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Pretherapeutic staging of locally advanced cervical cancer: Inframesenteric paraaortic lymphadenectomy accuracy to detect paraaortic metastases in comparison with infrarenal paraaortic lymphadenectomy

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HIGHLIGHTS

- Inframesenteric paraaortic lymphadenectomy seems to be effective in cervical cancer
- Pathological subtype (glandular or squamous) should not influence surgical decision
- Survival rate results are still pending and are eagerly awaited.

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ABSTRACT

Background. Extended-field chemoradiation therapy is usually performed in patients with locally advanced cervical cancer (LACC) and paraaortic (PA) node metastases. Considering the very low rate of skip metastases above inferior mesenteric artery, ilio-inframesenteric paraaortic lymph node dissection (IM-PALND) seems to be an adequate pattern of PALND. Our objective was to assess the accuracy of this management to determine PA nodal status in comparison with infrarenal paraaortic lymphadenectomy (IR-PALND) in case of squamous or glandular cervical cancer.

Methods. All patients with LACC and negative MRI and PET/CT imaging at paraaortic level had laparoscopic staging (followed, if negative, by extraperitoneal paraaortic lymphadenectomy). From January 2011 to September 2015, patients who had IM-PALND were included and were compared to a previous historical series of IR-PALND patients. The two groups differed only at the upper level of dissection. Characteristics of nodal involvement at paraaortic level depending on level of dissection, PET/CT imaging and histology were studied.

Results. 119 women were included in our study, with 56 patients in the IM-PALND group and 63 in the IR-PALND group. In the IM-PALND group, fewer nodes were resected ($p < 0.001$). There was no difference between the two groups regarding nodal status at paraaortic level ($p = 0.77$). Patterns of nodal involvement were similar whichever the histological subtype of cervical cancer (squamous or glandular).

Conclusion. IM-PALND appears to be equally effective to assess paraaortic nodal involvement in LACC for both histological subtypes – glandular and squamous carcinomas – and to select patients for extended-field chemoradiation therapy.

1. Introduction

Cervical cancer is one of the most common female neoplasia worldwide [1]. Its management is principally based on clinical tumor staging, as recommended by the International Federation of Gynecology and Obstetrics (FIGO) classification (revised in 2009) [2]. A tumor measuring more than four centimeters in greatest diameter without distant

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metastasis (FIGO stage ≥ IB2 up to IVA) is generally defined as locally advanced cervical cancer (LACC) [3]. Pelvic or extended-field chemoradiation therapy (CRT) followed by cervico-vaginal brachytherapy is the most usual management for these patients worldwide [4,5].

Paraaortic (PA) nodes involvement concerns approximately 15% of LACC cases [6]. Prognosis of patients presenting with PA node metastases has been significantly improved by use of extended-field CRT, but with an increased risk of bowel and/or hematologic toxicities [7]. Thus, proper patient selection for this indication is expected. If current morphologic (MRI and/or CT scan) or metabolic (PET/CT) imaging methods are efficient to diagnose macroscopic metastases [8], they prove to be less accurate when considering low volume nodal metastases [9–13]. In this situation, when imaging is negative or suspicious, surgery remains the best means to definitively detect nodal disease.

In the past, laparotomy was used to assess PA node status [8] but morbidity was significant. Since the early 90', it has been shown that laparoscopy was as efficient as laparotomy, with better outcomes, and, due to less postoperative adhesion formation, reducing the risk of radio-induced complications of CRT [14].

Laparoscopic paraaortic lymph node dissection (PALND) consists in the removal of nodes located from the common iliac nodes up to the left renal vein [15]. There is ongoing debate among surgeons on limiting nodes removal either to the inferior mesenteric artery (IMA), or to the right gonadal vein, or to the left renal vein [16–18]. Indeed, in cervical cancer, nodal metastases evolution is a step-by-step and orderly process occurring *via* the lymphatic route [19]. A recent prospective study confirmed that there is a very low rate of skip metastases above IMA [6]. Thus, ilio-inframesenteric dissection should be an adequate pattern for PALND.

If – this being probably due to size of the series – inframesenteric PALND (IM-PALND) failed to show a reduction in morbidity, it significantly reduced technical difficulty and operating time compared to infrarenal PALND (IR-PALND) [20]. Nevertheless, it remained necessary to confirm that IM-PALND was equivalent to IR-PALND to detect PA nodes involvement.

The objective of this paper was to compare the accuracy of IM and IR-PALND to detect PA node metastases, whatever the histological subtype of cancer (glandular or squamous cervical cancer).

2. Material and methods

All patients diagnosed with LACC (FIGO stage IB2-IVA) were submitted to a pretherapeutic imaging workup combining lombo-pelvic MRI and hybrid PET/CT. Patients without any suspicious PA node or hotspot above the level of external iliac vessels were offered a surgical laparoscopic staging and were included in the present study. Patients in a poor state of health (ASA ≥ 3) and/or aged (≥75 years old) or morbid obesity (BMI > 50) were excluded.

The study was approved by our local ethics committee and all patients had signed an informed consent for the use of their data.

Whatever the upper limit of PA node dissection, the surgical staging started with a diagnostic transperitoneal laparoscopy to rule out any occult peritoneal carcinomatosis that would preclude any nodal assessment. If normal, PALND was performed using a laparoscopic extraperitoneal approach, as previously described [21]. Lymphadenectomy included the removal of all latero-aortic, pre-aortic, inter-aorto-caval, pre-caval and latero-caval nodes. The inferior limit of dissection was both common iliac bifurcations, while the superior limit was IMA for the IM-PALND group and the left renal vein for the IR-PALND group.

We retrospectively identified the patients from our database (Clinsight™) and we collected anonymous data using computer medical records. IM-PALND patients were compared to a previous historical series of IR-PALND patients. Tumor features were recorded according to histological subtype, size, FIGO stage and lympho-vascular space invasion.

We recorded data from preoperative imaging (MRI and PET/CT scan) and pathological nodes examination.

Patients' characteristics were summarized using the following descriptive methods: mean, standard deviation, median and range for continuous parameters, and frequency and percentage for categorical parameters. The groups were compared using Chi-squared test for categorical variables or Fisher's exact test in the case of small counts. Regarding continuous variables, the Student *t*-test was performed if conditions for application were met. Otherwise the non-parametric Wilcoxon Mann-Whitney test was used. A $p < 0.05$ was statistically significant. The data were collected in *Ennov clinical™*, software specifically designed for database management. Statistical analyses were performed using Stata v13.1 (StataCorp 2013, Stata Statistical Software, Release 13, StataCorp LP, College Station, TX, USA).

3. Results

From January 2011 to September 2015, 119 women fulfilling inclusion criteria were included in our study, with 56 patients in the IM-PALND group and 63 in the IR-PALND group. The two cohorts of patients (IM-PALND group and IR-PALND group) were comparable in terms of numbers and on several parameters (age, BMI, performance status, tumor size, lympho-vascular space invasion, preoperative FIGO stage and histological subtype).

One patient was initially diagnosed with IA1 stage cervical cancer but she presented with vaginal recurrence five years after initial treatment, which led to perform ilio-PALND. Patients who had been included in the study with IB1 stage tumor presented with pelvic lymph node involvement at pelvic surgical staging or on pelvic PET/CT scan. No patient had any history of chemotherapy or radiotherapy related to cervical cancer management before performing lymphadenectomy. Only smokers were more frequent in the IR-PALND group ($p < 0.05$) (Table 1). There

Table 1
Population characteristics.

	IM LND	IR LND	p
	N = 56 (%)	N = 63 (%)	
Median age, years (range)	47.5 (28–73)	47 (30–72)	0.59
Median body mass index (range)	24.7 (15.9–53.8)	25.6 (17.8–49.5)	0.85
Co-morbidity	21 (37.5)	34 (54.0)	0.07
Smoking	5 (8.9)	14 (22.2)	<0.05
Other cancer	2 (3.6)	2 (3.2)	1.00
Cardiovascular	10 (17.9)	16 (25.4)	0.32
Diabetes	2 (3.6)	3 (4.8)	1.00
Neurologic	2 (3.6)	2 (3.2)	1.00
Respiratory	1 (1.8)	3 (4.8)	0.62
Hepatic	–	2 (3.2)	0.50
Others	5 (8.9)	5 (7.9)	0.85
Performance status WHO score			
0	53 (94.6)	59 (93.7)	0.50
1	3 (5.4)	2 (3.2)	
2	–	2 (3.2)	
Histologic subtype			
Squamous	42 (75.0)	44 (69.8)	0.80
Glandular	12 (21.4)	15 (23.8)	
Others	2 (3.6)	4 (6.4)	
- Adenosquamous	1 (1.8)	3 (4.8)	
- Glassy cell carcinoma	1 (1.8)	0 (0)	
- HSIL	0 (0)	1 (1.6)	
Median MRI tumor size (range)	50 (26–120)	50 (24–80)	0.79
Lympho-vascular space invasion	5/21 (23.8)	5/15 (33.3)	0.71
FIGO staging classification			0.31
IA1	1 (1.8)	–	
IB1	5 (8.9)	4 (6.3)	
IB2	17 (30.4)	26 (41.3)	
IIB	25 (44.6)	24 (38.1)	
IIIA	2 (3.6)	–	
IIIB	4 (7.1)	7 (11.1)	
IVA	2 (3.6)	–	
IVB	–	2 (3.2)	

Table 2
Pre-operative PET/CT characteristics.

	IM (N = 56)	IR (N = 63)	p
PET/CT (n (%))	50/54 (92.6)	54/56 (96.4)	0.43
Positive in right pelvic lymph nodes	5/50 (10)	14/54 (25.9)	–
Positive in left pelvic lymph nodes	8/50 (16)	15/54 (27.8)	–
Positive in pelvic lymph nodes (right and left)	10/50 (20)	19/54 (35.2)	0.08
Positive in right iliac lymph nodes	1/50 (2)	4/54 (7.4)	–
Positive in left iliac lymph nodes	2/50 (4.0)	3/54 (5.6)	–
Positive in iliac lymph nodes (right and left)	2/50 (4.0)	5/54 (9.3)	0.44
Positive in IM para-aortic lymph nodes	1/50 (2)	5/54 (9.3)	–
Positive in SM para-aortic lymph node	0/50 (0)	4/54 (7.4)	–
Positive in para-aortic lymph nodes	1/50 (2)	6/54 (11.1)	0.11
Negative in para-aortic and pelvic lymph nodes	40/50 (80)	34/54 (63)	0.06

Positive PET/CT = abnormal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
Negative PET/CT = normal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
IM = infra mesenteric.
SM = supra mesenteric.
IR = infra renal.

was no difference in time duration between diagnosis (biopsy) and lymphadenectomy (median time in month was 1.4 [0–62.5] in the IM-PALND group *versus* 1.5 [0.3–49.1] in the IR-PALND group; p = 0.91).

Details of preoperative PET/CT results at pelvic and iliac levels are presented in Table 2. 40 patients (80%) and 34 patients (63%) in the IM-PALND group and the IR-PALND group respectively (p = 0.06) had no evidenced disease in either the pelvic or para-aortic nodes.

3.1. Pathological examination of paraaortic lymph node removal

As expected, fewer nodes were resected in the IM-PALND group (13.6 ± 6.3 in the IM-PALND group *versus* 23.7 ± 9.1 in the IR-PALND group; p < 0.001). No difference between the two groups was shown concerning the numbers of metastatic lymph nodes. There was no difference between the two groups regarding nodal status at paraaortic level (para-aortic positive lymph nodes 17.9% in the IM-PALND group *versus* 15.9% in the IR-PALND group; p = 0.77) (Table 3).

3.2. Histological subtypes

Tables 4 and 5 summarize LND results and PET/CT imaging data with IM-PALND *versus* IR-PALND groups or glandular *versus* squamous cervical cancer populations comparisons. Results presented in Table 5 show that patterns of lymph node involvement are similar whichever the histological subtype of cervical cancer. Six patients were excluded from comparison between glandular carcinoma and squamous carcinoma as they presented with other histological subtypes of cancer. Patients presenting with adenosquamous carcinomas were excluded only from the analysis comparing glandular *versus* squamous carcinomas as we could not include those cases in one of the two groups.

Table 3
Lymph nodes characteristics.

	IM (N = 56)	IR (N = 63)	p
	n (%)	n (%)	
Lymphadenectomy para-aortic	56/56 (100)	63/63 (100)	
Positive lymph nodes	10/56 (17.9)	10/63 (15.9)	0.77
Total number of para-aortic lymph nodes	N = 56	N = 62	
Median – [range]	13 [4–37]	21 [9–46]	
Mean	13.6 ± 6.3	23.7 ± 9.1	<0.001
Total number of positive para-aortic lymph nodes	N = 10	N = 10	
Median – [range]	2 [1−22]	5 [1−10]	
Mean	4.9 ± 6.7	5.2 ± 3.8	0.40

Table 4
Lymph nodes, PET/CT and histological subtypes characteristics.
Level of LND comparison.

	IM (N = 56)	IR (N = 63)	p
	n (%)	n (%)	
All population (squamous ± glandular)			
PALND+	10/56 (17.9)	10/62 (16.1)	0.80
PET/CT+ in PLN	10/50 (20)	19/53 (35.8)	0.07
PALND+/PET/CT+ in PLN	2/10 (20)	6/19 (31.6)	0.51
PALND+/PET/CT− in PLN	6/40 (15)	4/34 (11.8)	0.75
Squamous population			
PALND+	7/42 (16.7)	8/43 (18.6)	0.82
PET/CT+ in PLN	8/37 (21.6)	15/37 (40.5)	0.08
PALND+/PET/CT+ in PLN	2/8 (25)	5/15 (33.3)	1.00
PALND+/PET/CT− in PLN	3/29 (10.3)	3/22 (13.6)	1.00
Glandular population			
PALND+	3/12 (25)	2/15 (13.3)	0.63
PET/CT+ in PLN	2/11 (18.2)	2/13 (15.4)	1.00
PALND+/PET/CT+ in PLN	0/2 (0)	1/2 (50)	1.00
PALND+/PET/CT− in PLN	3/9 (33.3)	1/11 (9.1)	0.29

Positive PET/CT = abnormal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
Negative PET/CT = normal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
IM = infra mesenteric.
IR = infra renal.
LND = lymph node dissection.
PALND = para-aortic lymph node dissection.
PLN = pelvic lymph nodes.

In squamous and glandular cervical cancer populations, there was no statistical difference in the number of positive lymphadenectomies between IR-PALND and IM-PALND (Table 4). In the squamous cell carcinoma population, there were 16,7% of positive paraaortic lymphadenectomies in the IM-PALND group *versus* 18.6% in the IR-PALND group (p = 0.82). In the glandular population, there were 25% of positive paraaortic lymphadenectomies in the IM-PALND group *versus* 13.3% in the IR-PALND group (p = 0.63).

Regarding IM-PALND patients, there was no difference in the number of patients with positive paraaortic LND in the squamous (16.7%) *versus* glandular (25%) cervical cancer subgroups (p = 0.67). The same results were observed among IR-PALND patients, with 18.6% of positive paraaortic LND in the squamous cell carcinoma population *versus* 13.3% in the glandular population (p = 1).

Table 5
Lymph nodes, PET/CT and surgery subtype characteristics.
Histological subtypes comparison.

	Squamous tumor (N = 86)	Glandular tumor (N = 27)	p
	n (%)	n (%)	
All patients (IM ± IR)			
PALND+	15/85 (17.7)	5/27 (18.5)	1.00
PET/CT+ in PLN	23/74 (31.1)	4/24 (16.7)	0.17
PALND+/PET/CT+ in PLN	7/23 (30.4)	1/4 (25)	1.00
PALND+/PET/CT− in PLN	6/51 (11.8)	4/20 (20)	0.45
IM patients			
PALND+	7/42 (16.7)	3/12 (25)	0.67
PET/CT+ in PLN	8/37 (21.6)	2/11 (18.2)	1.00
PALND+/PET/CT+ in PLN	2/8 (25)	0/2 (0)	1.00
PALND+/PET/CT− in PLN	3/29 (10.3)	3/9 (33.3)	0.13
IR patients			
PALND+	8/43 (18.6)	2/15 (13.3)	1.00
PET/CT+ in PLN	15/37 (40.5)	2/13 (15.4)	0.17
PALND+/PET/CT+ in PLN	5/15 (33.3)	1/2 (50)	1.00
PALND+/PET/CT− in PLN	3/22 (13.6)	1/11 (9.1)	1.00

*Positive PET/CT = abnormal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
**Negative PET/CT = normal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
IM = infra mesenteric.
IR = infra renal.
PALND = para-aortic lymph node dissection.
PLN = pelvic lymph nodes.

4. Discussion

This article presents results from one of the largest cohorts of patients assessed by exclusive inframesenteric lymphadenectomy in the pretherapeutic surgical staging of locally advanced cervical cancer with no evidence of metastasis above external iliac vessels. IM-PALND appears to be as effective as IR-PALND to assess paraaortic nodal involvement in LACC for both histological subtypes, *i.e.* glandular and squamous carcinomas, and to select patients who may require extended-field chemoradiation therapy.

According to Ramirez et al., when pelvic and para-aortic nodes are negative on preoperative PET/CT, the rate of positive para-aortic nodes at the time of extraperitoneal laparoscopic staging was 12%. However, when positive pelvic nodes were noted on preoperative imaging, the rate increased to approximately 25% [22]. In our institution, para-aortic LND is performed in case of negative para-aortic nodes on preoperative PET/CT, whatever the result of pelvic lymph node on PET/CT. In case of doubt about lymph node positivity at the para-aortic level due to low standardized uptake value (SUV) at PET/CT examination or due to clinical circumstances (for example one case of tuberculosis which may explain a false positive para-aortic PET/CT), the multidisciplinary committee of our institution could have maintained the indication to perform a surgical staging. Those situations explain the present cases with positive lymph node at the para-aortic level on PET/CT.

The goal of operative staging is not to increase survival. Nevertheless, it can allow tailored management by selecting patient with paraaortic involvement that may benefit from extended-field CRT, as prophylactic extended-field radiation therapy has been abandoned due to increased toxicity and no survival advantage following the results from several randomized trials [23]. In the 6th edition of Berek & Hacker's Gynecologic Oncology [24], the plan for management for advanced cervical cancer is described as follows: "All patients are subjected to a PET/CT scan. Patients with proven positive para-aortic nodes are given extended-field radiation with weekly cisplatin 30 to 40 mg/m^2, and all other patients are given pelvic chemoradiation. Pretreatment identification of positive para-aortic nodes is important so that extended-field radiation can be given. Distant spread remains a problem for this group of patients but a significant proportion with positive paraaortic nodes can be salvaged." Our patients have been managed following those recommendations and even knowing the risk for distant metastasis, patients with nodal involvement at para-aortic level may benefit from extended-field CRT.

It remains true that surgical staging may be responsible for complications, in particular laparotomy that increases radiation complications. Laparoscopy and extra-peritoneal approaches have to be preferred in order to improve tolerance and decrease morbidity [14]. Surgical staging should be performed by trained teams and laparotomy should be avoided. In our experience, surgical staging performed by extra-peritoneal laparoscopic approach is associated with an acceptable complication rate [20] and this approach should never delay extended-field CRT treatment.

Given the simplification of the surgical procedure which goes faster to perform than IR-PALND [20] and the potential reduction in terms of serious morbidity which is still expected, IM-PALND appears as an attractive option compared to IR-PALND in the pretherapeutic staging of LACC.

It was mandatory to prove the efficiency of IM-PALND to detect paraaortic nodal involvement. As expected, the average number of lymph nodes removed during IM-PALND was less than with the IR approach. Nevertheless, there were no differences in terms of number in patients presenting with nodal metastases at the paraaortic level between the two groups. Thus, IM-PALND would select the same numbers of patients who would benefit from extended-field chemoradiation therapy. This is consistent with our previous study showing a very low rate of skip metastases above IMA level in case of negativity of preoperative PET/CT imaging [6].

In cervical cancer, squamous cell carcinoma is the most frequent histological type compared to adenocarcinomas [25]. Although it seems that squamous cell carcinomas or adenocarcinomas of the cervix are at the same risk for paraaortic metastases, we wanted to ensure that an IM-PALND procedure may be applicable for both squamous and glandular cancers without increased risk of understaging. Data published by Schim et al. revealed that stage, SCC antigen, tumor size on MRI, pelvic lymph node metastasis on PET/CT, and paraaortic lymph node metastasis on PET/CT were significantly associated with paraaortic lymph node metastasis (univariate analysis). After a bootstrap resampling procedure with 1000 repetitions, their final model yielded two statistically significant predictors: tumor size and paraaortic lymph node metastasis on PET/CT. In their experience, there were no difference in terms of nodal involvement between adenocarcinomas and squamous cell carcinomas [26].

The originality of the present study was to compare the results obtained in two histological subgroups – squamous cervical cancer and glandular cervical cancer. We did not observe any differences between these two groups concerning nodal involvement at pelvic or paraaortic level regarding PET/CT results. Those findings are consistent with Schim et al. [26]. The 2013 study by Yang et al. showed that cervical adenocarcinoma increased the risk of lymph node metastases [27]. We did not confirm this result in our population.

Pathological status seems to be a significant predictor of overall survival in patient with IB-IIB cervical cancer [28]. A longer follow-up is needed to assess the true impact of IM-PALND compared to IR-PALND on recurrence-free and overall survival rates.

Previous retrospective studies showed a tendency toward survival advantage at resecting microscopic PA nodal metastasis followed by an adequate CRT [8,9,13]. Unfortunately, a first randomized trial failed to demonstrate any advantage in the pretherapeutic surgical staging of LACC [29], leading to consider this practice as experimental [30]. However, the preliminary results of a very recent German randomized trial confirmed the relative safety of a pretherapeutic PA laparoscopic surgical staging of LACC patients [10], with a higher rate of PA positive patients detected in the surgical arm compared to clinical staging only, leading to more extended-field chemoradiation therapy in this group [31]. Today, survival rate results are still pending and are eagerly awaited.

5. Conclusion

Through this series, we can confirm that IM-PALND appears to be as effective as IR-PALND to assess paraaortic nodal status in locally advanced cervical cancer, whatever its pathological subtype (glandular or squamous cell carcinoma). Cervical cancer histological subtype should not influence surgical decisions regarding para-aortic lymph node dissection strategies among patients with negative PET/CT imaging at paraaortic level.

Conflict of interest

None.

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