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# ▶ To cite this version:

Marie Pécout, Jérôme Phalippou, Henri Azaïs, Lobna Ouldamer, Pierre Adrien Bolze, et al.. Comparison of retroperitoneal and transperitoneal surgical routes in laparoscopic nodal staging for locally advanced cervical cancers (FIGO IB3-IVA). EJSO - European Journal of Surgical Oncology, 2022, 48 (9), pp.2061-2067. 10.1016/j.ejso.2022.05.005 . hal-03690683

# HAL Id: hal-03690683 https://hal.science/hal-03690683

Submitted on 3 Apr 2023

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# Comparison of retroperitoneal and transperitoneal surgical routes in laparoscopic nodal staging for locally advanced cervical cancers (FIGO IB3-IVA)

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ABSTRACT

*Background*: This study compares morbidity and mortality associated with retroperitoneal and transperitoneal para-aortic lymphadenectomy (PAAL) for pretherapeutic nodal staging of locally advanced cervical cancers (FIGO IB3–IVA).

*Methods:* Pre-, per- and postoperative data of patients treated for locally advanced stage cervical cancer between 1999 and 2018 in 12 French referral centers (FRANCOGYN Study Group) were retrospectively collected.

*Results:* The study was conducted using a sample of 448 patients, of whom 223 (49,8%) underwent retroperitoneal (group 1) and 225 (50,2%) had transperitoneal PAAL (group 2). No differences were noted concerning clinical and histological characteristics between the two groups. Among these 448 patients, 23 (5,1%) had an intraoperative complication (9 (2,0%) in group 1 and 14 (3,1%) in group 2, p = 0.28) and 47 (10,5%) had a postoperative complication (22 (4,9%) in group 1 and 25 (5,6%) in group 2, p = 0.44), only one of which required revision surgery but the patient died. The length of hospital stay was significantly shorter in group 1 than in group 2 (3.97 versus 4.88 days, p < 0.001). There was no significant difference in mortality between the two groups; 34 of 223 patients in group 1 (15.3%) and 40 of 225 patients in group 2 (15.6%) died (HR = 0.968, 95% CI [0.591–1.585]). There was no significant difference in recurrence-free or overall survival between the two groups.

The management of FIGO stage IB3 to IVA cervical cancers is based on an association of radiochemotherapy [1,2] followed by vaginal brachytherapy, with the height of the irradiation field being determined by the anatomical level of nodal invasion.

Para-aortic lymph node metastatic involvement, which is a major prognostic factor, occurs in approximately 15% of locally advanced cervical cancer (LACC) cases [3]. Hence, identifying patients with nodal involvement is a major issue to better adapt therapeutical management [4,5]. A PET-CT scan may be performed for FIGO IB3 stages and above; although it is considered as a standard imaging technique in the assessment of nodal metastases, several authors report a rate of false negatives cases ranging from 8% to 12% (especially for micrometastases) when compared to surgical staging [6,7]. The study Uterus-11 showed no difference in disease-free survival between surgical and clinical staging in patients with LACC [8]. While the surgical approach by para-aortic lymphadenectomy (PAL) is not currently systematized in the management of LACC (FIGO IB3-IVA), infra-mesenteric PAL is proposed as an option in the European guidelines of the European Society of Gynaecological Oncology (ESGO) for the management of LACC [9]. In the absence of a recent French recommendation on this specific topic, this attitude is promoted in the staging of LACC with lymph node negative on PET-CT [10].

Laparoscopic surgery is a validated surgical route for nodal staging in gynecological cancers with reduced morbidity and mortality and no impact on prognosis compared to standard laparotomy [11]. The indication of PAL by laparoscopy follows the standards of the French Society of Gynecological Oncology (SFOG) and the ESGO [12] and represents the reference method as it is associated with lower morbidity and mortality compared to laparotomy [13]. In case of laparoscopic nodal staging, two surgical approaches are currently used: transperitoneal or retroperitoneal techniques [11,14]. Both have advantages and disadvantages in terms of the surgical technique and the perioperative morbidity and mortality of the patients [15].

Currently, there is no consensus on the optimal surgical approach in case of laparoscopic nodal staging, particularly in LACC. In order to evaluate the two laparoscopic approaches, we conducted a large multicenter retrospective study comparing the morbidity and mortality of patients who had retroperitoneal or transperitoneal PAL in pretherapeutic lymph node staging of LACC (FIGO IB3–IVA).

#### 1. Material and methods

Our retrospective study was carried out using a French multicentric database (FRANCOGYN study Group), which included all the patients treated for LACC between 1999 and 2018 in 12 French referral centers (Centre Hospitalier Intercommunal de Créteil, Hôpital Jean Verdier de l'Assistance Publique des Hôpitaux de Paris, Centre Hospitalier Régional Universitaire de Lille, Centre Hospitalier de Lyon Sud, Hôpital Nord de l'Assistance Publique des Hôpitaux de Marseille, Hôpital de la Pitié Salpêtrière de l'APHP, Centre Hospitalier Intercommunal de Poissy, Centre Hospitalier Universitaire de Rennes, Centre Hospitalier Universitaire de Reims, Hôpital Tenon de l'APHP, CHU de Tours, Hôpital Universitaire de Strasbourg). Preoperative data included age, pregnancy, parity, body mass index (BMI), smoking status, completion of a PET-CT scan, and the FIGO stage [16] of the pathology at initial diagnosis. Intraoperative data included laparoscopic approach (retroperitoneal or transperitoneal), number of lymph nodes removed, and occurrence of procedure failures or complications. Postoperative data included the type of postoperative complication, length of hospital stay, and occurrence of recurrence or death. Postoperative complications were assessed according to the Clavien and Dindo classification [17]. The extent of the lymph node dissection (infrarenal or infra-mesenteric) was not recorded in our database. However, we assumed that infra-renal PAAL was performed, as infra-mesenteric lymphadenectomy was not yet widespread during our inclusion period. Therefore, we considered the number of lymph nodes removed during PAAL. Failure to perform PAAL laparoscopically was considered a procedure failure. Complications leading to laparoconversion were considered as a procedure failure. These situations were considered intraoperative complications. The primary outcome measures were the morbidity and mortality associated with each approach to PAAL (retro- and transperitoneal) and the length of hospitalization. The secondary outcomes were overall survival and recurrence-free survival.

Quantitative variables were described by mean and standard deviation or by median and interquartile range. The normality of the distributions was verified graphically, as well as with the Shapiro-Wilk test. Qualitative variables were described by frequency and percentage. When the numbers were sufficient, qualitative variables were compared between groups using chi-square tests. If these tests were not valid (theoretical numbers <5), Fisher's exact tests were used. When the numbers were sufficient, quantitative variables were compared using Student's tests. In cases of non-normal data, nonparametric Wilcoxon tests were used. Overall survival and recurrence-free survival were estimated by the Kaplan-Meier method and compared between groups using Cox proportional hazards models. The significance level was set at 0.05. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA).

## 2. Results

The database included 1977 patients treated for cervical cancer between 1999 and 2018 of whom 448 patients had LACC (stages IB3 to IVA of the current FIGO classification). Of these patients, 223 underwent retroperitoneal dissection (49.8%), and 225 had transperitoneal dissection (50.2%) (Fig. 1). The mean age was 50.5 years  $\pm 11.6$  and the mean BMI was 25.0 kg/m2  $\pm 5.6$  (BMI ranging from 14.3 to 48.8). No differences were noted between the two groups concerning age, menopausal status, BMI, pregnancy, parity, and smoking (Table 1). No differences were noted between the two groups concerning FIGO stages (Table 2). Eight procedural failures were identified (1,8%), 4 (0,9%) in the retroperitoneal group (2 conversions to laparotomy including one for inferior vena cava injury, 1 impossible approach and 1 with no pneumoperitoneum created) and 4 (0,9%) in the transperitoneal group (2 conversion to laparotomy, 2 procedural failures including one for obesity) (p = 0.73). We also noted 4 cases of conversion to laparotomy

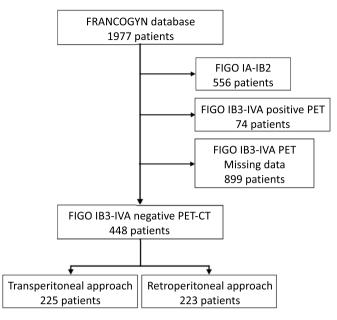


Fig. 1. Flow chart.

Table 1	Table	1
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Population.

1			
APPROACH	TRANSPERITONEAL	RETROPERITONEAL	р
Number	225	223	
Age at diagnosis (years)	50,3 ± 11,9	50,7 ± 11,4	0,86
Menopause (%)	106 [1,47]	108 [5,49]	0,97
BMI (kg/m2)	24,7 ± 5,5	25,2 ± 5,8	0,54
Smoking (%)	53 (53)	57 [6,45]	0,62
Gestity	3,0 [0,0,2,4]	2,0 [0,0,1,4]	0,98
Parity	2,0 [0,0,1,3]	2,0 [0,0,1,4]	0,92

#### Table 2

FIGO in population.

1 1			
APPROACH	TRANSPERITONEAL	RETROPERITONEAL	р
Number	225	223	
FIGO IB3	36 (16%)	32 (14,35%)	0,27
FIGO IIA	6 (2,67%)	6 (2,69%)	
FIGO IIA1	5 (2,22%)	8 (3,59%)	
FIGO IIA2	12 (5,33%)	5 (2,24%)	
FIGO IIB	150 (66,67%)	147 (65,92%)	
FIGO III	2 (0,89%)	1 (0,45%)	
FIGO IIIA	1 (0,44%)	2 (0,90%)	
FIGO IIIB	7 (3,11%)	7 (3,14%)	
FIGO IIIC	2 (0,89%)	0	
FIGO IVA	4 (1,78%)	15 (6,72%)	

(0,9%): 2 in each group. All immediate intraoperative complications are reported in Table 3. We individualized 23 intraoperative complications (5,1% of all patients); 14 in the transperitoneal group (6.7%) related to i) vascular injuries (8 cases), ii) digestive injuries (2 cases) and iii) injuries of the urinary tract (3 cases), and there was no precision in 1 file, and 9 in the retroperitoneal group (4.3%), linked to vascular injuries (2 cases including an inferior vena cava injury with conversion to laparotomy) and 2 ventilatory complications leading to incomplete sampling. The type of intraoperative complication was not defined in 5 files. No difference between the two laparoscopic approaches was found in terms of intraoperative complications (p = 0.28).

Postoperative complications are presented in Table 3. We found 47 postoperative complications (10.49% of all patients): 22 in the

retroperitoneal group (10.4%) and 25 in the transperitoneal group (12.4%) (p = 0,44). In group 1, there were 11 stage I, 3 stage II, 3 stage IIIA, 1 stage IIIB and 3 stage IVA complications according to Clavien and Dindo classification, and in group 2 there were 7 stage I, 7 stage II, 1 stage IIIA, 4 stage IIIB, 1 stage IVA, I stage IVB and 1 stage V complications: one patient died after a new surgery for incarceration of an intestinal loop in a trocar opening.

Regarding postoperative lymphocysts, there was no difference between the two laparoscopic approaches (p = 0.86) (Table 3). Major postoperative complications were treated by radiological interventions in 5 cases: lymphocyst puncture (4 cases) and arterial embolization (management of a retroperitoneal hematoma in one case). Surgery was required in 6 cases: nephrostomy (ureteral obstructions in 2 cases), ureteral stenting (2 cases), laparoscopic lymphocyst puncture in one case and surgery for incarceration of an intestinal loop in a trocar opening. No difference was found between the two surgical approaches concerning the occurrence of postoperative complications (p = 0.44). The length of hospital stay was significantly shorter in the retroperitoneal group (p < 0.001) (Table 3).

14,72  $\pm$  9,89 lymph nodes were removed in group 1, and 13,56  $\pm$  9,0 in group 2. There were significantly more lymph nodes removed in group 1 (p = 0,020). However, the number of positive lymph nodes was not significantly higher in the transperitoneal group (0.52  $\pm$  1.45 positive nodes against 0.40  $\pm$  1.32 positive nodes in the retroperitoneal group, p = 0.35) (Table 3).

The median follow-up was 6,80 years. 56 patients in the retroperitoneal group (25,1%) and 55 patients in the transperitoneal group (24.4%) experienced a recurrence. There was no difference in recurrence-free survival between the two groups (HR = 0.996, 95% CI [0.675–1.469]) (Fig. 2). Regarding overall survival, 34 of the 223 patients in the retroperitoneal group (15.25%) and 40 of the 225 patients in the transperitoneal group (17.78%) died, with no difference between the two groups (HR = 0.968, 95% CI [0.591–1.585]) (Fig. 3). Treatments received were the same in both groups (p=0.95, *Table 3*).

## 3. Discussion

In our study, we found no difference between transperitoneal and retroperitoneal approaches concerning per and postoperative complications as well as prognosis. However, the length of hospital stay was significantly shorter in the retroperitoneal group.

In 2012, Souadka et al. assessed the morbidity of PAL by laparoscopy. They found low morbidity and no delay in starting concomitant radiochemotherapy [18]. Other studies have obtained similar results [19]. However, the literature remains elusive on the choice of laparoscopic route. Indeed, it has been the case in Ramirez and al. study in 2010 [20]. In 2015, Akladios and al., did not find any significant difference between the two approaches with regard to intraoperative or postoperative complications (16 postoperative complications in the transperitoneal group and 5 in the retroperitoneal group, p 0.28) [21]. The results of this study should be qualified, however, since PAL by laparoscopy is performed under different conditions depending on the origin of the cancer (cervix or endometrium). In our study, we identified 4 laparoconversions, which is lower than the rates of between 3% and 5% reported in other studies [22,23] and the rate of 1.3% reported by Akladios et al. [21]. Some research teams, such as that of Gouy and al., have suggested that single-port laparoscopy can limit the risk of laparoconversion or transperitoneal conversion when approaching the retroperitoneal space [24].

Regarding complications, our study mainly found complications of classes I to III according to the classification of Dindo and Clavien [17]. However, some data was missing, and it is possible that more

## Table 3

Peri operative and post-operative data.

194 (93,3) 14 (6,7) 17 177 (87,6)	200 (95,7) 9 (4,3) 14	0,28
14 (6,7) 17	9 (4,3)	0,28
17		
	14	
177 (87,6)		
177 (87,6)		
	190 (89,6)	0,44
25 (12,4)	22 (10,4)	
23	11	
214 (98,2)	193 (98,0)	
		0,73
7	26	
14 (6,7)		0,28
8	2	.,
-	-	0,44
		0,86
		0,00
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-		
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	-	
	-	
		<0,00
	-	0,02
		0,02
-	-	0,35
		0,55
	-	0,02
0,000	3,027	0,02
214	213	0,95
		0,95
	25 (12,4) 23 214 (98,2) 4 (1,8) 7 14 (6,7)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

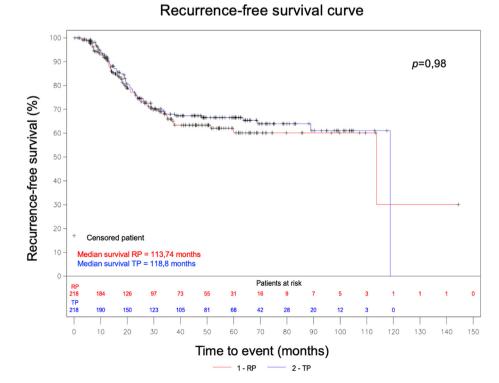
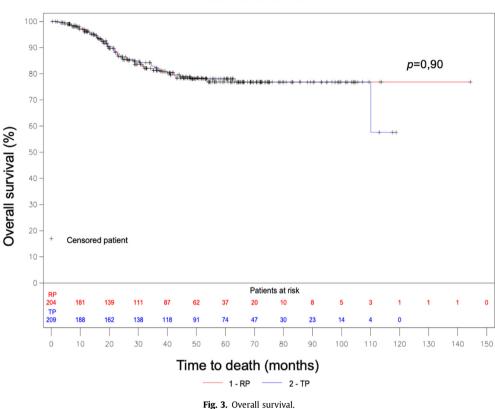


Fig. 2. Recurrence free survival.



Overall survival curve

ing. S. Overan Sarviva

patients required postoperative recovery. Neither surgical route resulted in a type V complication (death of the patient). In Akladios and al. study, 16 postoperative complications were reported in the transperitoneal group and 5 in the retroperitoneal group, which does not represent a significant difference (p = 0.40) [21]. These results are comparable with the results of our study, and other studies have same results [25,26].

The main postoperative complication reported in our study was lymphocele, with no significant difference between the transperitoneal and the retroperitoneal routes. The literature, particularly Achouri and al. study, indicates that lymphoceles after PAL are more frequent in cervical cancer [27]. However, this article did not specify which surgical route. In our study, the risk of developing postoperative lymphocele was greater with PAL by the retroperitoneal route (7,2% versus 3,6% in the transperitoneal group, p = 0.88). This result is similar to the results found in the literature. The only prospective study comparing the two laparoscopic approaches for performing lymph node staging, found a significantly increased risk of developing postoperative lymphocele after surgery via the retroperitoneal route: no cases of lymphocele were found in the 33 pigs in the transperitoneal group, whereas 13 cases (43.33%) were found in the 33 pigs in the retroperitoneal group (p = 0.0002) [28].

In our study we found no difference in recurrence-free survival or in overall survival between the two surgical routes. In the literature, there is no comparison of these two approaches in terms of overall survival or recurrence-free survival. However, the study Uterus-11 showed no difference in disease-free survival between surgical and clinical staging in patients with LACC [8].

In our study, the length of hospital stay was shorter in the retroperitoneal group, with an average length of stay of 3.97 days (p < 0.001). Gouy and al. Found similar length of stay, although

their study examined retroperitoneal staging using the single-port technique, with no comparison with transperitoneal surgery [24]. Morales and al. [29] found that the retroperitoneal route significantly reduced the duration of stay in the intensive care unit (0.59 days for the retroperitoneal group versus 1.1 days for the transperitoneal group, p = 0.02). However, this study found no significant difference between the groups in terms of total duration of hospitalization (p = 0.72); this was also the case in Akladios and al. Study (p = 0.49) [21].

Our database did not contain information regarding the extent of the lymphadenectomy performed. However, this should not represent a bias, since in their 2016 study on the management of locally advanced cervical cancers, Petitnicolas and al. Found no difference between infra-renal PAL and infra-mesenteric PAL in terms of surgical complications [30]. In their study, 18 of 56 patients in the infra-mesenteric group had a postoperative complication versus 19 of 63 patients in the infra-renal group (p = 0.82). The rate of metastases above the inferior mesenteric artery is very low: Leblanc and al. Showed that 15% of patients had positive lomboaortic lymph node metastases, and only one of those was positive above the supra-mesenteric artery [3]. The advantages of PAL over the inferior mesenteric artery and up to the renal vein are debated by surgeons, although the 2018 ESGO recommendations suggest the inferior mesenteric artery as the upper limit for PAL in cervical cancers IB3-IVA [12].

Although no minimum quantity is specified, removal of less than 10 lymph nodes may call into question the quality of the PAL [31], especially since a 2006 randomized study found that lymph node picking could lead to under-staging without reducing the morbidity of the surgical procedure [32]. In our study, we found no difference between the two surgical routes in terms of the number of lymph nodes removed. This result is comparable to that of Dargent and al. [22]. However, the ratio of positive lymph nodes to the total of lymph nodes removed shows a significant difference for the transperitoneal approach. This result should be qualified due to the lack of precision on the extent of the lymphadenectomy in our study.

Our study has certain limitations that should be noted: it is a retrospective study, and during the 19 years of inclusion some changes in medical practices must be considered, in particular the place of PET-CT. Finally, although the multicentric character of the study adds statistical power, it is also a limitation due to differences in the proportions of the two techniques performed in all centers.

### 4. Conclusion

Patients who underwent a transperitoneal PAL did not present with more complications (intra- or postoperative) than those who underwent a retroperitoneal PAL. However, transperitoneal PAL patients had a longer hospital stay than those who underwent lombo-aortic lymphadenectomy by the retroperitoneal route. No significant difference was found between the two types of lumbaraortic lymphadenectomy for advanced cervical cancers (stages IB3 to IVA) in terms of recurrence-free survival or overall survival.

#### Disclosure

This work received no funding. There was no commercial interest that any author may have in the subject of study and the source of any financial or material support.

#### **CRediT** authorship contribution statement

Marie Pécout: Research and, Investigation, Communication, Writing – original draft, preparation, Conceptualization. Jérôme Phalippou: Writing - review & editing, Communication, Reviewing. Henri Azaïs: Writing - review & editing, Data collection, Reviewing. Lobna Ouldamer: Writing – review & editing, Data collection, Reviewing. Pierre Adrien Bolze: Writing - review & editing, Data collection, Reviewing. Marcos Ballester: Writing review & editing, Data collection, Reviewing. Cyrille Huchon: Writing - review & editing, Data collection, Reviewing. Camille Mimoun: Writing - review & editing, Data collection, Reviewing. Cherif Akladios: Writing - review & editing, Data collection, Reviewing. Lise Lecointre: Writing - review & editing, Data collection, Reviewing. Emilie Raimond: Writing - review & editing, Data collection, Communication, Reviewing. Olivier Graesslin: Writing - review & editing, Data collection, Reviewing. Xavier Carcopino: Writing – review & editing, Data collection, Reviewing. Vincent Lavoué: Writing - review & editing, Data collection, Reviewing. Sofiane Bendifallah: Writing – review & editing, Data collection, Reviewing. Cyril Touboul: Writing – review & editing, Data collection, Reviewing. Yohan Dabi: Writing - review & editing, Data collection, Reviewing. Geoffroy Canlorbe: Writing - review & editing, Data collection, Reviewing. Martin Koskas: Writing - review & editing, Data collection, Reviewing. Pauline Chauvet: Writing - review & editing, Data collection, Reviewing. Pierre Collinet: Data collection, Methodology, Reviewing, Writing original draft, Original draft preparation, Supervision. Yohan Kerbage: Data collection, Visualization, Supervision, Investigation, Conceptualization, Methodology, Reviewing, Original draft preparation, Writing – original draft.

#### **Declaration of competing interest**

This work received no funding. There was no commercial interest that any author may have in the subject of study and the source of any financial or material support.

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