

# Para-aortic workup in locally advanced cervical cancer: heterogeneity is still the rule. Results from a retrospective multicenter study

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## Abstract

**Purpose** We retrospectively studied the different strategies of para-aortic (PA) staging of patients with PA involvement in locally advanced cervical cancer as conducted in eight centers in France and their impact upon survival and management.

**Methods** All patients enrolled in this multicenter study presented with cervical cancer with PA involvement. The diagnosis of PA spread was based on imaging assessment of the PA area and/or pathological examination of harvested PA lymph nodes when staging lymphadenectomy was performed. Imaging modalities comprised positron emission tomography (PET), magnetic resonance imaging and/or computed tomography. Survival outcomes were evaluated retrospectively.

**Results** One hundred and fifteen women were retrospectively studied. Radiological staging was conducted in 101 (87.8 %) patients. PET was performed in 66 patients (57.4 %). Its FN rate was 22.7 % (15/66) and its sensitivity 77.3 %. Para-aortic lymphadenectomy was conducted in a large proportion of patients (67.8 %). Its indications were not restricted to negative radiological workup. The lymphadenectomy rate was significantly higher in patients with earlier stages ( $p = 0.02$ ) and lower tumor volume ( $p = 0.01$ ). Treatment consisted of chemoradiation therapy with extended-field radiotherapy in all patients, followed by intracavitary brachytherapy in 94 cases (81.7 %) and completion surgery in 69 cases (60 %). Patients without para-aortic metastasis on radiological examination were more likely to receive all treatment modalities ( $p = 0.04$ ).

**Conclusion** Despite established recommendations, our results point out the tremendous heterogeneity regarding para-aortic assessment. These differences in management are perhaps related to a recommended therapeutic strategy that does not appear to improve the poor prognosis associated with PA involvement.

**Keywords** Cervical cancer · Lymphadenectomy · Para-aortic involvement · Para-aortic staging

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## Background

Fifteen to 30 % of patients with locally advanced cervical cancer (LACC) are diagnosed with para-aortic (PA) metastasis [17, 20]. It is thus mandatory to accurately define extra-pelvic spread to tailor adjuvant chemoradiation therapy (CRT) [18, 25]. To date, (18)F-fluorodeoxyglucose positron emission tomography (PET) scanning is the most reliable imaging modality for the detection of microscopic PA involvement [23, 12, 13]. Nevertheless, false-negative results in the PA area have been recorded in 8–13 % patients [2]. Therefore, additive surgical staging may be beneficial in women with negative PET-CT for the detection of occult PA metastases [2, 14]. It might also provide a therapeutic impact in the subgroup of patients with PA lesions  $\leq 5$  mm [10, 15]. However, a recent meta-analysis failed to demonstrate any benefit associated with pretreatment PA lymph node dissection in the setting of LACC, mostly due to a lack of randomized controlled trials addressing this topic [3, 22]. It is thus unclear whether surgical staging should be achieved in the absence of PA uptake on initial PET-CT imaging.

Herein we aimed to underline the heterogeneity surrounding PA assessment in the setting of LACC, through the evaluation of day-to-day practice in eight gynecologic oncology units.

## Materials and methods

### Study design

This retrospective study included 115 patients suffering from LACC with PA involvement and treated in eight French gynecologic oncology units from August 1999 to August 2012. The study received the agreement of local institutional review board.

### Disease characteristics

Disease was classified according to the 2009 FIGO staging system [19]. All patients had PA involvement at baseline. The diagnosis of PA spread was based on imaging assessment of the PA area and/or pathological examination of harvested PA lymph nodes when staging lymph node dissection was achieved. Imaging modalities comprised PET-CT, MRI and/or CT. The para-aortic lymph nodes were evaluated by PET, MRI or CT according to the established criteria for lymph node detection. The nodes were over one centimeter in size on the CT scan and MRI. On PET images, nodes in the para-aortic area were considered suggestive of abnormality if, during the visual

interpretation, they exhibited FDG uptake above background uptake.

### Patterns of treatment

All patients received CRT with extended-field radiation (EFR). EFR delivered 45 Gy to the pelvis and PA area over 5 weeks at 1.8 Gy per fraction, using a four-field arrangement. Concurrent cisplatin chemotherapy (40 mg/m<sup>2</sup>) was given weekly on days 1, 8, 15, 22 and 29.

Intracavitary brachytherapy consisted of 15 Gy (patients with surgery) or 22 Gy (patients without surgery). It was delivered in patients with neither tumor progression nor local contraindications (vaginismus, genital tract malformations, uterine perforation).

Partial response to treatment systematically led to completion surgery. In patients achieving complete response, surgery was not performed routinely.

### Statistical analysis

All analyses were performed using Stata Statistical Software<sup>®</sup> release 11.2 (Stata Corporation, CollegeStation, TX). Rates of lymphadenectomy have been compared according to FIGO stage, tumor volume and detection of pelvic nodes on imaging workup, using Chi-square or Fisher exact tests. Overall survival (OS) was computed from the date of initial diagnosis. The OS function has been estimated applying the Kaplan–Meier method. We used a log-rank test to compare the OS according to lymphadenectomy. All variables with  $p < 0.05$  on univariate analysis were included in this model. All statistical tests were two-sided and differences were considered statistically significant when  $p < 0.05$ .

## Results

### Demographics

One hundred and fifteen patients were observed. The main pathology type was squamous cell carcinoma (82.6 %). Most tumors had a volume greater than 41 mm (73.9 %) (Table 1).

### Patterns of PA staging

A radiological workup of PA area was conducted in 101 patients (87.8 %) and concluded in PA spread in 67 cases (66.3 %). PET was performed in 66 patients (57.4 %). Its FN rate was 22.7 % (15/66) and its sensitivity 77.3 %. MRI was performed in 92 patients (80.0 %). MRI FN rate

**Table 1** Demographics

Characteristics	<i>n</i>	%
Histological type		
Squamous cell	95	82.6
Adenocarcinoma	20	17.4
FIGO stage		
IB1	6	5.2
IB2	15	13.0
IIA	5	4.3
IIB	54	47.0
IIIA	8	7.0
IIIB	16	13.9
IVA	8	6.9
IVB	3	2.6
Tumor diameter		
20–40 mm	30	26.1
41–60 mm	60	52.2
>60 mm	25	21.7

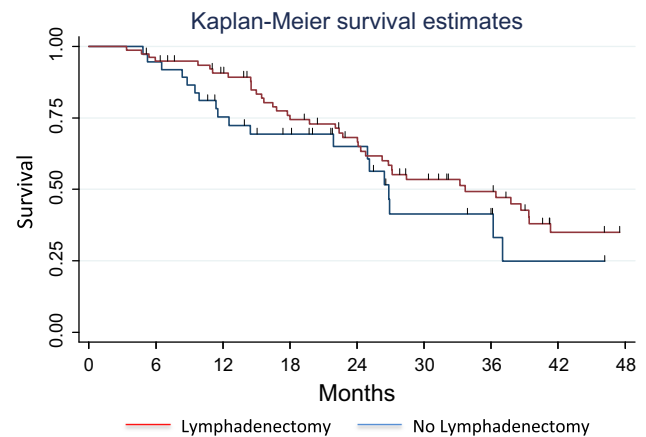
and sensitivity were 67.4 and 32.6 %, respectively. PA investigation was exclusively based on conventional imaging in 11 patients (seven by MRI and four by CT scanning), all treated before 2001. Metastasis volume was greater than 1 cm in all cases.

Exclusive surgical assessment was achieved in 14 women (12.2 %). These patients, referred before 2001, did not benefit from PET-CT workup. PA surgical staging was performed because of pelvic lymph node invasion on MRI. Seventy-eight patients (67.8 %) underwent surgical staging. All lymphadenectomies were carried out by laparoscopy, in the same way in all centers, based on surgical practice guidelines: up to the left renal vein, the lateral aortic, pre-aortic precaval, interaortico-caval, lateral caval nodes, and the nodes of promontory.

Pathological examination concluded on PA microscopic involvement (tumor burden <2 mm) in four patients (5.1 %). We observed a trend toward improved survival outcomes in patients who underwent surgical staging, but the difference did not reach statistical significance ( $p = 0.31$ ) (Fig. 1).

### Pelvic features of cancer modulate indication for surgical staging

The lymphadenectomy rate was significantly higher in patients with earlier stages ( $p = 0.02$ ) and lower cervix tumor volume ( $p = 0.01$ ) (Table 2). Surgical staging was required more often in patients presenting with pelvic nodal involvement (PN+) on imaging workup (69 % were PN+ while 48.3 % had no pelvic nodal involvement,  $p = 0.05$ ) (Table 3).

**Fig. 1** Overall survival according to surgical staging ( $p = 0.31$ )**Table 2** Incidence of surgical staging according to tumor characteristics

	Lymphadenectomy				<i>p</i>
	No ( <i>n</i> = 37)		Yes ( <i>n</i> = 78)		
	<i>n</i>	Row (%)	<i>n</i>	Row (%)	
FIGO stage					
IB1, IB2, IIA	5	19.2	21	80.8	0.02*
IIB, IIIA	18	29.0	44	71.0	
IIIB, IVA	12	48.0	13	52.0	
IVB	2	100.0	0	0.0	
Tumor volume					
20–40 mm	5	16.7	25	83.3	0.01†
41–60 mm	18	30.0	42	70.0	
>60 mm	14	56.0	11	44.0	

\* Fisher exact test

† Chi-square test

**Table 3** Incidence of surgical staging according to pelvic nodes

	Lymphadenectomy				<i>p</i>
	No ( <i>n</i> = 37)		Yes ( <i>n</i> = 64)		
	<i>n</i>	Row (%)	<i>n</i>	Row (%)	
Positive pelvic nodes (radiologic workup, <i>n</i> = 101)					
No	15	51.7	14	48.3	0.05*
Yes	22	30.6	50	69.4	

\* Chi-square test

### Impact of PA workup on treatment pattern

Treatment consisted in CRT with EFR in all patients, followed by intracavitary brachytherapy and completion surgery in 94 (81.7 %) and 69 cases (60 %), respectively.

Patients without PA metastasis on radiological examination (PAN−) were more likely to receive all treatment modalities (74 vs. 42 % in PAN+ patients,  $p = 0.04$ ).

## Discussion

Our results point out the tremendous heterogeneity regarding para-aortic assessment in patients with locally advanced cervical cancer. Multicenter design and long study period (1999–2012) have undeniably contributed to heterogeneous assessment, but such finding is also explained by the fact that surgical staging is recommended but not mandatory according to French national guidelines.

In our study, PA lymphadenectomy was conducted in a large proportion of patients (67.8 %). Its indications were not restricted to negative radiological workup. PET-CT imaging is currently an option in the workup of lymphatic spread in LACC [1, 11, 26]. PA surgical staging contributes to optimal definition of radiation fields whenever PET scan has not shown any uptake in PA area [15]. In addition, as its therapeutic impact has never been demonstrated by a prospective study, several patients who had positive PA lymph nodes on PET scan did not undergo surgical staging. However, few practitioners, carried out lymphadenectomy in spite of a positive para-aortic PET scan (5 % of patients in our study), considering that it was likely to be of therapeutic benefit [7].

We have also observed a trend toward better survival outcomes in patients with surgical staging, but not significantly ( $p = 0.31$ ). This would not be attributed to a possible therapeutic role but rather that surgical staging was generally carried out in patients with small tumor volume and a less advanced disease stage (Table 2). Although there is a lack of literature data on this subject, this further accounts for the heterogeneity of staging within a given center. Some practitioners considered that patients with advanced-stage cancer and/or large tumor volume as well as PA involvement had disease that was already too advanced for them to benefit from a non-obligatory surgical procedure of unproven therapeutic value, unlike patients who had received a less aggressive or less « complete » range of treatments [5]. Once again, currently there are no relevant data in the literature, but it is important to emphasize that differences in management are perhaps related to a recommended therapeutic strategy that does not appear to improve the poor prognosis associated with PA involvement [4]. These differences highlight the current debate surrounding PA lymphadenectomy in the era of PET. To date, only one randomized trial has compared surgical staging vs. clinical assessment by conventional imaging, and it showed a significant increase in OS and DFS in the clinical arm [23]. However, flaws in design and the small-

sized study population (61 patients) considerably reduced the strength of the conclusions. Lymph node evaluation in the clinical arm was based on CT scan and MRI, which have low sensitivity for recognition of nodal involvement [15, 24]. In our cohort, the sensitivity of MRI for PA spread was 32.6 %.

Among imaging modalities, PET is the most reliable technique for detection of microscopic nodal involvement. However, its sensitivity is hindered by spatial resolution limitations [26], leading to a risk of undertreatment [27]. We observed a false-negative rate (FNR) of 22.7 %, including four cases of microscopic metastasis. In the literature, overall FNR for PA status ranges from 5 to 17 % [8]. However, FNR is greater, from 20 to 25 % (overall 22 %), when pelvic nodes show uptake of FDG. Our results are consistent with these data by demonstrating that surgical staging was required more often in patients presenting with pelvic nodal involvement (PN+) on radiological workup (69 % were PN+ while 48.3 % had no pelvic nodal involvement (PN−) ( $p = 0.05$ ) [16].

Moreover, some studies have shown that patients with PA metastasis  $\leq 5$  mm detected on pathological examination of harvested nodes have the same survival as women without PA involvement [9, 21]. Conversely, survival of patients with PA metastasis larger than 5 mm remains poor, despite the use of EFR [9]. Indeed, these patients with para-aortic lymph node micrometastasis who received EFR after surgical staging had a same survival as women without para-aortic involvement. So, staging surgery remains evident in women with no PA uptake of FDG, to adapt the extent of radiotherapy [8]. Further trials will determine whether tailored CRT after staging lymphadenectomy will improve survival [6].

However, this interest remains highly controversial in patients with positive FDG because of the poor prognosis of para-aortic lymph node detecting by imagery [18], associated with the lack of therapeutic benefit established.

Our study has limits. The main one is probably that it is a retrospective, and observational study. Multicenter design and long study period (1999–2012) have undeniably contributed to heterogeneous assessment but it reflects the reality of practices in eight centers in France.

In conclusion, our results point out the tremendous heterogeneity regarding para-aortic assessment in LACC. These differences in management are perhaps related to a recommended therapeutic strategy that does not appear to improve the poor prognosis associated with PA involvement.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest, and they have no financial relationship with the organization that sponsored the research.

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