

Should Systematic Infrarenal Para-aortic Dissection Be the Rule in the Pretherapeutic Staging of Primary or Recurrent Locally Advanced Cervix Cancer Patients With a Negative Preoperative Para-aortic PET Imaging?

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Background: Extended-field chemoradiation is the usual management of patients with locally advanced cervical cancer (LACC) and para-aortic node metastases (PA pN1). It is efficient but not without morbidity. Assessment of PA lymph node positivity by PA lymphadenectomy is the most accurate method to select the candidates for this treatment. Hence, to clarify the dissection pattern, we wanted to test the true incidence of isolated/skip node metastasis, above the level of the inferior mesenteric artery (IMA).

Materials and Methods: All patients with LACC and negative magnetic resonance imaging and positron emission tomography–computed tomography imaging at the PA level were offered a laparoscopic staging encompassing a diagnostic laparoscopy followed, if negative, by an extraperitoneal PA lymphadenectomy. All nodes were removed from both common iliac bifurcations up to the left renal vein. Node groups, below and above the IMA, were separately sent to the pathologist for definitive examination.

Results: From January 2010 to December 2013, 196 stage IB1 with pelvic pN1, IB2, to IVA LACC patients from 2 cancer centers who fulfilled the criteria were included in this institutional review board–approved study after informed consent. Thirty patients (15%) had PA pN1. Only 1 patient had positive nodes exclusively located above the IMA (3.3% of the pN1 group; 95% confidence interval, 0%–9.7%). Complications were observed in 15 (7.6%) of 196 patients.

Conclusions: Given the very low rate of skip metastases above the IMA and the potential additional morbidity of a systematic extended dissection, a bilateral ilioinframesenteric dissection seems to be an acceptable pattern of PA lymphadenectomy in LACC patients.

Key Words: Cervical cancer, Para-aortic lymphadenectomy, Laparoscopy

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With approximately 527,624 cases in 2012, cervical cancer is the fourth most common cancer in women

worldwide after breast, colorectal, and lung.¹ Locally advanced forms represent 36% to 50% of cases.² This definition

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encompasses large centropelvic tumors (FIGO IB2-IVA) with a risk of involved para-aortic (PA) node ranging from 15% to 35% and earlier tumors (FIGO IA1 with lymph vascular space involvement, IA2, or IB1) with proven positive pelvic nodes for which the risk of PA node positivity ranges from 3% to 5.5%.³ All these patients are usually managed by chemoradiation therapy (CRT).

We join in this indication, PA staging for centropelvic recurrences of cervical carcinoma, potentially curable with a pelvic CRT or exenteration.

Despite the fact that node status is not included in the FIGO staging system of this tumor, its strong prognostic impact is no longer left to be demonstrated and usually triggers important modifications in the management. Indeed, presence of disease in PA nodes is managed by extended-field CRT, up to T12-L1 or at least up to the left renal vein as defined on imaging. Even if this treatment increases cure rates of these patients, significant hematologic toxicity and gastrointestinal early and late morbidity are frequently observed.⁴⁻⁸

Current imaging methods (magnetic resonance imaging, computed tomography [CT] scan, and positron emission tomography [PET]-CT) are necessary to find gross metastatic disease outside the pelvis, either within or outside the nodes. Despite a high specificity and a good rate of detection of PA disease in large bulky tumors, morphologic imaging as well as PET-CT has a poor sensitivity in case of low-volume disease.⁹⁻¹¹

In this situation, staging surgery may still have a role to play today. A possible therapeutic role of surgery for nodal staging, related to the adaptation of chemoradiation fields, has been addressed in some retrospective studies^{10,11} and is being evaluated in 2 randomized trials.^{12,13} However, a significant perioperative morbidity of an open approach for this staging procedure is reported as well; it varies from 12% to 18% according to the surgical route.^{14,15} A minimal invasive approach is currently preferred in staging procedures. The morbidity (~2%) is much less than the one observed by laparotomy.^{16,17} But whatever the rate, it may impair survival because of the complication itself and/or by delaying the initiation of the curative treatment.

To reduce morbidity of the staging, the question of limiting the extent of PA dissection is raised. If there is no place for a unilateral dissection given the ubiquity of nodal spread, it may be interesting to investigate whether limiting the cranial extent of the dissection is accurate. In other words, what is the incidence of skip metastases above the level of the inferior mesenteric artery (IMA)?

To answer this question, we performed a prospective longitudinal observational study in 2 cancer centers experienced in this laparoscopic operation using a similar pattern of nodal dissection. The local institutional review boards of the participating hospitals approved the study, and all patients were included after informed consent.

MATERIALS AND METHODS

This is a prospective longitudinal study carried out in 2 tertiary cancer centers from 2008 to 2013. All patients with a LACC (stage IB1 with proven positive pelvic nodes, IB2, up

to IVA) or a centropelvic cervical cancer recurrence eligible for a curative treatment and no evidence of distant or common iliac or PA nodal metastases at lumbopelvic magnetic resonance imaging and hybrid PET-CT scan were candidates for this laparoscopic staging. Patients having contraindication to laparoscopic surgery (medical) or to extraperitoneal lymphadenectomy (previous renal/vascular surgery) were excluded from the study.

The operation consisted of performing first a transperitoneal diagnostic laparoscopy to rule out an occult carcinomatosis. It was performed through a 10-mm port inserted thanks to an open laparoscopy technique and a 5-mm trocar for an instrument placed in the right internal iliac fossa. In this case, the patient was excluded from the study and immediately sent for chemotherapy. If normal, an extraperitoneal PA retroperitoneal lymph node dissection was immediately performed through an extraperitoneal internal iliac approach as previously described.¹⁸

All nodes were removed from both common iliac bifurcations up to the left renal vein. All chains, lateroaortic, preaortic, interaortocaval, precaval, and laterocaval, were removed. Nodes resected from both common iliac bifurcation up to the origin of the IMA, called the inframesenteric group, and those from the IMA up to the left renal vein, called the supramesenteric group, were extracted separately in endoscopic bags. Marsupialization of the retroperitoneum, by incising the peritoneum of the lateral paracolic gutter, was done to prevent lymphocyst formation. The respective pathologists of the 2 centers then examined the supramesenteric and inframesenteric resected nodes separately. Pathological examination of nodes was done as follows: separate count of nodes, half node examination ± serial sections after hematoxylin/eosin staining. All results were recorded. The postoperative complications were recorded. Patients were discharged on an average on day 2 after surgery. Radiation therapy could be initiated within a mean of 14.2 days (SD, 5.1) after the staging surgery. Patterns of irradiation were adapted to tumor shape and presence of PA node involvement. Chemoradiation therapy consisted of external beam radiotherapy with extended fields in positive PA node patients, delivered by tomotherapy in 2 planned target volumes. Planned target volume 1 encompassed the lumbopelvic volume up to the left renal vein. Twenty-eight fractions of 1.8 Gy were delivered on this planned target volume 1 for a total dose of 50 Gy. Concomitantly, areas with macroscopic disease at imaging (parametria, pelvic nodes) were treated by fractions of 2.4 Gy to finally receive a 60-Gy total dose. Concurrent chemotherapy consisted of Cis-platinum at a dose of 40 mg/m² per week. At completion of external beam treatment, 2 sequences of pulsed dose rate brachytherapy delivered 6.5 Gy for an equivalent biological dose of 80 to 90 Gy on the cervical tumor. This treatment was planned for a total duration not exceeding 55 days.¹⁹

The surgical morbidity was evaluated (intraoperative and 30-day postsurgical morbidity) using the Clavien-Dindo scoring system.²⁰ The postradiotherapy morbidity was reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.0-2009) classification. The patients were followed up until March 2014.

TABLE 1. Patients characteristics

Patient Characteristics	Center 1	Center 2	P
Mean age (SD; range)	46.7 (9.3; 24–69)	49.4 (10.4; 28–74)	0.21
Mean body mass index (SD; range)	24.8 (5.8; 16.3–42)	26.8 (7.13; 15.2–50.2)	0.03
Histologic subtype			0.97
Squamous	63	86	
Glandular	20	28	
Undifferentiated	1	1	
Stage (FIGO 2009)			0.92
IB1 with pelvic pN1	5	0	
IB2	20	53	
IIA2	4	5	
IIB	43	31	
IIIA	2	3	
IIIB	7	13	
IVA	1	4	
Recurrence	2	3	
Total	84	112	

The local and distant recurrences and mortality were also recorded.

RESULTS

From January 2010 to December 2013, 202 patients who fulfilled the inclusion criteria were included in the study. Of these, 6 (2.9%) patients were found to have an unsuspected peritoneal carcinomatosis at diagnostic laparoscopy and had to be censored. For the remaining 196 patients, the extraperitoneal PA lymphadenectomy was carried out as described. Patients' characteristics are listed in Table 1. Besides true centropelvic advanced carcinomas, we pooled some cases of earlier tumors but with pelvic node involvement, which are at risk of PA spread as well and 5 cases of centropelvic recurrences after initial surgery or CRT eligible for a curative pelvic CRT or exenteration.

Except for body mass index, no difference was observed concerning populations of the 2 centers. On pathological analysis, a mean of 22.3 nodes (SD, 9.04; range, 3–48) were retrieved. The mean inframesenteric yield was 12.47 nodes (SD, 5.63; range, 2–32), whereas the average supramesenteric yield was 9.78 (SD, 5.73; range, 2–28). There was no statistical difference between the results of the 2 institutions.

Out of 196 patients, 30 patients had positive PA lymph nodes (15.3%; 95% confidence interval [95% CI], 10.3–20.3%). Patients had between 1 and 11 positive lymph nodes. None was detected at preoperative imaging (all metastases measured ≤ 6 mm except for 1 patient [9 mm]). Fifty percent of them were located in the inframesenteric area alone, 46.7% at both inframesenteric and infrarenal levels, whereas a single patient (3.3%; 95% CI, 0%–9.7%) had 2 positive nodes located at the infrarenal area, without any inframesenteric spread. This patient had a stage IIB squamous tumor and was managed, as any positive PA node patient, by definitive extended-field chemoradiation. Despite this treatment, this patient developed a peritoneal carcinomatosis 12 months later and died of disease. Incidence and distributions of positive PA nodes are displayed in Tables 2 and 3. If no metastasis was observed in the group of 5 patients with IB1 with positive pelvic nodes, 3 of 5 pelvic recurrences had occult PA metastases that eventually altered their therapeutic plan. In the main group of 186 patients with a FIGO IB2 to IVA, 27 had metastatic PA nodes, with 1 patient with 2 isolated positive nodes (metastasis < 5 mm in size) above the IMA (3.7%; 95% CI, 0%–10.8%).

The perioperative morbidity was also evaluated according to the Clavien-Dindo scoring system (Table 4). Two

TABLE 2. Pathological analysis

No. Nodes (Mean, SD, Range)	Center 1	Center 2	P	Pooled Data
Full	22.91; 8.21; 11–46	21.83; 9.63; 3–48	0.4	22.30; 9.04; 3–48
Inframesenteric area	13.10; 5.81; 3–32	12.00; 5.46; 2–28	0.18	12.47; 5.63; 2–32
Supramesenteric area	09.64; 4.81; 2–24	09.89; 6.35; 1–28	0.74	9.78; 5.73; 1–28
Positive nodes	12 (14.2%)	18 (16%)	0.73	

TABLE 3. Distributions of pathologically positive lymph nodes (pN1)

Distribution by Anatomical Level	No. Patients	% (95% CI) of Total
Total	30	15.3 (10.3–20.3) of the whole series
With inframesenteric alone	15	50* (32–68)
With supramesenteric and inframesenteric	14	46.67* (28.8–64.5)
With isolated supramesenteric	1	3.33* (0–9.8)
Distribution by FIGO stage		
Ib1 with pelvic pN1	0	0
IB2	8	10.9 (3.8–18)
IIA2	1	11.1 (0–31.6)
IIB	14	18.9 (10–27.8)
IIIA	2	40 (0–83)
IIIB	4	20 (2.5–37.5)
IVA	0	0
Recurrence	3	60 (17–100)
Distribution by size of metastasis		
pN1 ≤ 5 mm	9†	
pN1 > 5 mm or ≥ 2 pN1	20	
Fixed	1	

*No. pN1 patients.
†Included the patient with 2 isolated supramesenteric node metastases.

intraoperative significant bleedings occurred, but only one had to be converted into laparotomy (aorta injury above the IMA), with possible risks of radiation-induced complications. Postoperatively, 11 grade 3a and 2 grade 3b complications were observed. One postoperative umbilical herniation necessitated an immediate bowel reintegration through the same umbilical port incision. None of these 15 complications (7.5%) delayed the curative treatment. There was no difference according to institution ($P = 0.06$). The combined surgery and radiation-induced complications were also recorded. Distantly, there were 4 leg lymphedemas, 5 grade 3 complications were 3 vaginal stenoses, 1 enteritis/rectal inflammation, 1 vesicovaginal fistula.

With a median follow-up period of 21 (3–92) months, 44 patients (with 8 PA pN1) recurred (22.4%): 16 had local recurrences (within the treatment field), with 1 PA relapse (fixed node), 23 (52%) had distant metastases, and 5 had both local and distant metastases (Table 5). There is no significant difference according to institution ($P = 0.68$). So far, 29 (66%) of these patients already died of the disease.

DISCUSSION

The upper level of PA node dissection in cervical cancer patients is still a matter of debate among surgeons: some limit

the pattern to the IMA, others to right gonadal vein, others to left renal vein.^{21–23} Traditionally, though, it was known that skip metastases to the infrarenal PA lymph nodes may occur in ovarian and endometrial cancers.^{24,25} In cervical cancer, it is still believed that the spread progresses by the lymphogenous route in an orderly fashion.²⁶ However, the studies by Gil-Moreno et al²⁷ and Michel et al²⁸ have shown that there are a significant number of cases of skip metastases. One theory proposed for this spread is that, in locally advanced cervical cancer with involvement of the corpus uteri, the disease can spread through the posterior cervical lymph trunk to the PA lymph nodes.²⁸

However, pretreatment staging surgery remains a debatable topic in LACC with bulky tumors, although now, gradually, it is being established as a standard for planning the extent of radiotherapy. Indeed, a randomized trial by Lai et al²⁹ has shown a trend toward a lower survival rate in the surgical staging arm, and although it was terminated early, there are some sources of bias in this trial. In fact, this study encompassed 2 randomized trials (2 approaches were randomized in the surgical arm). Groups were not well balanced in their characteristics, and some deaths were caused by chemotherapy in the surgical group. Moreover, more patients received concurrent chemotherapy in the group radiologically staged compared with the group surgically staged. By contrast, some retrospective nonrandomized studies by Gold et al,³⁰ Leblanc et al,³¹ and Gouy et al¹¹ have all suggested a possible positive survival impact of this surgical staging.

In addition and although no positive nodes were found in this small group, we think that this inframesenteric pattern of dissection should be safely applied as well to patients with early cervical tumors but with proven pelvic positive nodes because the pathway of spread is not different from a more locally advanced tumor. Indeed, a PA node information will spare them a systematic extended-field CRT that can be a useless overtreatment.^{6,32} Similarly, the choice of management for a local recurrence is of crucial importance for patient's survival and quality of life. A selection for exenterative surgery or adequate CRT, according to presentation or previous treatments, is necessary. Para-aortic node information is thus very important to reorient the management if nodes are positive at this level.

Having said that surgical staging is possibly of positive prognostic value and although studies have established that laparoscopic extraperitoneal PA lymph node dissection has less morbidity compared with transperitoneal and open techniques, the fact remains that the procedure still carries a certain degree of morbidity.^{18,33}

To assess all abovementioned aspects, we performed this prospective study to see whether we can limit the level of dissection to the inframesenteric level in a group of LACC patients selected on PET-CT results.

Indeed, limiting the PA dissection to the ilioinframesenteric area may reduce the operative challenge of any infrarenal bilateral dissection and, possibly, the lymphatic morbidity (lymphocyst or chylous ascites) caused by the transection of large perirenal lymph channels. To our knowledge, there are only 2 studies that have specifically addressed this question, one by Michel et al²⁸ and the other a review by Gouy et al¹¹ with

TABLE 4. Morbidity data

Center	No. Patients	Intraoperative Complication	≤30 Days Complication (Clavien-Dindo Scoring System)	CTCAE v4.0-Distant Morbidity Related to the Procedure
Center 1	84	1 aorta injury, above the IMA (laparoconversion)	2–grade 3a: 1 lymphocyst 1 retroperitoneal abscess: radiologic drainage 3 deep vein thromboses with 1 pulmonary embolism 1 bowel obstruction incisional hernia	3–Grade 2/3 leg lymphedemas 1 infected lymphocyst: radiologic drainage 1 vesicovaginal fistula
Center 2	112	1 gonadal vein injury (clips)	9–grade 3a: 8 lymphocysts 1 hematoma: radiologic drainages 2–grade 3b: 1 recurrent lymphocyst: surgical drainage; 1 bowel obstruct caused by umbilical port herniation: surgery	1–Grade 3 leg lymphedemas 1 ureter stenosis 2 urinary incontinences

CTCAE indicates Common Terminology Criteria for Adverse Events.

similar conclusions. However, surgeons performing strict inframesenteric dissection for LACC patients have not reported an unusually high incidence of infrarenal node recurrences.²² In the literature, there are few articles reporting on isolated PA lymph node metastases.³⁴

In our study, we had a lymph node positivity rate of only 3.3% in isolated supramesenteric lymph nodes, which was much lower compared with the literature, in which 25% to 31.2% have been reported.^{27,28} Moreover, in our study, criteria for patient selection were strict, based on both morphologic and functional imaging findings. To our knowledge, the present series is so far the largest in the medical literature.

Although very specific, the sensitivity of PET-CT remains rather low; this was confirmed in this prospective study in which the 30 patients with positive nodes had not been detected by this method. The PET-CT imaging system has a poor resolution for low-volume metastases.³¹ This represents a justification of the use of surgical staging in the group of LACC patients with no visible extrapelvic hotspots.¹¹ In this series, treatment plan was modified in 15% of our cohort, who would have been otherwise undertreated.

This study was performed in 2 tertiary centers with trained laparoscopic surgeons with experience of more than 100 laparoscopic extraperitoneal PA lymphadenectomies each before starting this study. The 1% intraoperative complications and 6.5% perioperative morbidity rates were within acceptable limits,¹¹ and no delay in treatment occurred. Concerning the intraoperative morbidity, one must stress the fact that the 2 vascular complications of this series occurred during the supramesenteric dissection. Limiting the dissection up to the IMA would have avoided these problems. In addition, it would reduce the technical difficulty of an infrarenal dissection and, consequently, the operative time.

The morbidity in patients undergoing extended-field CRT after this procedure was also within acceptable limits and did not increase in comparison with historical morbidity rates.³⁵

Because we have a short follow-up duration and because there is no set pattern for the recurrence and distant metastases, it is difficult to conclude about the prognostic and/or therapeutic impact of this procedure. Two randomized trials are ongoing to address this question in the United States¹³ and Germany.¹² However, our result of 22.4% of recurrence at 21 months, with more than 50% of distant failures, should prompt clinicians to accrue into trials testing a systemic treatment after CRT such as the GOG 274 (the “Outback trial” NCT01414608).

In conclusion, the results of the present prospective study confirm the low incidence of isolated infrarenal PA lymph node metastases and consequently the stepwise upward progression of nodal disease in cancers of the cervix. Considering the risk-benefits ratio of this procedure in LACC patients, a more limited dissection from common iliac bifurcations up to the IMA should be systematically considered,

TABLE 5. Recurrences

	Center 1 (n = 84, 12 pN1)	Center 2 (n = 112, 18 pN1)
Local (pelvis)	6 (3 pN1)	10 (1 pN1)
Local and distant	1 (1 pN1)	4
Distant	13	10 (3 pN1)
Total	20	24

reserving a more extended pattern to selected situations, for example, a high isolated PA hotspot at hybrid PET-CT scan. The 2 upcoming randomized trials will further throw light on the true prognostic and therapeutic impact of this laparoscopic surgical staging.

The future will bring more information about the comparative assessment of morbidity with infrarenal dissections.

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