Laparoscopic surgery in treatment of Stage IIb cervical cancer after neoadjuvant chemotherapy. A case report and review of the literature

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Summary

Background: A detailed operative procedure of laparoscopic radical hysterectomy (type III) with pelvic and aortic lymphadenectomy after neoadjuvant chemoterapy in treatment of Stage IIb cervical cancer is described.

Case Report: A 50-year-old patient with Stage IIb squamous cell carcinoma of the uterine cervix, who initially was not surgically resectable, received three courses of neoadjuvant chemotherapy that included ifosfamide 5 g/m^2, cisplatin 50 mg/m^2 and paclitaxel 175 mg/m^2 (TIP). Following a partial clinical response to chemotherapy, the patient underwent laparoscopic type III radical hysterectomy with bilateral salpingo-oophorectomy and pelvic and paraaortic lymphadenectomy. The surgical procedure lasted 250 minutes. Blood loss was 310 ml. The patient was discharged on postoperative day 4. The mean length of the resected parametria and paracolpia was 4.1 cm and 2.0 cm, respectively. The number of dissected lymph nodes was 48: 29 pelvic and 19 paraaortic nodes. No major intraoperative or postoperative complications occurred. The patient also underwent adjuvant radiation therapy. Follow-up was performed at six months so far.

Conclusions: This experience suggests that such a surgical procedure is safe. Laparoscopic radical hysterectomy potentially allows for decreased perioperative morbidity and blood loss, faster recovery and better cosmetic results. Large studies with long term follow-up are needed to confirm that this approach may be proposed as an alternative to conventional surgery.

Key words: Cervical cancer; Neoadjuvant chemotherapy; Laparoscopy; Radical hysterectomy.

Introduction

Since the first experiences in 1990, following a learning curve necessary for surgeons to improve surgical techniques, currently the laparoscopic procedure is increasingly proposed in treatment of various types of gynaecologic malignancies.

Video-laparoscopy allows for identification of cleavage planes better than laparotomy, as well as use of more delicate surgical instrumentation. Extended abdominal incisions are also avoided with a consequent decrease in postoperative pain and hospital stay. All of these features turn out to be particularly favourable to those patients who must undergo subsequent adjuvant therapies [1-6].

Laparoscopic surgeons in the USA tend to perform radical hysterectomy through an entirely laparoscopic approach [4-6]. On the other hand, surgical techniques are greatly influenced in Europe by the important tradition in vaginal surgery: vaginal hysterectomy in association with laparoscopic lymphadenectomy has been proposed in treatment of cervical cancer. Thus, the abdominal approach, typical of such interventions, may be converted to a vaginal one with equal adequacy, but with important advantages in postoperative course and hospital stay [1-3].

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Laparoscopy has a high potential of treatment aimed at a permanent cure in cases of cervical cancer at early stages; nevertheless, advanced stage cancer, whose surgical treatment is not feasible or turns to be insufficient, still represents a problem [7]. Chemotherapy, which in the past was considered as palliative and/or a supplement to radiation therapy, has been proposed as a neoadjuvant regimen in order to increase the surgical resectability of tumours judged inoperable [8].

We report a case of Stage IIb carcinoma of the uterine cervix sensitive to neoadjuvant chemotherapy and treated by a totally laparoscopic procedure of radical hysterectomy (type III) with bilateral salpingo-oophorectomy and pelvic and aortic lymphadenectomy. To our knowledge, there are no other studies in the literature reporting such a treatment in similar cases.

Case report

Clinical condition of the patient

M.G., a 50-year-old female, was referred to our Unit of Laparoscopic Surgery in September 2001 due to histological diagnosis of squamous cell cervical carcinoma. Clinical staging of the cancer was assessed on the basis of clinical examination, biopsy, colposcopy, cystoscopy and proctoscopy. Ultrasound, abdominal-pelvic computed tomography (CT) and nuclear

magnetic resonance (NMR) of the pelvis were also performed. The clinical stage was classified as IIb, according to the International Federation of Gynaecology and Obstetrics (FIGO) of 1995. There was no clinical or diagnostic evidence of either metastases or further severe systemic pathologies. After an informed consent was obtained, the patient underwent the following treatment.

Neoadjuvant chemotherapy

A multiagent regimen with ifosfamide, cisplatin and paclitaxel (TIP) was used. The full neoadjuvant chemotherapy consisted of three courses, repeated every 21 days, according to the following sequence: ifosfamide 5 g/m^2 and mesna in a 24-hour continuous infusion (day +1), cisplatin 50 mg/m^2 and paclitaxel 175 mg/m^2 given over three hours (day +2). Before every cycle of the therapy, complete haemachrome, plasma indexes of renal and liver function, and study of the respiratory function were performed.

Clinical examination, colposcopy and pelvic ultrasound were used to evaluate the responsiveness of the primary tumour to chemotherapy. The therapeutic response, which was classified according to the World Health Organization (WHO) guidelines of 1979, was partial: the central tumour decreased more than 50% in volume and the parametrium recovered the normal clinic characteristics with regard to consistency and elasticity.

Surgical technique

Since the patient proved to be sensitive to neoadjuvant chemotherapy, she was submitted to surgery four weeks after completion of the therapy. A laparoscopic type III radical hysterectomy, as defined by Piver MS *et al.* (1974), with bilateral salpingo-oophorectomy and pelvic and aortic lymphadenectomy was performed.

General preparation. A standard bowel preparation one day before surgery was used. The procedure was performed under combined general and epidural anaesthesia. The uterus was mobilised by a "Clermont Ferrand" manipulator (smooth cannula) and cervical dilation was avoided.

Initial operating steps. A 10-mm laparoscope was inserted through a sovraumbilical incision. Three ancillary trocars were placed 2-3 cm under the umbilicus: one 5 mm in the mid-line (surgeon), one 5 mm in the left side (surgeon) and one 10 mm in the right side (first assistant; extraction of lymph nodes). The patient was placed in the Trendelenburg position (15 degrees).

The round ligament was coagulated next to the pelvic wall with bipolar forceps (40W) and transected with endoscopic shears. The anterior and posterior peritoneal layers of the broad ligament were opened and the ureter was identified. A fenestration in the posterior leaf of the broad ligament was performed and the infundibulo-pelvic ligament was coagulated and transected.

Development of pelvic spaces. Retroperitoneal spaces were prepared in order to assess whether or not the neoplasia was surgically resectable. If macroscopically gross parametrial extension (or bulky lymph nodes) is identified, the laparoscopic procedure should be abandoned in favour of laparotomy. Dissection of the paravesical space was aided by introducing endoshears and the bipolar forceps initially in the areolar tissue laterally to the obliterated umbilical artery; subsequently, the space medial to such artery was prepared, thereby skeletonising the artery. The pararectal space was developed between the internal iliac artery laterally, the cardinal ligament anteriorly and the rectum medially. The same surgical procedure was performed bilaterally. The vesico-uterine fold was grasped with an endoclinch and dissected with endoshears, thus allowing for dissection of the urinary bladder from the cervix and upper vagina. Then the uterus was anteverted and anteflexed to develop the rectovaginal space. An assistant performed simultaneous rectal (rectal probe) and vaginal examination (valve of the uterine manipulator), thus delineating the rectovaginal septum. The rectum was dissected from the posterior vaginal wall.

Aortic lymphadenectomy. The surgical access was transperitoneal, according to the technique by Childers *et al.* [1]. The patient was placed in a more stressed Trendelenburg position (approximately 30 degrees). With endoclinch and endoshears the sigmoid meso was mobilised in order to aid dislocation of the bowel to the superior part of the abdomen. Without previous coagulation, the peritoneum was elevated and incised, medially to the right infundibolo-pelvic ligament. The incision was extended from the right to the left and in a caudo-cranial direction, over the vena cava and the aorta, up to the duodenal bulb. The intra-abdominal pressure and the insufflation of CO_2 into the retroperitoneal space facilitated the dissection of the peritoneum. Two tapes blocked by endoclips were used for mobilisation of the ureters. The right ovarian vein and artery were clamped with ligaclips and dissected by endoshears from vena cava and aorta, respectively. Using bipolar forceps and endoshears, a precaval (n = 4 nodes at definitive histology) and paracaval (n = 3) lymphadenectomy was carried out. Then, the ventral tributaries of the inferior vena cava were identified and a retrocaval lymphadenectomy was performed (n = 1). Subsequently, the interaorto-caval nodes (n = 3) were removed. The left ovarian artery was then transected and the preaortic lymph nodes (n = 2) were dissected, while preserving the inferior mesenteric artery. After identification of the left ovarian vein and the lumbar vein, both draining into the left renal vein, a higher paraaortic (n = 2) lymphadenectomy was performed. Lower paraaortic nodes (n = 3) were then dissected, while preserving the fourth and fifth lumbar arteries. Finally, subaortic lymph nodes were removed (n = 1). Nodal tissues were removed separately by a coelio-extractor or by endobag for gross lymph nodes in order to avoid fragmentation and spillage of tumor cells. Adequacy of lymph node dissection was determined visually.

Pelvic lymphadenectomy. The retroperitoneum was opened. Nodal tissue was removed from around the common iliac vessels (n = 7). Preserving the superior hypogastric plexus, lymph nodes of the presacral area (n = 3) were removed. External iliac vessels were separated from the psoas muscle, while preserving the genitofemoral nerve. The external iliac lymph nodes were dissected and removed from lateral surfaces of these vessels (n = 4), and the circumflex iliac vein was identified. Interiliac or "Leveuf et Godard area" [9] lymph nodes, medial and caudal to the external iliac vessels, were then removed (n = 3). The obturator fossa was entered laterally and the obturator nerve and vessels were skeletonized, before removing superficial obturator lymph nodes (n = 6). Finally, respecting the hypogastric nerve, the hypogastric artery and vein were skeletonized (internal iliac nodes n = 2) and parametrial nodal tissue (n = 4) was removed.

Radical hysterectomy. The uterine artery was coagulated and transected at its origin from the internal iliac artery. Introducing a curved dissector into the ureteral tunnel and separating the jaws of a forceps aided the dissection of the ureter from the tunnel. The roof of the ureteral tunnel was transected with cold endoshears. Haemostasis was achieved with endoclips. The cardinal ligament was then coagulated and transected with the bipolar forceps next to the pelvic wall, so that the anterior and

posterior web became communicating. After transection of the external part of the vesicouterine ligament, the ureter was dissected from the medial part of the vesicouterine ligament. This part of the ligament was then coagulated and transected near the bladder, in contrast to the technique of nerve-sparing proposed by Possover *et al.* [10]. The same procedure was performed bilaterally. The uterosacral ligaments were cut next to the rectal wall. Fibers of the autonomic nervous system, localised next to the rectum were preserved. The upper third of the vagina was removed by a circular vaginal incision carried out 3-4 cm under the cervix using monopolar current (80W).

Vaginal procedure. The uterus, the ovaries, the parametria and the upper third of the vagina were removed vaginally. The vaginal vault was closed with continuous sutures of 1-0 polyglactin (polisorb®). A surgical glove filled with sponges was placed in the vagina.

Laparoscopic control. Pneumoperitoneum with CO_2 was re-established and laparoscopic control of haemostasis was performed. Two Robinson drains were placed in the peritoneal cavity.

Postoperative course and histology. These procedure lasted 250 minutes with an estimated blood loss of 310 ml. Bowel function was resumed on the second postoperative day and the patient began eating. The Robinson drains were removed within the third day. The patient was discharged on postoperative day 4 with the bladder catheter in place; she underwent bladder training for 16 days. The patient had a neurogenic bladder dysfunction that has gradually resolved. There were no major intraoperative complications involving injury to major blood vessels, nerves, bowel, bladder or ureters. Lymphocele, pelvic haematoma, fistula or bowel obstructions were not observed. Definitive histology confirmed a moderately differentiated (G2) squamous cell cervical carcinoma with only small residual disease. The median length of lateral parametria was 4.1 cm (right-left: 3.7-4.5 cm); the vaginal margin and paracolpia measured 3.1 cm and 2.0 cm (right-left: 1.8-2.2 cm), respectively. Parametria and paracolpia were negative for neoplasia and surgical margins were adequate. Lymph-vascular space involvement was absent. The number of aortic and pelvic lymph nodes removed was 19 and 29, respectively. Two positive lymph nodes alongside the medial surface of the external iliac vein were found.

Radiation therapy and follow-up

External-beam adjuvant radiotherapy on the whole pelvis (50 Gy) for five weeks was started four weeks after surgery. Six months after this treatment, a follow-up including clinical examination, vaginal cytology and total body CT, was performed. Until now, no recurrence has been observed.

Discussion

The procedure of entirely laparoscopic radical hysterectomy with pelvic and aortic lymphadenectomy was first described by Nezhat *et al.* [4]: the operation was applied to a Stage Ia cervical cancer and lasted 315 minutes. The average operative time reported in the literature for this intervention ranges between 205 and 375 minutes (Table 1) [3-6, 11-13]. The length of procedure in our case was 250 minutes. The differences in operative time could also be attributed to a learning curve of the individual surgeons. Vidal and Garza [14] compared laparoscopic radical hysterectomy with pelvic node dissection versus laparotomy. The operative time was remarkably longer as compared to that of the abdominal operation (4.5 vs 3 hours), but hospital stay was significantly decreased and costs were quite similar [14]. In our case, the hospital stay of four days was much shorter than that reported in the world literature for laparotomy. Short hospital stay might be attributed to early ambulation and return of intestinal function as a result of decreased manipulation of the bowel and stomach. The estimated blood loss in our case (310 ml) compares favourably to that reported [15] as equal to 600 ml for laparotomic radical hysterectomy. Blood transfusions are reported in up to 40% of patients undergoing abdominal radical hysterectomy [15]. In our patient transfusion was not necessary. In laparoscopy, blood loss is minimised by the possibility to identify small vessels through the magnification allowed by laparoscopic optics and the use of bipolar coagulation and endoclips.

Reportedly, the morbidity of recent laparoscopic procedures is no higher than that of conventional techniques [6, 12]. Intraoperative complications, including cystotomy during bladder dissection and difficulty to control bleeding sites requiring conversion to laparotomy, are reported to be infrequent [5]. The reported incidence of postoperative complications (approximately 9%) also compares favourably to other procedures: in particular, unusual or unique complications associated with the laparoscopic features of the technique have not been observed [5]. This may be in part ascribed to improvement of instrumentation: in particular, reduction of secondary electrical injury has been obtained through use of a bipolar coagulator and endoclips as opposed to monopolar cautery.

Table 1. — *Laparoscopic radical hysterectomy (LRH).*

Authors		No. of cases	Stage FIGO	*Type of hysterectomy	Operative time (mins.)	No. of Pelvic nodes	No. of Aortic nodes	Blood loss (ml)	Hospital stay (days)
Nezhat *et al.* [4]	(1993)	7	Ia_2-IIa	NI	315	22	6	30-300	2.1
Sedlacek *et al.* [6]	(1994)	14	Ib	NI	NI	NI	NP	NI	NI
Canis *et al.* [11]	(1995)	13	Ia_2-IIa	III	300	NI	NP	NI	7
Possover *et al.* [3]	(1998)	2	NR	II	375	26.8	7.3	NI	11.6
Hsieh *et al.* [12]	(1998)	8	Ia_2-Ib_1	III	298	19.2	6.6	476	6.5
Kim and Moon [13]	(1998)	18	Ia_2-Ib_1	NI	363	22	NP	619	12
Spirtos *et al.* [5]	(2002)	78	Ia_2-Ib	III	205	23.8	10.3	225	2.9

NI = not indicated; NP= not performed

*Type of hysterectomy according to Piver M.S. *et al.* (1974).

When laparoscopy is applied to oncology, the radicalness of surgery must not be compromised by the technique. Choosing a 5 mm incision instead of a 25-30 cm one should not influence the extent of surgery. In our case, the size of parametrial resection and vaginal margin are equal to those achieved by laparotomy [16]. Moreover, the lymph node count was 48. In the Gynaecologic Oncology Group (GOG) protocol n° 9207, in which 85% of patients were considered to have had a complete lymphadenectomy, the lymph node counts averaged 43.2. In this study, in which nodal dissection was performed endoscopically, all aortic lymph node dissections were found to be adequate [17].

There is no agreement about the usefulness of aortic lymphadenectomy in the treatment of cervical cancer. Paraaortic lymph node metastases are reported in 20-30% of Stage IIb cervical carcinoma, [7]. Because of such a high prevalence, we believe that systematic aortic lymphadenectomy should be performed in this stage of the neoplasia. Moreover, paraaortic lymphadenectomy reduces the need of extended field radiation therapy as treatment of aortic node metastases. Such therapy has been associated with an increase in morbidity, without a significant impact on the overall survival [19]. In our case, the neoadjuvant chemotherapy also did not permit us to modulate the extent of lymphadenectomy on the basis of frozen section analysis.

Systematic aortic and pelvic lymphadenectomy with integral dissection of the entire lymphatic and connective tissue up to the tunica adventitia, seems to permit removal of a greater number of lymph nodes and interruption of most of the collectors between the neoplastic focus and the Pequet's Cysterna, drainage station of most of the lymph originating in the pelvic organs [18].

The transperitoneal approach used, has the advantage of being easier for gynaecologists who are not familiar with direct retroperitoneal surgery. However, when using this route, the surgeon faces the technical difficulties related to bowel loops. This technical point could partly explain why most reported cases of laparoscopic paraaortic lymphadenectomy are limited to the level of the inferior mesenteric artery. Nevertheless, such surgical procedure involves a particularly difficult learning curve in order to achieve a standard similar to that of laparotomy.

Another issue is the possible dissemination of malignant cells following laparoscopic surgery. Port-site recurrence (PSR) following laparoscopy for cervical cancer is uncommon and concerns squamous or adenocarcinoma of the cervix with disseminated intraperitoneal cancer [20]. PSR descriptions after laparoscopy for cervical carcinomas have always concerned laparoscopy with pelvic exploration or hysterectomy with or without lymphadenectomy. The PSRs were probably due in part to direct contamination during extraction of the node involved without a bag through a small wound incision [21]. In our case, nodal tissues were removed separately by a coelio-extractor or by endobag for gross lymph nodes in order to avoid fragmentation. However, Kadar [20] reported two women with port-site recurrences at the lower and upper abdominal trocar sites after laparoscopic aortic lymphadenectomy for the treatment of squamous cell carcinoma of the cervix. All recurrences occurred at untreated 5-mm trocar sites, which were not used for lymph node extraction. No recurrences developed at the 10 mm trocar sites (umbilical or suprapubic) that were used for tumour extraction. An intact surgical specimen and the use of a plastic retrieval bag did not exclude the risk of recurrence. Kadar suggest that port-site recurrences are preventable by appropriate postoperative chemotherapy and radiation. In the present study all PSRs were associated with persistent or metastatic disease, making the probability of tumour exfoliation into the peritoneal cavity extremely high; isolated port-site recurrences were not observed. The question is whether PSRs are simply an unusual local manifestation of disseminated intra-abdominal disease, or indicative of a recurrence that would not have occurred with laparoscopy. Lavie *et al.* [22] reported the first case of port-site recurrence in a patient with Stage Ib adenocarcinoma of the cervix and negative lymph nodes; however some authors have suggested that adenocarcinomas are more likely to recur at the port site [23]. Recently, Kohberger *et al.* [24] reported the first case of port-site recurrence after laparoscopic surgery in a patient with node-negative Stage Ib squamous cell cervical carcinoma. Nineteen months postoperatively, the patient presented with a soft tissue mass at the suprapubic laparoscopic trocar site. The patient has been followed for 24 months without evidence of recurrence. In patients with negative lymph nodes and no intraperitoneal disease, it may be postulated that cells dislodged at the time of cervical manipulation and biopsy passed out through the fallopian tubes and implanted in the laparoscopic port site by the chimney effect created by the pneumoperitoneum [23]. In our case, the mechanical irritants of the port site were reduced and trauma to the tumour was minimized: the uterine cannulation applied on the external cervical surface was smooth and cervical dilation was avoided. Therefore, all patients undergoing laparoscopic surgery for malignancies should have careful follow-up with special attention to the port sites.

As regards survival, to which the effectiveness of any oncologic procedure is definitely related, Spirtos *et al.* reported on a minimum follow-up of three years of 78 patients with cervical cancer (Stage I), who underwent laparoscopic radical hysterectomy with aortic and pelvic lymphadenectomy. They found a recurrence rate of 11% (8 patients) and an overall-survival rate of 92% [5]. Due to the small number of cases observed, any firm conclusion on recurrence and survival rates related to the procedure may not be drawn.

Various series published in the literature and our case suggest that laparoscopy may represent an interesting alternative in the surgery of some types of gynaecological cancer. Large prospective randomised studies are needed to confirm this issue.

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