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Pelvic lymphadenectomy for cervical carcinoma: Laparotomy extraperitoneal, transperitoneal or laparoscopic approach? A randomized study

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Abstract

Objective. To compare transperitoneal, extraperitoneal and laparoscopic pelvic lymphadenectomy in terms of feasibility and morbidity in patients affected by cervical cancer undergoing radical hysterectomy.

Methods. Consecutive patients affected by stage IB–IIB cervical carcinoma scheduled for radical surgery entered the study. Patients were randomly assigned to transperitoneal (TPL), extraperitoneal (EPL) or laparoscopic pelvic lymphadenectomy (LPL). All patients underwent classical radical hysterectomy. Perioperative data were recorded. Follow up examinations were performed at the 15th, 30th and 60th day after surgery.

Results. 168 patients entered the study. The mean operative times were: 63 ± 7.6, 54 ± 6.7 and 75 ± 8.4 min (TPL vs EPL $P < 0.001$; EPL vs LPL $P < 0.001$; TPL vs LPL $P < 0.001$) for TPL, EPL and LPL respectively. The feasibility of the procedures, analyzed on an intention-to-treat basis, was 96%, 93% and 95% for TPL, EPL and LPL group respectively (P = ns). The average hospitalizations were: 5.6 ± 0.9, 3.2 ± 0.4 and 3.1 ± 0.3 days (TPL vs EPL $P < 0.001$; TPL vs LPL $P < 0.001$) for TPL, EPL and LPL respectively.

Conclusions. EPL and LPL are as feasible and effective as TPL and can be adequately performed with a reasonable complication rate. LPL showed a statistically significant longer operative time. However, both EPL and LPL can minimize some postoperative complications reducing length of stay.

Keywords: Cervical cancer; Pelvic lymphadenectomy; Laparoscopic lymphadenectomy; Extraperitoneal lymphadenectomy

Introduction

Radical hysterectomy and systematic pelvic lymphadenectomy is considered the standard treatment for patients affected by early stage (FIGO stage IA2–IB1) cervical carcinoma. This surgical procedure could be performed also in patients with locally advanced disease (FIGO stage IB2–IIIB) who respond to neoadjuvant chemotherapy [1].

During the last decades, several surgical approaches have been attempted in order to reduce morbidity of lymphadenectomy. The laparotomy extraperitoneal and, more recently, the laparoscopic approach have been demonstrated to be valid surgical options [2,3]. Concerning laparoscopic pelvic lymphadenectomy, several authors have discussed indications, feasibility and results. They concluded that: (a) in experienced hands, it is a feasible procedure with acceptable morbidity [4]; (b) this technique has a longer learning curve and operative time [4,5] when compared to laparotomic approach; (c) in several reports, the number of removed lymph nodes by laparoscopy is still considered unacceptable for systematic lymphadenectomy [4,6–8]; (d) the number of nodes removed may increase in direct proportion to operator experience [6]. For all the abovementioned reasons, laparotomy is still considered the standard approach for systematic pelvic lymphadenectomy in cervical cancer patients.

As to laparotomic transperitoneal pelvic nodal dissection, it was first proposed in 1898 by Wherteim [9] and the technique was later better described by Taussing and Leveuf [10,11].

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Since then, several authors have proposed laparotomic extraperitoneal pelvic lymphadenectomy highlighting the low morbidity of this approach [3,12,13].

However, to our knowledge, no randomized trials comparing laparoscopic, laparotomic transperitoneal and laparotomic extraperitoneal pelvic lymphadenectomy in gynecological malignancies have been reported. The aim of the present study is to compare these different surgical approaches in a randomized setting for systematic pelvic lymphadenectomy in terms of feasibility and morbidity in patients affected by cervical carcinoma undergoing radical surgery.

Patients and methods

Consecutive patients with proven invasive cervical carcinoma scheduled for radical hysterectomy plus systematic pelvic lymphadenectomy entered the study.

Eligibility criteria were: stage IB1 or stage IB2–IIB cervical carcinoma, already submitted to neoadjuvant chemotherapy with an objective response, age ≤ 70 years, no concurrent or previous malignant disease (excluded skin basalioma), no previous radiation therapy, WHO performance status ≤1, adequate renal, hepatic and cardiac function, signed informed consent, BMI < 40.

The pre-treatment evaluation consisted in: complete history, physical and gynecologic examination, laboratory work-up, EKG, chest X-ray, hepatic and pelvic ultrasonography. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Patients were randomly assigned to transperitoneal laparotomic pelvic lymphadenectomy (TPL), extraperitoneal laparotomic pelvic lymphadenectomy (EPL) or laparoscopic pelvic lymphadenectomy (LPL) using a computer-generated coded table.

Before surgery, all patients were submitted to mechanical bowel preparation, deep venous thrombosis prophylaxis with low molecular weight heparin (2 h before the operation and postoperatively until complete ambulation), and antibiotic prophylaxis. "All patients underwent classical (type 3–4) radical hysterectomy as previously reported [14] using a vertical median incision". All surgical procedures were performed by the same surgical team.

The Foley catheter was removed in the third postoperative day, after that, patients were instructed to void every 3 h and, if necessary to use clean intermittent self-catheterization, until post-void residual urine was <100 ml for two consecutive times. During the period of self-catheterization, regular urinalysis and bacteriological cultures were carried out and antibiotic therapy was administered when necessary.

Operative data, intra- and postoperative complications and length of hospital stay were recorded.

The postoperative pain (48 h after surgical procedure) was evaluated using a 10-grade visual analogue symptoms scale (VAS). Wound infection was defined as a wound purulent drainage with tissue warmth, erythema and increasing tenderness. Postoperative fever was defined as temperature elevation ≥38°C on two consecutive occasions 6 h apart, starting 24 h after surgery; postoperative ileus was considered solved after the first passage of flatus.

Follow up examinations were performed, in the absence of symptoms, at the 15th, 30th and 60th postoperative day and included physical and gynecologic examination, laboratory work-up and pelvic ultrasonography.

Feasibility, primary endpoint, was defined as successfully completing entire procedure according to randomization and adequacy of number of lymph nodes removed (>25) [14].

Past literature reported that the feasibility rate for laparoscopic and transperitoneal/extraperitoneal pelvic lymphadenectomy was in the range of 74–76% [15,16] and 95–98% [14,17–19] respectively. A calculated power study indicated that 56 patients would be necessary to demonstrate (with a power of 90%) a reduction of feasibility rate from 97% to 75% among patients who underwent the different procedures.

Data from all eligible patients were analyzed for feasibility on an intention-to-treat basis. Instead, postoperative complications were evaluated in the valuable patients.

ANOVA with post hoc test and Fisher's Exact Test was used for comparison among groups. Statistical significance was set at a P value of <0.05.

Approach to the retroperitoneum: laparoscopic, transperitoneal and extraperitoneal techniques

Patients randomized to EPL or TPL group, to enter abdomen, were submitted to umbilico-pubic incision, the subcutaneous fat dissected by electrosurgery until the recto-abdominis fascia was exposed, the recto-abdominis fascia incised longitudinally either electrosurgery or by cold knife until the fascia trasversalis became visible.

After this, in EPL group, fascia trasversalis was incised caudally and the dissection proceeded laterally, identifying the inferior epigastric vessels, until the psoas muscle was exposed moving the peritoneum medially. At this point, the round ligament was evidenced, ligated (or coagulated) and resected. Retroperitoneum was then developed by careful sharp dissection and peritoneal sac with the underling bowel displaced upward and medially.

On the opposite, in the TPL group, fascia trasversalis was incised and then peritoneum was opened.

As to the LPL group, a 10-mm trocar, holding the laparoscope, was introduced with "direct puncture technique" or by "open laparoscopy technique", pneumoperitoneum was obtained, and a total of 4 5-mm trocars were introduced in the abdomen to perform the lymphadenectomy procedure.

Systematic pelvic lymphadenectomy: surgical technique

After the preparation of the para-rectal and para-vesical spaces, the dissection was began at the origin of the external iliac vessels and continued caudally around them along the medial border of the psoas muscle, preserving the aponeurotic fascia covering it and sparing the branches of the genitofemoral nerve. The external iliac vessels were completely separated from each other. The lower limit of external iliac lymphadenectomy is represented by the deep inferior epigastric vessels. The lateral boundaries of dissection were superficially delineated by the fascia covering the psoas muscle and deeply by the fascia covering the internal obturator and levator ani muscles. The lateralization of the external iliac vessels and obturator nerve allowed the identification of the medial margin of the lymphadenectomy, represented by an imaginary plane which is parallel to the umbilical artery and is delineated by the umbilico-pubic fascia, the bladder and the rectum. The clearing of the obturator fossa began with the mobilizations of superficial obturator nodes which were completely dissected after the identification of the upper face of the obturator nerve. Usually, the obturator lymph nodes were first separated by the psoas and obturator muscle with lateral access to the iliac vessels and then removed from the medial side of the iliac vessels. A vessel retractor (vessel hook) was used to move the iliac vessels laterally during the obturator lymphadenectomy. These nodes were removed en block with the lymphatic fatty tissue which had been previously separated from the internal iliac vessels to the origin of the internal pudendal vessels. The lymphadenectomy continued with the dissection of the deep obturator nodes and gluteal nodes. At the end of the procedure, hemostasis was carefully checked.

Lymphadenectomy was extended cranially to aortic nodes in case of intraoperative detection of bulky nodes or if common iliac node resulted metastatic at frozen section.

Results

From January 1996 to October 2005, 168 patients fulfilling the abovementioned criteria were enrolled in the study and randomized to receive EPL or TPL or LPL. At the end of the study, 56 patients were randomly assigned for each group. Seven patients (4%) were excluded from the study because pelvic lymphadenectomy was not performed (2 and 1 patients of EPL and TPL group respectively for inoperable extensive disease (extracapsular nodal metastases) and 2 and 1 of EPL and TPL group respectively for severe retroperitoneal fibrosis). Clinical characteristics of the patients are shown in Table 1.

The other 161 patients successfully complete pelvic lymphadenectomy according to randomization arm.

All patients in the TPL and EPL groups showed an adequate number of pelvic lymph nodes removed, nevertheless, in 3 patients

Table 1
Characteristics of enrolled patients

	EPL 56 pts	TPL 56 pts	LPL 56 pts	*P*
Mean age ± SD	49 ± 17.2	48 ± 20.3	47 ± 21	ns
Mean BMI ± SD	25 ± 12.4	23 ± 11.8	20 ± 18.4	ns
Cervical cancer stage				
IB1	23	24	24	ns
IB2–IIB	33	32	32	ns
Type of surgery				
Modified radical hysterectomy	0	0	0	ns
Classical radical hysterectomy	56	56	56	ns
Neoadjuvant chemotherapy	28	31	26	ns
PS				
0	39	41	42	ns
1	12	12	11	ns
2	5	3	3	ns

SD = standard deviation.
BMI = body mass index.
PS = performance status.
ns = not significant.
pts = patients.

of LPL group, lymphadenectomy was inadequate. However, these data are not statistically significant (P = ns).

Thus, feasibility of the procedures, analyzed on an intention-to-treat basis, was 96% (2 patients were inoperable), 93% (4 patients were inoperable) and 95% (3 patients had inaccurate lymphadenectomy) for TPL, EPL and LPL group respectively (P = ns).

The mean operative times to perform pelvic lymphadenectomy, the mean number of pelvic lymph nodes, and the intraoperative blood loss (calculated at the end of the lymphadenectomy procedure before starting radical abdominal hysterectomy) are shown in Table 2 (excluding the seven patients who did not undergo pelvic lymphadenectomy). Vascular injuries occurred in 2 EPL patients, 1 TPL patient and in 1 LPL patient. In particular, 2 patients had a lesion of the lumbar vein tributary of common iliac vein, 1 patient had laceration of the internal iliac vein due to a retractor incorrectly placed and 1 patient a lesion of obturator vein. Hemorrhages were controlled easily by suturing with monofilament 5-0 polypropylene in all cases. No intraoperative bowel and urinary complications were recorded.

Table 2
Intraoperative data

	TPL 54 pts	EPL 52 pts	LPL 56 pts	*P*
Operative time (min)	63 ± 7.6	54 ± 6.7	75 ± 8.4	ANOVA test $P < 0.001$ TPL vs EPL $P < 0.001$ EPL vs LPL $P < 0.001$ TPL vs LPL $P < 0.001$
Number of pelvic lymph nodes	36 ± 7.2	35 ± 6.9	30 ± 6.7	ANOVA test $P < 0.001$ TPL vs EPL P = ns TPL vs LPL $P < 0.001$ EPL vs LPL $P < 0.01$
Blood loss (ml)[a]	110 ± 160	110 ± 130	100 ± 120	ANOVA test P = ns post hoc test P = ns

ns = not significant.
[a] Calculated at the end of the lymphadenectomy procedure before starting radical abdominal hysterectomy.

Table 3
Postoperative complications

Complication	EPL 50 pts	TPL 48 pts	LPL 52 pts	*P*
Lymphocyst	4 (8%)	5 (10%)	7 (13%)	EPL vs TPL P = ns EPL vs LPL P = ns TPL vs LPL P = ns
DVT	3 (6%)	2 (4%)	4 (7%)	EPL vs TPL P = ns EPL vs LPL P = ns TPL vs LPL P = ns
Lymphoedema	2 (4%)	2 (4%)	2 (4%)	EPL vs TPL P = ns EPL vs LPL P = ns TPL vs LPL P = ns
Mild paresthesia	4 (8%)	3 (6%)	2 (4%)	EPL vs TPL P = ns EPL vs LPL P = ns TPL vs LPL P = ns
Fever	6 (12%)	4 (8%)	4 (7%)	EPL vs TPL P = ns EPL vs LPL P = ns TPL vs LPL P = ns
Surgical site infection	4 (8%)	3 (6%)	3 (6%)	EPL vs TPL P = ns EPL vs LPL P = ns TPL vs LPL P = ns

DVT = deep venous thrombosis.
ns = not significant.

Twelve patients (6, 2 and 4 patients for TPL, EPL and LPL respectively) were not valuable for postoperative complications because of required addiction of aortic lymphadenectomy.

One hundred and fifty patients (89%), who completed the assigned surgical procedure, were valuable at 2 months (48, 50 and 52 patients for TPL, EPL and LPL respectively).

Considering the entire procedure, including radical abdominal hysterectomy, 8 (19%), 9 (18%) and 10 (20%) patients in TPL, EPL and LPL group respectively required blood transfusions. Postoperative complications of the three groups are shown in Table 3. Lymphocysts were diagnosed in 16 (11%) patients by ultrasonography between the 14th and 20th postoperative day (median 15th). Asymptomatic patients were monitored echographically until spontaneous remission (average time of 50 days); in three cases, drainage was performed.

Mild paresthesias occurred in 4, 3 and 2 patients of EPL, TPL and LPL group respectively. All cases were successfully cured by physiatric therapy.

Table 4
Postoperative parameters

	TPL 48 pts	EPL 50 pts	LPL 52 pts	*P*
Postoperative pain (Vas values)	7.2 ± 2.8	5.2 ± 1.2	4.9 ± 1.1	ANOVA test $P < 0.001$ TPL vs EPL $P < 0.001$ EPL vs LPL P = ns TPL vs LPL $P < 0.001$
Time of postoperative ileus (hours)	68 ± 12.5	37 ± 5.8	34 ± 6.2	ANOVA test $P < 0.001$ TPL vs EPL $P < 0.001$ EPL vs LPL P = ns TPL vs LPL $P < 0.001$
Hospitalization (days)	5.6 ± 0.9	3.2 ± 0.4	3.1 ± 0.3	ANOVA test $P < 0.001$ TPL vs EPL $P < 0.001$ EPL vs LPL P = ns TPL vs LPL $P < 0.001$

ns = not significant.

Postoperative pain, the average time of postoperative ileus and duration of hospitalization are shown in Table 4. In addition, it is worth to note that, concerning operative data, statistically significant differences on radical hysterectomy procedure among groups and between patients affected by early (59 patients) and locally advanced cervical cancer (81 patients) do not exist.

Discussion

Pelvic lymphadenectomy is a fundamental step of the surgical treatment for cervical carcinoma [20–23]. In the past years, different surgical approaches have been described to perform pelvic lymphadenectomy including laparotomy transperitoneal or extraperitoneal and, most recently, the laparoscopic approach has also been introduced. The use of laparoscopy for gynecologic procedures has expanded rapidly: improvements in instrumentation and video technology have allowed the surgeon to perform more complex and major operations through laparoscopy [24]. Recently, several papers have been published about laparoscopic lymphadenectomy in gynecologic malignancies in an effort to determine whether or not laparoscopic lymphadenectomy is comparable to those performed via laparotomy.

To evaluate the adequacy of laparoscopic pelvic lymphadenectomy, the Gynecologic Oncology Group (GOG) has conducted a study on 40 patients submitted to immediate laparotomy after pelvic laparoscopic lymphadenectomy: authors concluded, in regard to the numbers of removed nodes, that in 15% of the cases laparoscopic lymphadenectomy was incomplete [4]. On the other hand, Childers et al. and Hatch et al. reported a median number of 31.4 and 35.5 pelvic nodes removed laparosopically respectively [25,26] which should be considered an adequate number.

In a recent retrospective study, comparing laparoscopic and extraperitoneal lymphadenectomy, the median number of pelvic lymph nodes removed was 18 (7–28) and 32 (16–42) ($P < 0.05$) for laparoscopic and extraperitoneal dissection respectively [13].

In this series, the number of pelvic lymph nodes removed in the LPL group is near the upper limit of what has been reported in the literature; nevertheless, it remains significantly lesser if compared to the numbers of nodes removed via laparotomy.

Moreover, all patients in the TPL and EPL groups showed an adequate number of pelvic lymph nodes removed, nevertheless, in 3 patients of LPL group, lymphadenectomy was inadequate, but these data are not statistically significant (P = ns).

In recent years, several authors have advocated the use of extraperitoneal pelvic lymphadenectomy and different techniques have been used to perform this operation [3,11–13]. In this study, we have used a median vertical incision, as previously described [19], from the umbilicus to the pubis: the retroperitoneal space is therefore easily developed bilaterally with only one incision.

Gallup et al., in a study conducted on 30 patients who underwent extraperitoneal bilateral pelvic lymphadenectomy, concluded that advantages of extraperitoneal approach include easy access on either side of the pelvis, obturator space and short operative time [19].

In addition, Larciprete et al. in a retrospective study reported that the median time required to perform lymphadenectomies using the laparoscopic procedures was significantly higher than for the extraperitoneal route (68 (range 42–92) versus 48 (range 36–64) min, $P < 0.05$) [13].

In our series, the mean operative time for EPL group was significantly shorter if compared to other groups (EPL vs TPL $P < 0.001$; EPL vs LPL $P < 0.001$). On the other hand, patients submitted to laparoscopic lymphadenectomy showed a statistically significant longer time (TPL vs LPL $P < 0.001$).

During pelvic lymphadenectomy procedures, a common intraoperative complication was vascular injury [27]. In general, vascular lesions are represented by lacerations of small vessels draining from fatty lymph node tissue adherent to vessels. However, these lacerations are usually easy to repair and preventable using careful dissection, hemoclips and electrocautery techniques to close the small blood vessels [27]. Major injuries usually involve the lumbar veins, sacral veins and arteries. Injuries are more frequent in the presence of vascular anomalies [28]. In this series, no significant differences were found concerning intraoperative complications and blood loss among groups.

Nine patients developed mild paresthesias but in all cases resumed spontaneously after physiatric therapy. In five patients, an obturator neuropathy was suspected. They presented with adductor weakness with sensory loss over the medial thigh. Genitofemoral neuropathy was identified in four women. These patients presented with “numbness” of the anteromedial thigh.

However, no injury was specifically described during surgical procedures, and the nerves were visualized intact in all patients. Thus, a stretch injury, probably by retractors incorrectly placed, was presumed in all cases.

Lymphocyst formation was the most frequent postoperative complication observed; however, most of the lymphocysts reabsorbed spontaneously (average time of 50 days). In order to decrease lymphorrea, the cranial margin of dissection was clipped in all patients. No significant differences, on this topic, were observed among groups.

Because all patients after the lymphadenectomy procedure underwent transperitoneal radical hysterectomy, postoperative complications will be influenced by the radical hysterectomy. However, all patients were submitted to the same procedure and same radicality on anterior, posterior and lateral parametria.

Concerning postoperative variables, we found that ileus, pain and length of hospitalization were significantly lesser in EPL and LPL than in TPL group.

In particular, postoperative ileus, which is a normal and inevitable response to laparotomy [29–31], was significantly lesser for EPL and LPL group compared to TPL. Kalff et al., studying pathophysiologic mechanisms of postoperative ileus after abdominal surgery, reported that incremental degree of bowel manipulation caused a progressive increase in neutrophil infiltration and a decrease of bowel contractions. They concluded that the degree of gut paralysis is directly proportional to the degree of trauma [30,31]. In a subsequent series, they reported that a simple surgical manipulation of the intestine results in massive movements of leukocytes into intestinal

muscularis and muscle inhibition [32]. In the EPL group, ability to use the peritoneum to retract and protect the bowel allows the surgical team to work without tension with less degree of trauma on the bowel and without direct manipulation. On the other hand, during transperitoneal lymphadenectomy, the bowel is frequently directly manipulated, and the retractors produce a progressive compression. In addition, peritoneum opening allows a major bowel drying and cooling that is not present during laparoscopic and extraperitoneal procedures. We can speculate that transperitoneal approach resulted more "traumatic" for the bowel.

Strictly correlated to postoperative ileus are the postoperative pain and the length of stay. Indeed, the recovery of intestinal peristaltic function and resumption of oral intake, after surgical procedure, is the major obstacle for discharge after surgery [33]. Our data support this correlation.

Our data confirm that: (a) operative time is shorter in EPL group, (b) postoperative recovery and ileus are faster in LPL as well as in EPL group, (c) differences in intra and postoperative complications are not statistically significant among groups, (d) number of lymph nodes removed and, therefore, adequacy of lymphadenectomy are significantly lesser in LPL group even if it could be considered adequate for "systematic lymphadenectomy".

However, this study enrolled 168 patients, and the number of patients per group is relatively small which could account in some observed differences in the characteristics of patients (Table 1) (e.g. BMI), but these are not statistically significant.

In conclusion, in our opinion, EPL and LPL are as feasible and effective as TPL and can be adequately performed with a reasonable complication rate in specialized centers. On the other hand, LPL showed a statistically significant longer operative time.

Both EPL and LPL approaches followed by radical hysterectomy can minimize some postoperative complications reducing length of stay.

Even if the study compares 3 methods of pelvic lymphadenectomy followed by laparotomic radical hysterectomy and the use of laparoscopy followed by laparotomy in the same patients seems to be unreasonable for most surgeons, this could really represent an alternative option to laparotomy. However, considering that laparoscopic radical hysterectomy is not standardized to date, at the present time, EPL plus radical hysterectomy represent the best treatment in patients affected by cervical cancer scheduled for radical surgery.

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