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Para-aortic plus pelvic lymphadenectomy in locally advanced cervical cancer: A single institutional experience

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ABSTRACT

Objective: The aim of the study is to assess the safety and efficacy of transperitoneal laparoscopic para-aortic and pelvic lymphadenectomy in the setting of surgical staging of patients with locally advanced cervical cancer (LACC), and to analyse the prognostic value and impact of this staging on the survival prognosis of this condition.

Study Design: Data from 67 patients with LACC who underwent transperitoneal laparoscopic para-aortic and pelvic lymphadenectomy and who received chemo-radiation therapy were retrospectively analysed.

Results: Metastatic lymph nodes (LN) were identified in 32 patients (47.7%), 20 (29.8%) had metastatic LN in the pelvic area and 12 (17.9%) had metastatic LN in the pelvic and para-aortic area. There were no skip metastases in the para-aortic area.

After a median follow-up of 54.6 months (5–122.2 months), the 5-year local control and disease-free survival (DFS) rates for the whole group were 91.1% and 60.5% respectively. The five-year DFS for patients without LN metastasis was 86.4%, while for patients with pelvic LN metastases or pelvic and para-aortic metastases was 34.2% and 24.2% respectively ($p < 0.001$).

The five-year overall survival (OS) for the whole group was 67.3%. The mortality rate in patients with para-aortic nodal metastases was increased compared to patients with negative nodes (5-year OS 21.3% vs 81.6% respectively, $p = 0.005$), but the OS rate was similar in patients with negative nodes and those with only pelvic nodes affected (5-year OS 81.6% vs 70.8% respectively, $p = 0.380$).

This approach allowed the modification of the initial treatment plan in the para-aortic area in 13.4% of patients and in the pelvic area in 28.3%.

The overall intraoperative morbidity rate was 5.9%, while the postoperative morbidity rate was 10.4%, with only 3 patients presenting grade 3 morbidity.

Conclusions: Transperitoneal para-aortic and pelvic lymphadenectomy provides precise information about nodal state and allows personalized treatment planning in patients with LACC, avoiding false negative (FN) and false positive (FP) imaging results. In 17.9% of patients, the external beam radiotherapy (EBRT) field had to include the aortic area, whilst 47.7% received pelvic boost to the involved nodes.

Introduction

Cervical cancer is the third most commonly diagnosed female cancer and the fourth leading cause of mortality worldwide [1]. While most cases present with early stage disease, there are still patients who present with LACC with a 5-year OS of 22–75% [2].

The staging for cervical cancer was based on clinical features according to the International Federation of Gynecology and Obstetrics (FIGO), without taking into account one of the main prognostic factors which is LN status [3,4]. In 2018 the staging system was revised and the new classification clearly reflect the importance of LN metastasis as a major prognostic factor in cervical cancer [5].

Pre-treatment evaluation of the LN status through imaging techniques is of limited value. The sensitivity for LN involvement in

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the pelvic area by computed tomography (CT) is 65%, and by magnetic resonance imaging (MRI) is 70% [6]. Regarding para-aortic LN (PALN), sensitivity is even lower (57.5% for CT scan, 55.5% for MRI) [7]. Positron emission tomography (PET/CT) is more accurate than CT and MRI for detecting LN spread, but its sensitivity is still 82–84% for detecting PALN and 79% for pelvic LN (PLN) [8,9]. Several publications have shown that the rate of FN and FP in the aortic area, based on PET/CT, is 8% and 27% respectively [10]. As a result, patients may be under- or over-treated, with potentially worsening survival rates.

Surgical staging for the assessment of pelvic and para-aortic involvement provides precise information on LN status and, therefore more personalized treatment, which may result in better clinical outcomes [11–13].

The treatment of choice for patients with LACC is concurrent chemo-radiation therapy, using cisplatin-based chemotherapy. The extent of the radiation field is critical and may be guided by assessment of nodal involvement in the pelvic and para-aortic nodes [14].

The aim of this study was to assess the safety and impact on survival of pelvic and para-aortic transperitoneal lymphadenectomy in the staging of patients with LACC.

Materials and methods

This is a retrospective study at a single institution. Between January 2006 and December 2015, 95 patients with LACC (FIGO stages IB2, IIA2, IIB-IVA) were diagnosed and treated at the Gynecologic Oncology Department of Complejo Hospitalario de Navarra, Pamplona, Spain. Institutional Review Board approval was obtained.

All patients who underwent transperitoneal pelvic and para-aortic laparoscopic lymphadenectomy followed by chemoradiotherapy were included in the study. Exclusion criteria were: contraindications to laparoscopy, concurrent pregnancy, evidence of metastatic disease outside the pelvis, concurrent malignancies at other sites or patients who had surgical treatment as a first option.

Pre-treatment MRI and/or CT studies were performed in all patients. Criteria for LN involvement were based on size. Enlarged LNs were defined if the maximum short axis was >10 mm [15].

Patients were treated with chemo-radiation therapy after surgical staging. The regimen consisted of pelvic radiotherapy (45 Gy in 25 fractions) concomitantly with a weekly single dose of cisplatin (40 mg/m2) for 5 weeks. All patients received EBRT to the pelvic region, including tumor, internal iliac LNs, external iliac LNs and common iliac LNs up to L4-L5. Patients with PALNs metastases received extended field radiation therapy (EFRT) of 45 Gy up to T12 level. Patients with metastatic PLNs received a pelvic boost to the area of positive PLNs up to 60 Gy. High dose brachytherapy with total dose of 7 Gy in 4 fractions was delivered after completion of chemo-radiation treatment by means of two implants at week 6^{th} and 7^{th}.

Transperitoneal laparoscopic pelvic and para-aortic lymphadenectomy was performed in all patients after excluding intraperitoneal disease. PALN dissection consisted of removing the entire lymphatic fat pad from the distal common iliac bifurcation bilaterally, anterior and left aorta, vena cava and aorto-caval space, up to the left renal vein [16]. Pelvic lymphatic fat pad was systematically removed on each side of the pelvis, medially and externally to the external iliac vessels including distal nodes up to deep circumflex iliac vein, internal iliac vessels, above the obturator nerve and common iliac region [17].

Intraoperative and postoperative morbidity was recorded and classified according to Memorial Sloan Kettering Cancer Centre (MSKCC) surgical grading system [18].

Outcomes analysed

Primary outcome:

1 Survival: OS and DFS.

Secondary outcomes:

1 Morbidity
2 Predictive value of MRI/CT scan versus surgery for LN metastases

Statistics

Statistical analysis was performed with the statistical package for the social sciences (SPSS) for Windows 15.0 (SPSS Inc. Chicago, IL, USA).

Continuous data are presented as mean with standard deviation (SD). Categorical data are presented as the number of cases and percentages. Categorical data were compared using two-tailed Fisher's exact test. OS was defined as the end of treatment time to the date of death or to the last follow up. DFS was defined as the end of treatment time to the diagnosis of recurrence. Survival analysis was done with the Kaplan- Meier method, compared by the long-rank statistical method. Univariate and multivariate Cox proportional hazard ratio (HR) analysis was performed to identify independent prognostic factors. Multivariate Cox models included factors associated with statistical increased risk of death or recurrence in the univariate study. A p value <0.05 was considered statistically significant for all tests.

Results

General characteristics

67 patients underwent transperitoneal pelvic and para-aortic laparoscopic lymphadenectomy followed by chemoradiotherapy and were finally included in the study.

Clinical characteristics and surgical details are shown in Table 1.

Safety and feasibility

Mean operative time was 238 min (SD +/- 69.6). Mean time of hospital stay was 3.8 days (SD +/- 1.6). Mean time from surgery to initiation of radiotherapy was 23 days (SD +/- 8.6).

Table 1
Characteristics data.

General characteristics	Data
Age, years, mean (SD)	56, (+/-11.7)
Parity, mean (SD)	2, (+/-1.6)
Previous laparotomy, %	26.8
BMI, Kg/m, mean (SD)	26.8, (+/-5.3)
Histologic subtype, Nº of patients, (%)	
Squamous	52, (77.6)
Adenocarcinoma	13, (19.4)
Other	2, (3)
Tumor grade, Nº of patients, (%)	
Grade 1	12, (17.9)
Grade 2	38, (56.7)
Grade 3	17, (25.4)
FIGO stage, Nº of patients, (%)	
IB2	2, (3)
IIA2	2, (3)
IIB	52, (77.6)
IIIA	3, (4.5)
IIIB	5, (7.4)
IVA	3, (4.5)

Positive PLN were documented in 32 (47.7%) patients, 12 (17.9%) of whom also had positive PALN. There were no skip metastases in the para-aortic area. Table 2 shows the number of LN removed.

Operative complications occurred in four patients: one obturator nerve injury that was fixed with end to end suture, two ureteric injuries, one of which was resolved with a double J-stent, and the other one with end-to-end suture, and one vascular injury to the vena cava that was controlled with Floseal®. Postoperative complications occurred in seven patients, 4 of them (57.1%) experienced G1-G2 morbidity and 3 of them (42,9%) experienced G3 morbidity. In particular we documented two lymphoceles in the pelvic area, both of which were drained by percutaneous ultrasound-guided needle suction, two unilateral lower extremity lymphedemas that improved with physical therapy, one chylous ascites that resolved with specific diet, one umbilical port site hernia that required surgery and one umbilical port site cellulitis that was treated with oral antibiotics (Table 3).

There were nine patients (13.4%) who had persistent disease confirmed with pre-operative biopsy. Eight patients were treated with type B radical hysterectomy based on the Querleu and Morrow classification [19], and two of them had partial cystectomy; one patient was treated with type D radical hysterectomy and anterior pelvic exenteration.

Outcome

Performance of surgery versus Image to predict LN involvement

Preoperative image findings were compared to final pathologic report. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are shown in Table 4.

There were no statistically significant differences in sensitivity and specificity between CT and MRI for LN detection in pelvic and para-aortic areas ($p > 0.05$).

Thirty-six patients had pre-operative CT and MRI negative for pelvic lymphadenopathy. Of these, ten patients (27.8%) were found to have histopathologically positive PLN. Thirty-one patients had pre-operative CT and/or MRI positive for pelvic lymphadenopathies, but nine (29.0%) had histopathologically negative nodes.

Table 2
Surgical data.

Lymphadenectomy	Data
Metastatic PLN, no. (%)	20 (29.8)
Metastatic PLN and ALN, nº (%)	12 (17.9)
Metastatic ALN, nº (%)	0 (0)
Right pelvic lymph nodes, mean (SD)	7.4 (+/- 4.0)
Left pelvic lymph nodes, mean (SD)	6.6 (+/- 3.3)
Paraaortic lymph nodes, mean (SD)	8.5 (+/- 5.6)

Table 3
Intraoperative and postoperative complications.

Type of complications	N (%)	
Intraoperative	4 (5.9)	
Ureteral injury	2	
Vascular injury	1	
Nerve injury	1	
Postoperative	7 (10.4)	**Grade**[a]
Lymphocele	2	3
Lymphedema	2	2
Chylous ascites	1	1
Umbilical hernia	1	3
Cellulitis	1	1

[a] According to MSKCC grading system (18).

Table 4
MRI and CT Sensitivity, Specificity, PPV and NPV.

	CT		*MRI*	
	Pelvic	Aortic	Pelvic	Aortic
Sensitivity	57.0%	75.0%	67.7%	66.7%
Specificity	90.0%	89.8%	73.5%	96.2%
PPV	85.0%	64.3%	70.0%	80.0%
NPV	68.3%	93.6%	71.4%	92.6%

Nineteen (28.3%) patients had treatment modification to the pelvis based on pathologic findings.

Fifty-two patients had pre-operative CT and MRI negative for para-aortic lymphadenopathy. Of these, three patients (6.0%) had histopathologically positive PALN. Fifteen patients had pre-operative CT and/or MRI positive for para-aortic lymphadenopathy, but the histopathology was negative in six (40.0%) of them. Nine (13.4%) patients had treatment modification to the para-aortic area based on pathological findings.

Overall survival and disease free survival

After a median follow-up of 54.6 months (range 5.0–122.2), 17 patients (25.4%) of the 67 patients with complete or partial response relapsed during follow up.

Regional metastases were observed in only two (2.9%) patients and both of them had metastatic PLN at the time of diagnosis.

Distant metastases were observed in 8 (11.8%) patients and para-aortic recurrence was observed in 7 (10.4%) patients. Table 5 shows characteristics, treatment response and recurrence rate related to LN status.

The 5-year rate of OS and DFS was 67.3% and 60.5% respectively for the whole group.

Patients with negative LN and patients with exclusive positive PLN had better OS (89.5 months [95% CI, 75.4–103.5] and 78.5 months [95% CI, 55.2–102.3] respectively) than patients with positive PLN and PALN (40.1 months [95% CI, 67.0–92.4]). However, the differences between patients with positive PLN vs. positive PLN and PALN did not reach statistical significance, ($p = 0.005$ and $p = 0.076$ respectively). No statistically-significant differences in OS were observed between patients with negative LN and patients with positive PLN ($p = 0.380$).

The 5-year rate of OS for patients with negative LN and patients with positive PLN was 81.6% and 70.8% respectively, while for patients with positive PLN and PALN the 5-year rate of OS dropped to 21.3%.

Patients with FIGO stage I-II had better OS than patients with FIGO stage III-IV (87.3 months [95% CI, 74.3–100.4] vs. 41.1 months [95% CI, 17.1–65.0], $p = 0.001$). And patients with tumor size < 4 cm had also better OS than patients with tumor size ≥ 4 cm (97.5 months [95% CI, 81.1–113.8] vs. 66.2 months [95% CI; 51.5–80.8]) $p = 0.049$).

Multivariate analysis showed that the presence of exclusive positive PLN did not affect the OS. Positive PLN and PALN, FIGO stage III-IV and tumor size ≥ 4 cm increased the risk of mortality (HR 2.7, 3.3 and 2.1 respectively) which did not reach statistical significance; only a trend (Table 6).

Patients with negative LN had better DFS than patients with positive PLN or patients with positive PLN and PALN (98 months [95% CI, 85.4–110.5] vs. 61.1 months [95% CI, 35.4–86.8] and 30 months [95% CI, 10.1–49.8]), $p = 0.013$ and $p = 0.001$ respectively). Patients with positive PLN had slightly better DFS than patients with positive PLN and PALN, although the differences did not reach statistical significance, ($p = 0.052$). The 5-year DFS for patients with no metastatic LN was 86.4%, while for patients with pelvic

Table 5
Characteristics, treatment response and recurrence rate related to LN status.

LN status	Age *(mean)*	Histologic Subtype *(p = 0.940)**		Grade *(p = 0.720)**			Treatment response *(p = 0.449)**		Location of the recurrence *(p = 0.001)**			
		Squamous	Adeno	G1	G2	G3	Complete	Partial	No recurrence	Pelvic area	Para-aortic area	Distant metastasis
N 0 (n = 35)	51.9	27 (77.1)	8 (22.9)	8 (22.8)	17 (48.6)	10 (28.6)	32 (91.5%)	3 (8.5%)	33 (94.3%)	0 (0%)	0 (0%)	2 (5.7%)
Pelvic N1 (n = 20)	51.7	16 (80.0)	4 (20.0)	3 (15.0)	13 (65.0)	4 (20.0)	16 (80%)	4 (20%)	13 (65%)	2 (10%)	2 (10%)	3 (15%)
Pelvic + Para-aortic N1 (n = 12)	50.9	9 (75.0)	3 (25.0)	1 (8.3)	8 (66.7)	3 (25.0)	10 (83.3%)	2 (16.7%)	4 (33.3%)	0 (0%)	5 (41.7%)	3 (25%)

* Fisher exact test.

Table 6
Multivariate Cox model for OS and DFS.

OS	*N*	*HR*	*95% CI*	*P value*
Pelvic N1	20	0.97	0.25-3.82	0.967
Pelvic and para-aortic N1	12	2.70	0.71-10.22	0.147
FIGO III-IV	11	3.30	0.99-10.88	0.051
Tumor size ≥ 4 cm	44	2.10	0.54-7.96	0.287
DFS				
Pelvic N1	20	2.98	0.70-12.67	0.139
Pelvic and para-aortic N1	12	7.80	1.84-33.05	0.005
FIGO III-IV	11	2.72	0.92-8.06	0.071
Age ≥ 45 yo	48	2.23	0.48-10.34	0.304

metastatic LN was 34.2% and 24.2% for patients with pelvic and para-aortic metastatic LN (p = 0.001).

Patients with FIGO stage I-II had better DFS than patients with FIGO stage III-IV (86.2 months [95% CI, 72.2–100.1] vs. 27.4 months [95% CI, 12.2–42.8], p = 0.001).

Multivariate analysis showed that DFS was significantly associated with the presence of metastatic LN in the pelvic and para-aortic area (HR: 7.8, p = 0.005). Positive PLN, FIGO stage III-IV and patient age over 45 years old increased the risk of recurrence (HR 2.9, 2.7 and 2.2 respectively) without reaching statistical significance (Table 6).

Fig. 1 shows the OS and DFS according to LN status.

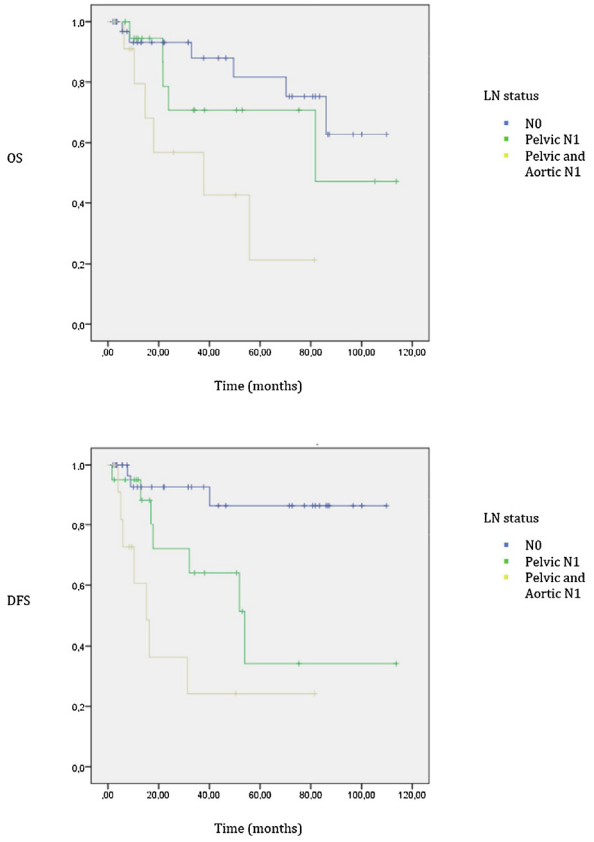

Fig. 1. OS according to LN status (p = 0.015). DFS according to LN status (p < 0.001).

Discussion

Identification of positive LNs by imaging modalities such as CT or MRI is still challenging. In patients with LACC, the sensitivity and specificity for detecting metastatic nodes reported in the literature are 57% and 92% respectively for CT and 55% and 93% for MRI [7]. Our results are in agreement with previous findings [9,10]. Treatment modification rates based on para-aortic lymphadenectomy range from 7 to 58% [20]. Our results showed a modification of the initial therapeutic plan in the para-aortic area in 13.4% of patients and in the pelvic area in 28.3%.

Whereas laparoscopic lymphadenectomy is considered a safe and feasible procedure, the therapeutic benefit is still unclear [21]. While laparoscopic staging surgery is considered to be of therapeutic benefit [4,11,22], the only prospective study that compared surgical versus clinical staging found that women who underwent surgical staging had significantly higher risk of death than women who underwent clinical staging [23]. More recently Pomel et al., in a retrospective cohort analysis, found that para-aortic surgical staging is worse for patients with LACC than clinical staging in terms of OS and DFS [24].

The main strength of this study is that all women were diagnosed, treated and followed-up in the same institution, reducing possible bias. However, in our institution, PET/CT imaging is not available, which is currently considered the imaging technique of choice. Another limitation is the lack of a control group of patients staged based on imaging tests.

PLN dissection is not standard practice in the surgical staging for patients with LACC and there is no definitive data about its value for improving survival [25]. Nevertheless, this approach could increase pelvic control as well as possibly decrease extra pelvic failures in patients with metastatic PLN. In our series, there were only two patients (2.9%) that experienced recurrence in the pelvic area, with a 91.1% of local control. In addition, there was no significant difference in OS between patients with negative LN and those with only PLN affected (p = 0.380). Therefore, pelvic lymphadenectomy and pelvic boost in patients with positive PLN could improve the local control of the disease and improve the OS.

On the other hand, patients with PALN metastasis had a higher risk (HR: 7.80, 95% CI (1.84–33.05) of recurrence than those with negative LN (p = 0.005) and those with exclusive pelvic LN affected, but this differences did not reach statistical significance (p = 0.052).

Recently, Gallota et al have brought up a new discussion assessing the feasibility of total robotic radical hysterectomy plus pelvic and para-aortic lymphadenectomy in patients with LACC who have received prior chemoradiotherapy, providing perioperative outcomes comparable with those registered in early stage disease and LACC patients receiving neoadjuvant chemotherapy [26].

In our study, operative time and hospital stay was longer than previous studies where only para-aortic lymphadenectomy was performed [14,27,28]. However, the mean time from surgery to initiation of radiotherapy was only 22.9 days (SD+/-8.6), without delaying patient treatment and is in accordance with other publications [11,29]. The rate of complications when pelvic lymphadenectomy is added is still low, and similar to those studies using similar laparoscopic approach [30], but morbidity should always be considered. Adding pelvic lymphadenectomy, the risk of lower extremity lymphoedema is increased (3% of the patients in our study). A similar rate of complications was observed in patients who underwent robotic transperitoneal aortic lymphadenectomy after chemoradiotherapy, where 4.2% and 18.3% of the patients had intraoperative and postoperative complications respectively [31].

In summary, transperitoneal para-aortic plus pelvic lymphadenectomy for pre-treatment surgical staging in LACC is a safe and efficacious procedure, and provides valuable information for mortality and recurrence risk of patients helping clinicians individualize treatment.

Pelvic lymphadenectomy plus pelvic boost in patients with positive PLN could improve local disease control and may impact in OS without delaying chemo-radiation therapy. However, the therapeutic benefit of laparoscopic surgical staging is still unclear and must always be balanced against the increased risk of morbidity.

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