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**TOTAL LAPAROSCOPIC RADICAL HYSTERECTOMY AND PELVIC
LYMPHADENECTOMY IN LOCALLY ADVANCED STAGE IB2-IIB CERVICAL CANCER
PATIENTS AFTER NEOADJUVANT CHEMOTHERAPY**

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ABSTRACT

Objective. To evaluate the feasibility and morbidity of total laparoscopic class C2 radical hysterectomy with pelvic lymphadenectomy (TLRH) in patients with locally advanced cervical cancer stage IB2 to IIB after neoadjuvant chemotherapy (NACT).

Methods. A prospective study was conducted from October 2004 to September 2009. Cervical cancer patients, stage IB2-IIB with complete clinical response after 3 courses of NACT with paclitaxel 175 mg/m², ifosfamide 5 g/m² and cisplatin 75 mg/m² (TIP). underwent TLRH.

Results. Forty patients were included, with a median age of 46 years (range, 25 – 65), BMI of 24 kg/m² (range, 15 – 49). FIGO staging was IB2 in 23, IIA > 4 cm in 6 and IIB in 11 patients. Four patients required conversion to laparotomy. Pathological evaluation showed 9 complete response (pCR), 9 partial response (pPR1) with microscopic tumour, and 15 partial response (pPR2) with macroscopic tumour. Three patients had no response. The median operative time was 305 min (range, 215 – 430); the median estimated blood loss was 250 ml (range, 100 – 400), with four postoperative blood transfusion; the median number of removed pelvic lymph nodes was 25 (range, 11 – 64). The median length of hospital stay was 6 days (range, 3 – 12). The median follow-up time was 37 months (range, 10 – 69), with three patients having a recurrence. One patient died of disease (DOD) after 12 months.

Conclusions. TLRH can be safely performed in patients with stage IB2-IIB carcinoma of cervix after NACT, with advantages of minimal blood loss and morbidity.

Keywords: total laparoscopic radical hysterectomy; cervical cancer; neoadjuvant chemotherapy.

INTRODUCTION

In the recent years, locally advanced cervical cancer treatment has changed from single radiation therapy [1] to concurrent chemo-radiotherapy, since the 1999 National Cancer Institute Alert strongly supported its use in all patients with cancer requiring radiation, based on results of five large randomized trial [2-3]. Neoadjuvant chemotherapy followed by surgery is a completely different therapeutic approach that seems to offer some specific advantages over chemoradiation, such as a potential higher activity against micrometastatic disease, a debulking effect improving subsequent surgical outcome, less toxicity, and an easier management of salvage therapy [4].

Laparoscopic assisted vaginal radical hysterectomy and total laparoscopic radical hysterectomy (TLRH), and, more recently, robotic surgery, have been performed in early stage cervical cancer, with no adverse effect in patient's overall prognosis and survival [5]. This data has also been confirmed by our recent experience [6]. The feasibility of this procedure in locally advanced cervical cancer, especially in patients treated with neoadjuvant chemotherapy, has not been investigated.

The purpose of the present study was to evaluate the feasibility and morbidity of total laparoscopic radical hysterectomy (type C₂ according to Querleu and Morrow classification [7]) with pelvic lymphadenectomy in stage IB2-IIB cervical cancer patients after neoadjuvant chemotherapy.

MATERIALS AND METHODS

Study design and data collection

Patients with histological confirmed locally advanced cervical carcinoma (International Federation of Gynaecology and Obstetrics (FIGO) stages IB2–IIB) [8] were eligible for the study; from October 2004 to September 2009 patients received 3 courses of neoadjuvant chemotherapy, and were then evaluated under anaesthesia in combination with MRI, before and after chemotherapy. Further eligibility criteria included: ECOG performance status of 2 or less, adequate bone marrow reserve (absolute granulocyte count $\geq 2000/\text{ml}$, platelet count $\geq 100\,000/\text{ml}$); and adequate renal, hepatic, and cardiac function. Patients who showed clinical response to NACT were eligible for TLRH with pelvic lymphadenectomy. Patients that were not considered candidates for the laparoscopic approach underwent abdominal radical hysterectomy (ARH). Previous abdominal surgery was not considered a contraindication for the laparoscopic approach.

Approval to conduct the study was obtained independently from an internal review board at each participating institution. Informed consent, including to neoadjuvant chemotherapy, clinical evaluation and laparoscopic surgery, was obtained from all patients in accordance with local and international legislation (declaration of Helsinki). All the patients who underwent TLRH were informed that ARH would be carried out if difficulties were encountered with the laparoscopic approach.

Surgery was performed at the department of surgical gynaecologic oncology of two Italian hospitals, the San Gerardo Hospital, Monza (16 patients), and National Cancer Institute “Regina Elena” of Rome (24 patients). Clinical patient characteristics including age, body mass index (BMI), clinical stage according to FIGO, histopathologic subtype, and tumour grade were recorded. Intraoperative parameters evaluation included complications, blood loss and haemoglobin (Hb) drop. Blood transfusions were administrated if Hb value was $\leq 7\text{ g/L}$. Postoperative parameters included short-term (within 30 days of the procedure), and long-term complications (more than 30 days after the procedure); moreover, status of the surgical margins, status and number of pelvic lymph nodes removed, length of

dissected vagina, width of bilateral parametrium were evaluated, along with pathological response evaluation, length of hospitalization, time to recovery of normal bladder function, median follow-up duration, recurrence, and disease-free interval (DFI).

Neoadjuvant chemotherapy and evaluation of clinical response

Neoadjuvant chemotherapy was chosen according to the regimen of the European study SNAP01 [9]. Clinical objective tumour responses were evaluated according to the Response Evaluation Criteria in Solid Tumours criteria [10]. Pathological responses were defined as follows: optimal response (OPR) included complete pathologic response (PRC) with complete disappearance of tumour in the cervix and negative nodes, or a residual disease with <3mm stromal invasion including in situ carcinoma (pPR1); suboptimal response (SOR) consisted of persistent residual disease with >3 mm stromal invasion on surgical specimen (pPR2). After clinical evaluation of response, before and after NACT, all patients deemed operable underwent total laparoscopic radical hysterectomy (type C₂) with pelvic lymphadenectomy within 4 weeks from the last chemotherapy cycle.

Women with positive nodes, parametrial involvement, cut-through or SOR or OPR but with positive nodes underwent further treatment (chemotherapy, external beam irradiation plus brachytherapy or chemoradiation). Patients with inoperable tumours because of lack of response, defined as <50% decrease or <25% increase in the product of the two largest perpendicular diameters of the measurable lesion, or patients progressive after neoadjuvant chemotherapy, defined as >25% increase in the product of the two largest perpendicular diameters of one measurable lesion or the appearance of new ones, were offered radiotherapy.

Surgical procedure and characteristics

No uterus manipulator devices were used, but the cervix were grasped with a tenaculum and a medical grade silicone balloon, named *colpo-pneumo occluder* (Cooper Surgical) were emplaced in vagina in order to preserve an adequate pneumoperitoneum during colpotomy.

The first step of our technique consist in opening the retroperitoneal spaces according to the following sequence: paravescical space, pararectal lateral space (Latzko), pararectal medial space (Okabayashi), rectovaginal space and vescicovaginal space.

The second step is the “en bloc” level 1 and level 2 pelvic lymphadenectomy according to Querleu and Morrow classification [7]. Para-aortic lymphadenectomy is not routinely performed unless suspicious pelvic lymph nodes are confirmed to have metastatic disease on frozen section evaluation in order to determine the field of postoperative radiation.

Afterwards, type C2 radical hysterectomy is performed as described by Querleu and Morrow [7]. The uterosacral ligament is isolated into two parts according to Yabuki [11], the middle part and the lateral part, which can be coagulated and then dissected by scissors, respectively from the shallow layer to the deep layer close to the pelvic sidewall. The ureter is dissected free from the overlying uterine artery and vesicouterine ligament using the curved tip of the gyros shears and the anterior parametrium is coagulated laterally so that the ureter can be completely unroofed to the point of insertion into the bladder according to Tokyo technique [11-12]. To prevent heat damage to the ureter, saline irrigation is performed during Gyros coagulation. Finally uterosacral ligament is transacted close to the rectum, vesicouterine ligament close to the bladder. Paracervical tissue is also completely removed, including the part caudal to the deep uterine vein.

In young patients whose ovarian function needs to be preserved, the ovaries are transposed laterally to the para-colic gutters and fixed securely to the abdominal wall.

After a careful control of blood loss, to minimize the risk of port site metastases, the vagina and all the ports sites are irrigated with 5% povidine-iodine solution before completion of the surgery.

In all patients the urine catheter is removed 3 days after operation and an intermittent self catheter is used for voiding until the residual urine volume is less than 100 ml.

RESULTS

Patient characteristics (Table 1)

From October 2004 to September 2009, forty patients were included into the study. The median age was 46 years (range 25 – 65), median BMI was 24 kg/m² (range 15 – 49 kg/m²). Four patients converted to laparotomy for the following reasons: one was found with a diaphragm hernia, one was diagnosed as pneumoderma, one was found with a rupture of the uterus at the isthmus due to cancer and the remaining patient was diagnosed with a bulky pelvic lymph node metastasis of about 1.5 cm of diameter not evidenced by MRI and strongly adherent to the left iliac vein. A total of 36 patients underwent total laparoscopic radical hysterectomy (type C₂) and pelvic lymphadenectomy. All patients were evaluated for toxicity and response to chemotherapy.

Toxicity and response to chemotherapy

A total of 90 courses of chemotherapy were administered. Toxicity is shown in table 2. Thirty seven out of 40 patients had good clinical response to NACT. The median diameter of tumour evaluated before chemotherapy administration was 43 mm (range, 30 – 70 mm), while it was 14 mm (range, 0 – 40 mm) after chemotherapy (evaluated under anesthesia and MRI) and 11mm (range, 0 – 33 mm) by final pathological evaluation after surgery. Eighteen patients had an optimal response (pCR, pPR1) to chemotherapy, 15 patients had a pPR2 and 3 patients showed no response with parametrial invasion.

Perioperative parameters (Table 3)

Median operative time was 305 min (range, 215 – 430) and it was strongly correlated with patients BMI. In two patients with high BMI (49 and 43 kg/m²), the operative time was longer than 400 min, and in 5 patients with BMI less than 25 kg/m², the median operative time was 270 min (range, 215 – 300). The median blood loss was 250 ml (range, 100 – 400 ml); none of the patients required intraoperative blood transfusion, while four patients had a postoperative blood transfusion. The median Hb drop was 2 g/L (range, 0.3 – 4.8 g/L) before and 24 hours after operation.

The median number of removed pelvic lymph nodes was 24 (range, 10 – 64). Eight squamous cell carcinoma and one adenocarcinoma patients had a total of 9 positive pelvic nodes at frozen section. In these nine patients, lymphadenectomy was extended to the para-aortic nodes, with negative specimens. The superior border of the dissection in the para-aortic lymphadenectomy was the inferior mesenteric artery and the median number of removed para-aortic lymph nodes was 7 (range, 5 – 11).

The median length of dissected vagina was 21 mm (range, 15 – 45 mm). The median width of parametrium was 30 mm on the right side (range, 15 – 50 mm) and 30 mm on the left side (range, 15 – 60). The surgical margins were free of disease in all cases.

There was 1 intraoperative complication: one patient had injury of the left hypogastric vein and promptly repaired during the same laparoscopic surgery with a total blood loss of 300 ml without need of blood transfusion.

Postoperative parameters

There were 2 postoperative short term complications: in one case postoperative pelvic bleeding was successfully recovered by drainage; a second patient suffered from lymphocyst on the 10th day post-operation.

Long term complications were: bladder symptoms in 16 patients, reduction in bladder sensitivity in 8, recurrent urinary tract infection in 2 and urinary incontinence in 6. Moreover one patient had a left ureteral fistula that was diagnosed 3 month later by urography. This patient underwent placement of a nephrostomy for 5 months and then an ureteral stent that was removed after 3 months with no sequelae. Eleven patients had bowel symptoms: 9 constipation and 2 a reduction of sensitivity. Other 8 patients had symptoms relating to vaginal and sexual function: 3 a reduction of sensitivity, 3 a vaginal pain during sexual intercourse and 2 complaining of vaginal dryness. In contrast, 5 patients, of age less than 45 years who had kept their ovaries, had no change in sexual activity, except for one patient who underwent further radiotherapy. Self catheterization was started on day 3 from the intervention. The time to resumption of normal bladder function ranged from 10 days to 3 months. Four patients treated

with radiation therapy and three with chemoradiation plus brachytherapy showed a worsening in condition. The median length of hospital stay was 6 days (range 3 – 12 days).

Further management and long term follow up

Three patients with parametrial invasion underwent further adjuvant concomitant radio-chemotherapy. Nine patients with positive nodes underwent 3 further cycles of chemotherapy with TIP regimen, and five patients received adjuvant radiation therapy due to the coexistence of lymphovascular space involvement (LVSI).

The median follow-up was 37 months (range, 10 – 69 months). Thirty-three patients are free from recurrence at the time of this report. One patient, who had no pathological response with parametrial invasion, suffered from a central pelvic recurrence, with a DFI of 9 months, and died of disease after 12 months. Another patient, who obtained a partial response, demonstrated pelvic lymph node involvement after neoadjuvant chemotherapy, and treated with adjuvant chemotherapy, showed lung metastasis, with a DFI of 19 months; she underwent removal of metastases and is currently disease free after 56 months. Other two patients, who obtained a partial response, suffered from a pelvic lymph node and lung plus liver recurrence, with a DFI of 5 and 22 months respectively. They underwent chemotherapy and are currently alive with disease after 21 and 34 months respectively.

DISCUSSION

From a recent report, in locally advanced stages cervical cancer, NACT followed by radical hysterectomy showed an absolute benefit of 15% at 5-year survival [9]. Therefore we started the present study with totally laparoscopic radical hysterectomy and lymphadenectomy after NACT based on our previous experience of laparoscopic type III radical hysterectomy in early stage cervical cancer [5].

Response to neoadjuvant chemotherapy

We achieved a good clinical response after NACT by combined evaluation under anaesthesia and MRI. Pathological evaluation showed 9 pCR, 9 pPR1 and 15 pPR2. Notwithstanding the combined evaluation (anaesthesia and MRI) of the cervix size, three patients had no pathological response, with the invasion of parametrium, and one of them had a recurrence after 9 months after the operation and died of disease after 12 months. Therefore the importance of an accurate clinical evaluation after NACT is mandatory. In our study the TIP regimen as NACT has been confirmed to be effective and tolerable, as reported by other recent published trials [9,13].

Surgical procedure

Regarding the surgical procedure, we achieved 90% success rate of laparoscopic surgery with only 4 conversions. There was no limitation of BMI (range, 15-49 kg/m²). Using this technique, we performed total laparoscopic radical hysterectomy in early stage cervical cancer [7], extended to the locally advanced cervical cancer after NACT. To overcome the debate on the shortage of uterosacral ligament and length of vagina resection, several modifications were made in the laparoscopic procedure compared with laparotomy.

First we used the special colpo-pneumo occluder instead of uterus manipulator leading to a better direction of the vagina and sufficient vaginal resection.

Moreover changing the order of dissection in the laparoscopic procedure lead to several advantages. In fact, starting the dissection from the lateral parametrium resulted in significant uterus uplift, thus

making the dissection of the uterosacral ligament easier. In fact, the section of the lateral parametrial just after the section of the upper part of the posterior pillar allows lifting up the lower part of the posterior pillar leading to its better exposure.

The third characteristic of our procedure is the “en bloc” lymphadenectomy. The key point of this procedure is to make an advanced separation of the paravesical and the pararectal space laterally and medially, respectively, then remove pelvic lymph nodes around the vein, artery and nerves completely including the common iliac node pushing the nodes laterally or medially until all the nodes are removed together. So, we emphasize the step by step techniques. Never start the next procedure before you complete the previous one.

Finally when all the lymph nodes were well separated, they can be moved in the ‘En bloc’ way. Using this technique, an average of 24 lymph nodes were removed in both sides, and there were no significant complications except in one patient with lymphocyst.

Median length of hospital stay was 6 days (range, 3 – 12). The reason for this prolonged hospitalization was due to postoperative short term complications that requires a total of 12 days of hospitalisations. Indeed, without these three complications, the median hospital stay was 4 days (range, 3 – 7).

Oncological results

No large series are available thus far to analyze the surgical and oncological results of this approach. The effects of NACT on pelvic tissues are thought to increase the difficulties of surgical dissection, in particular on pelvic structures such as the bladder and ureters. Due to these difficulties, laparoscopic techniques are generally not used to perform radical hysterectomy after NACT. In our study, we demonstrated the feasibility of a laparoscopic approach in this setting in 90% of the cases. The low surgical difficulties of surgery on pretreated tissues were evidenced in our experience by the low rate of conversion to laparotomy. Moreover, we showed that surgical outcomes were similar to others reports on laparoscopic radical hysterectomy and pelvic lymphadenectomy in early cervical cancer without NACT [14-29,6].

1 Recently, Colombo et al. [30] has described the first experience of TLRH for locally advanced cervical
2 carcinoma after concurrent chemoradiation therapy in which he reviewed 102 patients treated 46 with
3 TLRH and 56 with ARH. In the laparoscopic group the intraoperative and postoperative complications
4 were 10.9% and 28.3% respectively, while incomplete resection, that was associated with microscopic
5 or macroscopic residual disease, in 8.7%. The OS and the DFS were 82% and 81% respectively.

6 Although the two studies are hardly comparable, we had less intraoperative complications and free
7 surgical margins compared to this study, probably reflecting the different anatomical alterations
8 induced by chemoradiation.

9 In the present initial experience a radical excisions of paracervix has been performed in all cases
10 because in the letterature there is not agreement on which radicality should be done after neoadjuvant
11 treatment. After the present results, to reduce postoperative long-term complications, in our istitution
12 we start to use of nerve sparing laparoscopic radical hysterectomy (type C₁) in patients with locally
13 advanced cervical cancer after clinical complete response to neoadjuvant chemotherapy.

14 The status of the pelvic lymph nodes and response to neoadjuvant chemotherapy were found to be two
15 major prognostic factors in our cohort of 40 patients operated on after NACT. Disease-free and overall
16 survivals with low local and distant recurrence rates were higher for patients with complete histological
17 response or microscopic residual disease on histopathologic examination. For patients with partial
18 response with significant residual disease after NACT, survival was poor with a high risk of local and
19 systemic relapse. This identified subgroup of patients could be submitted to adjuvant therapies.

20 The present study indicates that totally laparoscopic radical hysterectomy can be performed not only in
21 early stage cervical cancer but also in locally advanced stage cervical cancer after neoadjuvant
22 chemotherapy; this technique is feasible and safe, with less blood loss and less intraoperative and
23 postoperative short term complications. The key point is to make an accurate evaluation and restaging
24 of the patients after neoadjuvant chemotherapy.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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TABLES LEGENDS

Table 1: Clinical characteristics of the 40 women with cervical cancer operated by total laparoscopic type C2 radical hysterectomy (TLRH) with pelvic lymphadenectomy after neoadjuvant chemotherapy (NACT)

Table 2: Maximum grade of toxicity observed during neoadjuvant chemotherapy

Table 3: Surgical outcome of patients with cervical cancer operated by total laparoscopic type C₂ radical hysterectomy (TLRH) with pelvic lymphadenectomy after neoadjuvant chemotherapy (NACT)

TABLES

Table 1: Clinical characteristics of the 40 women with cervical cancer operated by total laparoscopic type C₂ radical hysterectomy (TLRH) with pelvic lymphadenectomy after neoadjuvant chemotherapy (NACT)

Characteristics	Patients (n° = 40)
Mean Age	46 (25-65)
Mean BMI (Kg/m ²)	24 (15-49)
Mean tumour size (mm)	43 (30-70mm)
Histology	
Squamous	33
Adenosquamous	2
Adenocarcinoma	5
FIGO stage	
IB ₂	23
IIA	6
IIB	11
Grading	
G1	2
G2	16
G3	22

Table 2: Maximum grade of toxicity observed during neoadjuvant chemotherapy

Toxicity	Grade	N° of patients (%)
Leukopenia	3 – 4	19 (47.3)
Neutropenia	3 – 4	24 (59.1)
Thrombocytopenia	3 – 4	6 (14)
Anemia	3 – 4	7 (18.3)
Nausea and vomiting	2 – 3	25 (62.4)
Alopecia	3 – 4	30 (75.3)
Sensory neuropathy	1	9 (21.5)
Renal	3 – 4	1 (2.2%)

Table 3: Observed responses after neoadjuvant chemotherapy (NACT) and total laparoscopic type C₂ radical hysterectomy (TLRH) with pelvic lymphadenectomy

Response	N° of patients (%)
pCR	9 (25)
pPR1	9 (35)
pPR2	15 (42)
SD	3 (8)
PD	0

pCR: Pathological complete response; pPR1: Pathological partial response with microscopic tumour; pPR2: Pathological partial response with macroscopic tumour; SD: Stable of disease; PD: Progression of disease

Table 4: Surgical outcome of patients with cervical cancer operated by total laparoscopic type C₂ radical hysterectomy (TLRH) with pelvic lymphadenectomy after neoadjuvant chemotherapy (NACT)

Characteristics	LRH type C ₂
Mean operative time (min.)	305 (215 – 430)
Mean blood loss (cc.)	250 (100 – 400)
Mean Hb drop (gr/dl)	2 (0.3 – 4.8)
Mean pelvic lymph nodes	24 (11 – 52)
Mean para-aortic lymph nodes	7 (5 – 11)
Mean length right parametrium (mm.)	30 (15 – 50)
Mean length left parametrium (mm.)	30 (15 – 60)
Mean length vaginal cuff (mm.)	21 (15 – 45)
Major intraoperative complications	1
Major postoperative complications	2
Blood transfusion	4
Conversion to laparotomy	4
Reoperation	0
Mean hospital stay (day)	6 (3 – 12)

Table 5: Intraoperative and postoperative complications after neoadjuvant chemotherapy (NACT) and total laparoscopic type C₂ radical hysterectomy (TLRH) with pelvic lymphadenectomy

Type of complication	Patients (n° 36)
Intraoperative	
<i>Vascular injury</i>	1 (2.7%)
Postoperative short-term (≤ 30 days)	
<i>Pelvic bleeding</i>	1 (2.7%)
<i>Symptomatic lymphocysts</i>	1 (2.7%)
Postoperative long-term (> 30 days)	
<i>Urinary dysfunctions</i>	16 (44.4%)
<i>Bowel dysfunctions</i>	11 (30.5%)
<i>Vaginal and sexual dysfunctions</i>	8 (22.2%)

Table 6: Adjuvant therapy and long term follow-up

Adjuvant therapy	Patients (n° 36)
None	19
CT	9
RT	5
RT + CT	3
Mean Follow-up (months)	37 (10 – 69)
NED	33
AWD	2
DOD	1

CT: chemotherapy; RT: radiotherapy; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease