy. However, again, the goal of our study was not to evaluate a model of patients' selection for laparoscopic surgery.

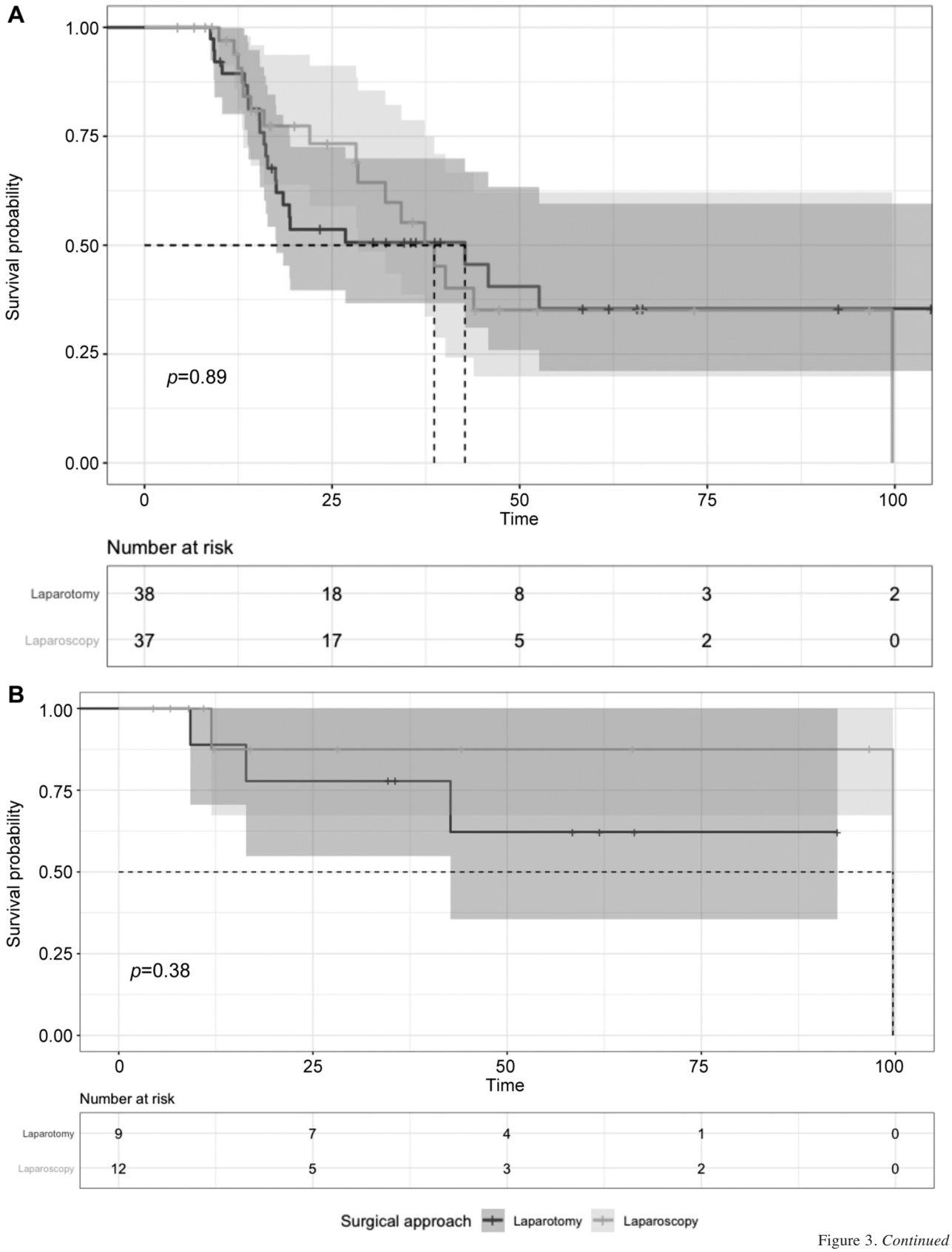

Figure 3. *Continued*

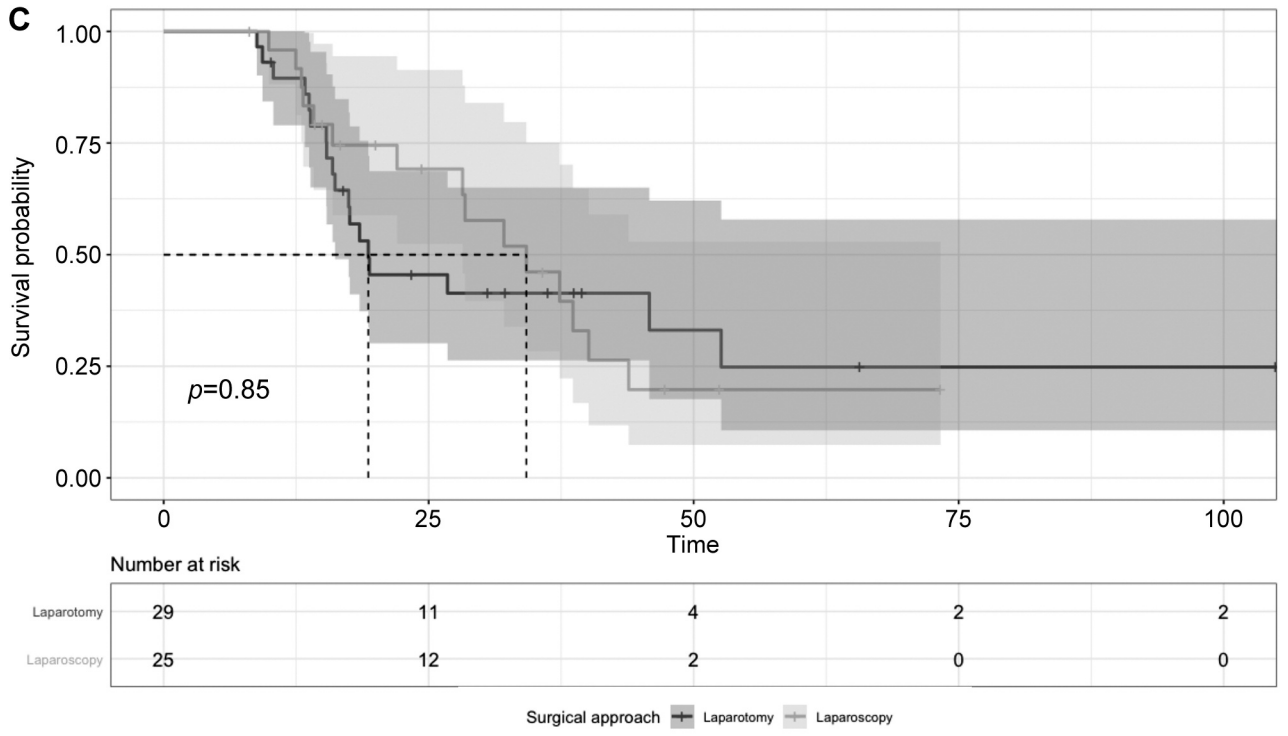

Figure 3. *Disease-free survival in all stages (A), early stages (B) and advanced stages (C).*

In general, what is most often criticized in laparoscopy is the possibility of port-site metastasis and the effects of CO_2 pneumoperitoneum, especially on tumor dispersion and growth rate (13). In ovarian cancer, some preclinical studies on rat models have demonstrated an increase of tumor cell growth in case of the use of CO_2 (32). Others have examined the role of CO_2 on peritoneal tumor dissemination and have shown more severe cancer dispersion than with open surgery (33), some with no increased effect on tumor growth (34). Nonetheless, our study found no difference in terms of survival, which indirectly shows the absence of any negative effect of CO_2 pneumoperitoneum.

One of the strengths of our study would be the use of a propensity score which aim is to estimate the effect of a treatment considering any unbalanced initial characteristics that may influence its choice. The propensity score is a quantitative value that summarizes the initial characteristics of the subjects to form comparable groups and to reduce the potential biases arising from the retrospective comparison of the two groups (18). In our study, as in other observational studies, the investigators have no control over treatment assignment. As a result, there may be large differences between the covariates observed in the two groups, and these differences could lead to biased estimates of treatment effects. Propensity score analyses attempt therefore to mimic randomized comparisons. However, unlike randomized treatment assignment, the propensity score generally does not balance covariates that were not observed. We cannot be certain that all the confounding variables were perfectly neutralized. Moreover, matching reduces the sample size, leading to a small population in our study.

In conclusion, to the best of our knowledge, this is the first comparative study based on a propensity score that evaluates in global terms the feasibility, morbidity, and impact on survival of laparoscopy for epithelial ovarian cancer. By including only patients who have undergone a complete resection or staging, our study makes it possible to study the use of minimally invasive surgery in the event of correct patient selection. Bearing in mind the limitations mentioned above, these findings suggest that, in well-selected patients, laparoscopic surgery may be a safe and effective alternative to laparotomy. The absence of residual tumor being the main prognostic factor, midline laparotomy remains the gold standard when laparoscopy reaches its limits, especially in supra-mesocolic diseases. Additional studies should be performed on the selection of patients who can benefit from laparoscopic cytoreduction.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study concept: FJ-GA-CA; Study design: FG-GA-CA; Data acquisition: FJ-GA-MP-CB; Quality control of data and algorithms: FJ-GA-MP-CB; Data analysis and interpretation: FJ-GA-EF-TB-LL-CA; Statistical analysis: FJ-CA; Manuscript preparation: FJ-GA; Manuscript editing: FJ-EF-TB-LL-CA; Manuscript review: FJ-EF-TB-LL-CA.

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Received January 4, 2021
Revised January 19, 2021
Accepted January 20, 2021