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Added value of para-aortic surgical staging compared to ^{18}F-FDG PET/CT on the external beam radiation field for patients with locally advanced cervical cancer: An ONCO-GF study

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ABSTRACT

Objective: Extended field chemoradiation is recommended for patients with locally advanced cervical cancer (LACC) and para-aortic lymph node (PALN) metastases. The radiation planning may be based on PET/CT while others recommend to rely on surgical staging. We report the rate of patients for whom the radiation field defined on PET/CT was modified by the histological PALN status.

Methods: Between March 2010 and December 2016, 168 consecutive patients with LACC underwent a pre-therapeutic PET/CT and PALN dissection. The data were reviewed retrospectively. The diagnostic performance of the PET/CT for definition of PALN status was calculated. We determined the percentage of patients for whom PALN dissection altered the external beam radiotherapy (EBRT) field defined on the PET/CT basis.

Results: Of 151 patients with negative PALNs on PET/CT, 26 had histological PALN metastases. Of 17 patients with positive PALNs on PET/CT, 9 were negative on histology of which 7 were located in the common iliac region. Sensitivity, specificity, positive and negative predictive value of PET/CT were 23.5, 93.3, 47.1 and 82.8% respectively. In total, 35 out of 168 patients underwent EBRT - field adaptation (pelvic vs extended field). The rate of radiation field modification (27,7%) was particularly high in the subgroup of patients with metastatic pelvic lymph nodes (PLNs) on PET/CT.

Conclusion: Para-aortic surgical staging contributes significantly to individualize the radiation treatment of patients with LACC, particularly for those with positive PLNs at PET/CT. Indication of surgical staging deserves particular attention when the PET/CT suggests positive LNs in the common iliac region.

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Abbreviations: ONCO-GF, Gynecological Working Group from the GGOLFB (Groupement des Gynécologues Obstétriciens de Langue Française de Belgique).

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Introduction

Platinum based concomitant pelvic field chemoradiation followed by image guided adapted brachytherapy (IGABT) is the treatment of choice for patients with locally advanced cervical cancer (LACC) (FIGO ≥1B2 − International Federation of Gynaecology and Obstetrics 2009) [1,2]. Para-aortic lymph node (PALN) metastasis are present in 15% (1B2/2B FIGO 2009) to 40% (3B/4 FIGO 2009) of patients with LACC [3]. Extended para-aortic field radiotherapy is proposed to patients with metastatic lymph nodes in that region [1]. A pre-therapeutic fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) demonstrates a high specificity regarding the para-aortic lymph node status but a suboptimal sensitivity particularly for detection of microscopic nodal extension [4,5]. With the aim to confirm a para-aortic nodal status, some centers propose a surgical node dissection while acknowledging the potential morbidity of the procedure [6]. Beyond its potential therapeutic impact, the rate of external beam field modification, either by extension or by reduction, must be cautiously assessed.

We report the results of a multi-institutional retrospective cohort analysis of successive patients with LACC who all benefited from a^{18}F-FDG PET/CT and a para-aortic surgical staging in their pre-therapeutic management. We focus on the proportion of patients for whom the external beam radiation field was modified by the knowledge of the para-aortic surgical staging results.

Materials and methods

Patients

Between March 2010 and December 2016, 168 consecutive patients with LACC were retrospectively identified in seven centers after obtaining institutional ethic committee approval.

Inclusion criteria were: a histologically proven cervical cancer at a FIGO 2009 clinical stage greater or equal to 1B2 [7]. All patients had a pre-treatment ^{18}F-FDG PET/CT demonstrating the absence of distant metastasis. Surgical para-aortic lymph node dissection (PALND) was conducted in all cases.

Pre-therapeutic assessment

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)

Patients fasted for at least 6 h before the intravenous injection of ^{18}F-FDG (120−463 mBq, according to the patient's weight). The mean blood glucose levels at the time of the ^{18}F-FDG injection were 98.61 mg/dl ^{18}F-FDG PET/CT studies were acquired using 3D PET/CT systems after a mean of 67 min of rest and bladder voiding. An unenhanced low-dose CT was performed, followed by a PET emission scan performed from the mid-thigh to the base of the skull. The PET and CT images were visually reviewed by one experiment nuclear medicine physician, unaware of the histologic PALN results and of the patient's outcomes. A positive result was defined as any focus of increased activity corresponding to a lymph node density visualized on the computed tomography.

The para-aortic lymph node boundaries considered were the left renal vein cranially with caudally the external and internal iliac bifurcation.

Surgical para-aortic lymphadenectomy

After having excluded the presence of peritoneal disease, the PALND through minimal invasive surgical approach, aimed at removing all of lymphatic tissue from the aorta, aortocaval space and vena cava. The mean time interval between PET/CT and para-aortic lymph node (PALN) surgical staging was 18 days (1−87). The procedure was performed either through a transperitoneal or a retroperitoneal approach, the decision being left to the surgeon's discretion. The caudal surgical boundary was defined as the bifurcation of the external and internal iliac artery. These anatomical limits were adopted with the aim to harvest lymph nodes located above a planned pelvic EBRT field. Cranially, the dissection was carried up to the inferior mesenteric artery or the left renal vein at its crossing over the abdominal aorta. The decision to limit the dissection to the sub-mesenteric region was adopted in some of the participating centers following the presentation of the French experience [8]. If a macroscopically suspicious lymph node was observed, elective para-aortic adenectomy was performed and submitted to frozen section. The PALN dissection was only continued if the frozen section was negative for metastasis. Pelvic lymphadenectomy was not routinely performed. Per-and post-operative complications were detailed according to the Clavien-Dindo classification [9].

Histological criteria of the analysis of para-aortic lymph nodes

All lymph nodes from the lymphadenectomy were studied individually. Each lymph node was examined microscopically after hematoxylin-eosin (HE) staining without ultrastaging and examined by an experienced pathologist who was blinded to the PET/CT results, to determine whether a metastasis was present. Macroscopic metastasis was defined as > 2 mm tumor deposits with or without capsular effraction. The definition of lymph node micrometastasis was 0.2−2.0 mm and of lymph node interstitial tumor cells (ITC) up to 0.2 mm or fewer than 200 cells as recommended by American Joint Committee on Cancer [10].

Results

Patients characteristics

One hundred and sixty-eight patients fulfilled the inclusion criteria. Table 1 summarizes the characteristics of the enrolled patients. The majority of patients presented with a FIGO 2009 stage 2B (75 out of 168) and squamous cell carcinoma (141 out of 168). Eighty-one patients (48.2%) had infra-mesenteric PALND, the others being dissected up to the left renal vein. The median harvested number of lymph nodes was 18.5 (range, 1−46). Thirty-four patients (20.2%) had histological metastatic PALN of which 73.5% were macroscopic.

Perioperative complications

Two patients (1.1%) showed significant per-operative complications. One patient needed a conversion to laparotomy after a hemorrhage due to a vena cava injury. The other patient suffered ventricular tachycardia and justified interruption of the procedure. In the post-operative period, twenty-two patients (13.1%) presented grade II to IVa complications according to the Clavien-Dindo classification. The majority being lymph related complications (lymphocele, chyle leakage), accounting for up to 6 out of 10 of the grade III/IV adverse events (Table 2).

Diagnostic performance of the PET/CT for detection of para-aortic lymph nodes

The PET/CT reported nodal spread in 84/168 patients (50%), including 67 (79.8%) with pelvic lymph node (PLN) involvement only, 16 (19%) with both PLN and PALN, and 1 (1.2%) with PALN only. Out of the 151 patients with negative PALNs on PET/CT, 26 had histological PALN metastasis (17.2%), including 21 with macroscopic

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Table 1
Clinico-pathological profile of the enrolled patients.

Characteristics		n = 168
Age, years	Mean (Min − Max)	52 (23–84)
BMI, kg/m^2	Mean (Min − Max)	25 (16–41)
FIGO 2009 stage, n (%)	1B2	21 (12.5)
	2A	34 (20.2)
	2B	75 (44.6)
	3A	6 (3.6)
	3B	22 (13.1)
	4A	9 (5.4)
	Unknown	1 (0.6)
Histology, n (%)	Epidermoid	141 (83.9)
	Adenocarcinoma	19 (11.3)
	Other	8 (4.8)
LN metastasis on PET/CT, n (%)		84 (50.0)
PLN metastasis on PET/CT, n (%)		83 (49.4)
PALN metastasis on PET/CT, n (%)		17 (10.1)
MIS, n (%)		166 (98.8)
Surgical PALN staging upper limit, n (%)	Left renal vein	76 (45.2)
	Infra-mesenteric	81 (48.2)
	Unknown	9 (5.4)
	Other	2 (1.2)
Number of harvested PALNs, n (%)		18.51 (1.0–46.0)
Histologic PALN metastasis, n (%)	Mean (Min − Max)	34 (20.2)
Number of histologic PALN metastasis per patient, n (%)	Mean (Min − Max)	2.74 (1.0–13.0)
Size of PALN metastasis, n (%)	Macroscopic	25 (73.5)
	Microscopic	7 (20.6)
	ITC	1 (2.9)
	Unknown	1 (2.9)
Severe per-operative complications, n (%)		2 (1.1)
Post-operative complications Gr II to IVa (Clavien-Dindo), n (%)		22 (13.09)

BMI, body mass index; *FIGO*, International Federation of Gynecology and Obstetrics; *MRI*, magnetic resonance imaging; *PET/CT*, positron emission tomography/computed tomography; *LN*, lymph node; *PLN*, pelvic lymph node; *PALN*, para-aortic lymph node; *MIS*, minimal invasive surgery; *ITC*, interstitial tumor cells.

Table 2
Postoperative complications according to the Clavien-Dindo classification.

Grade II	Infection (antibiotics)	3 (1.8%)
	Transfusion	4 (2.4%)
	Infection and transfusion	3 (1.8%)
	Deep veinous thrombosis/Pulmonary embolus	1 (0.6%)
	Unknown	1 (0.6%)
Grade IIIa	Chylous ascites	1 (0.6%)
	Lymphocoele	2 (1.2%)
	Abscess pelvis	1 (0.6%)
Grade IIIb	Abscess pelvis	3 (1.8%)
	Lymphocoele	1 (0.6%)
Grade IVa	Chylous peritonitis and sepsis	1 (0.6%)
	Chylothorax and cardiac failure	1 (0.6%)
TOTAL		**22/168 (13.09%)**

metastases. When the PLNs were considered metastatic on PET/CT, this percentage increased to 22.4% (15/67), including 12 with macroscopic metastases. Out of the 17 patients with positive PALNs on PET/CT, 9 were considered to be false positive (FP) (52.9%). Seven out of the nine FP PALNs were located in the common iliac region. Sensitivity, specificity, and positive and negative predictive value of PET/CT for the detection of PALN metastasis, were respectively 23.5, 93.3, 47.1 and 82.8%.

Proportion of patients with radiation field adaptation based on the PALN surgical staging results

Pre-operatively, the EBRT field was provisionally planned according to the PET/CT results. Patients with negative PALNs on PET/CT (151 pts/89.9%) were scheduled to receive pelvic field concurrent chemoradiation while those with positive PALNs (17 pts/10.1%) were planned to receive extended-field chemoradiation. After PALND, 35 patients out of 168 (20.8%) had a radiation field adaptation. Twenty-six patients (15.5%) received an adapted extended field radiation, while nine patients (5.3%) had a reduction of their external beam field. The PLN status on PET/CT is of particular interest. Patients with negative PLN had a 14.1% rate of EBRT field modification while those with positive PLN on PET/CT had their external field adapted in 27.7% of cases (23/83) (Table 3).

Discussion

The PALN status is a strong prognostic factor amongst patients with locally advanced cervical cancer [11]. The latest 2018 FIGO staging system allocates a stage 3C2 for patients with para-aortic extension [1]. With the aim to deliver an optimal radiation treatment, several prospective studies as of 1970 have tested the principle of a prophylactic extended field to the para-aortic region but observed a significant rate of radiation-induced bowel morbidity [12]. More recently the principle of systematic extended-field concurrent chemoradiation for patients suffering LACC with radiologically negative para-aortic lymph nodes has been readdressed. Institutional experiences have reported an improved outcome with a controlled morbidity cost in the extended field group [13,14]. However the issue remains a matter of debate. Modern practice favors individualized treatment and concentrates on the pre-therapeutic identification of patients at risk for para-aortic nodal disease. Extended field chemoradiation is then reserved to patients with para-aortic node extension for local control purpose and potential improvement of patient's outcome [15,16].

The ^{18}F-FDG PET/CT is considered to be the imaging of reference to assess lymph node involvement and metastatic disease [17].

Reported sensitivity and specificity of the technique to detect PALN metastases, respectively 75% and 98%, are superior to that of

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Table 3
External beam radiation field adaptation (pelvic to extended/extended to pelvic field).

PLN metastasis ABSENT on PET/CT (85/168 patients)		
PALN status before Sx	**PALN status after Sx**	**Radiation field adaptation 12/85 (14.1%)**
84 PALN negative	11 PALN positive	11/85 (▲12.9%) extended field
1 PALN positive	1 PALN negative	1/85 (▼1.2%) pelvic field
PLN metastasis PRESENT on PET/CT (83/168 patients)		
PALN status before Sx	**PALN status after Sx**	**Radiation field adaptation 23/83 (27.7%)**
67 PALN negative	15 PALN positive	15/83 (▲18.1%) extended field
16 PALN positive	8 PALN negative	8/83 (▼9.6%) pelvic field

PALN, para-aortic lymph node; PLN, pelvic lymph node; Sx, lymphatic surgical staging; PET/CT, positron emission tomography/computed tomography.

the magnetic resonance imaging (MRI) and computed tomography (CT) [18]. However, sensitivity for the detection of low volume para-aortic nodal disease drops to 22% [5]. Also, Gouy et al. [4] report in a meta-analysis a true positive rate of 78% implying a 22% false positive rate. In this context, a minimal invasive para-aortic lymph node dissection has been promoted with the aim to accurately adapt the external beam radiation field based on a definitive histological nodal status. The surgical approach has its own vascular and lymphatic morbidity profile [19]. Its contribution to the individualization on the radiation planning must be compared to that of the PET/CT based approach.

Compared to the literature [4,5], our series presents a lower sensitivity and an inferior positive predictive value for detecting PALN metastases of respectively 23.5% and 47.1%. In practice, 26 out of 151 patients with negative para-aortic nodes on ^{18}F-FDG PET/CT (17.2%) were found to be metastatic on histology, thus getting an adapted extended-field radiation therapy (EFRT) instead of pelvic field. That percentage was more important (18.1%) in the subgroup of patients with metastatic PLNs on PET/CT (Table 3) [20]. To avoid undertreatment, we suggest like most French centers [21] to proceed to PALND when no para-aortic uptake is observed on the ^{18}F-FDG PET/CT. Better local control [15] and reduction of distant metastatic events [22] after EFRT have been reported and support that approach. The potential impact of such treatment algorithm on disease free survival (DFS) and overall survival (OS) remains a matter of debate. Lai et al., in 2003 [23], closed prematurely a randomized controlled trial of 61 patients comparing clinical and surgical para-aortic staging due to a higher rate of local relapse and death in the surgically staged group. Conversely, as others [8,24], Dabi et al. [25] report, that the PALND had an independent positive impact on survival amongst 1447 patients with LACC and no para-aortic lymph metastasis on PET/CT. These findings are in line with those of Gouy et al. [26] in a prospective study of 237 patients supporting a survival benefit of an adapted external beam field

Table 4
Detail of the 7 patients with false positive common iliac lymph nodes.

1	1 left common iliac+ Left PLN +	Inframesenteric PALND, 0+/29 PALNs No PLNs resection	Died Recurrence sacrum	Recurred at the left commun (=presacral, beneath promontorium), region that was not resected.
2	2 left common iliac + Right PLNs +	Inframesenteric PALND, 0+/17 PALNs 0+ PLNs	NED	**FP remains**
3	1 right common iliac + 2 right PLNs + 4 left PLNs +	Inframesenteric PALND, 0+/25 PALNs 4+/7 right PLNs 4+/8 left PLNs	Died Recurrence omentum	Transperitoneal/robotic approach, LN maybe taken in pelvic dissection as presented at iliac bifurcation behind urether between psoas and promontorium.
4	1 left common iliac + No PLNs + General aspecific (+inguinal LN …), super metabolic primary tumor	Inframesenteric PALND, 0+/23 PALNs No PLN resection	NED	**FP remains**
5	2 right common iliac + 1 left PLN +	Inframesenteric PALND, 0+/8 PALNs No PLN dissection	Recurrence Local with planned exenteration	LNs probably not resected. As 1 at L5 and slightly retrocave; other just at iliac bifurcation (or high proximal external iliac) and no pelvic dissection performed.
6	1 left common iliac + 1 left PLN +	Inframesenteric PALND, 0+/19 PALNs 0+ PLNs	Died Diagnosis of pulmonary carcinoma - evolutive	LN probably not resected as common iliac is more pre-sacral located.
7	2 left common iliac + 1 right PLN +	Infrarenal PALND, 0+/5 PALNs No PLN PLNs dissection	No follow-up	**FP remains**

PALN, para-aortic lymph node*; PLN,* pelvic lymph node*; PALND,* para-aortic lymph node dissection; *NED,* no evidence of disease*; LN,* lymph node*; FP,* false positive.

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when para-aortic nodal metastasis less or equal to 5 mm were identified at surgery.

On the other hand, most series report a near optimal specificity (94.2%) for PET/CT in the para-aortic region [5]. Consequently, most centers consider that a PALND should not be considered when para-aortic hypermetabolic foci are diagnosed [4]. In our series however, 9 of the 17 patients (53%) considered as PALN positive on PET/CT were finally exempt of metastasis after surgery. Of particular interest, we observe that 7 of these 9 FP patients were so in the common iliac region (Table 4).

If 3 of those 7 cases (#2,#4,#7) remain FP after careful imaging and histology review, others were questionable. Patients #1 and #6 were positive on PET/CT in the common iliac/presacral region with the likelihood that they were located below the lower margin of surgical staging. Patients #3 and #5 were positive on PET/CT at the junction between the common iliac and the external iliac vessels with the risk that, at the time of surgery, they were considered to be within the future irradiation field and were therefore not dissected. Hence it is possible these lesions are false positive with regard to their location rather than their actual tumor involvement. Even so, the positive predictive value would remain fairly low, i.e. 53.8% [5].

Based on our experience, we suggest that a particular attention must be paid to PET/CT positivity in the common iliac region when discussing the principle of a PALND. A multidisciplinary consensus must define the inferior boundaries of the surgical dissection taking precisely into account the upper limit of the planned pelvic radiation field. In case of hypermetabolic lymph nodes above the aorto-iliac bifurcation, the decision to extend the radiation field or perform a para-aortic lymph node dissection must remain individualized and based on the number and the size of the suspicious lymph nodes [4].

Overall in our series (Table 3), 35 of 168 patients or 20.8% had a radiation-field adaptation. This proportion became even more important (27.7%) when the pelvic lymph nodes were positive on PET/CT. This, in addition to the distant staging, supports using PET/CT in the preoperative work-up of patients with LACC.

Conclusion

Despite its retrospective profile, we consider that the rate of EBRT field adaptation within this group of LACC patients homogeneously assessed (^{18}F-FDG PET/CT and PALND) before treatment supports the practice of a minimal invasive surgical PALND with the aim to adequately individualize our patient's treatment. PET/CT positivity in the common iliac region deserves special attention.

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