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Neoadjuvant chemotherapy followed by robotic radical hysterectomy in locally advanced cervical cancer: A multi-institution study

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HIGHLIGHTS

- Minimally invasive surgery is one of the most exciting areas of development in gynecologic oncology.
- Neo-adjuvant chemotherapy followed by radical surgery has become one of the alternatives to concomitant radio-chemotherapy.
- The development of robotic technology has facilitated the application of minimally invasive techniques in gynecologic oncology.

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ABSTRACT

Objective. Minimally invasive surgery has been performed in locally advanced cervical cancer (LACC) without adverse effect in patient's overall prognosis and survival. The aim of this report is to evaluate the feasibility and morbidity of total robotic radical hysterectomy (TRRH) with pelvic lymphadenectomy in patients with LACC after neo-adjuvant chemotherapy (NACT).

Methods. From February 2008 to April 2013 a retrospective data collection of women undergoing TRRH for cervical cancer stage FIGO IB2 to IIB, after neo-adjuvant chemotherapy, was conducted at "Regina Elena" National Cancer Institute of Rome and European Institute of Oncology of Milan. All patients deemed operable underwent TRRH with pelvic lymphadenectomy within 4 weeks from the last chemotherapy cycle.

Results. Median operative time was 225 min (range, 105–387 min). The median blood loss was 150 mL (range, 30–700 mL). The median number of removed pelvic lymph nodes was 23 (range, 8–69). Sixteen patients had an optimal response (12 PCR, 4 pPR1) to chemotherapy, 33 patients had a pPR2 and 11 patient showed stable disease. Adjuvant therapy was administrated in 36 patients (60%). We experienced one intra-operative complication and 19 post-operative complications, but no conversions to laparotomy were necessary to manage these complications. Six patients received a blood transfusion. At the time of this report, with a median follow-up of 28.9 months, 50 patients (83%) are free from recurrence.

Conclusion. This experience demonstrates the feasibility of TRRH pelvic lymphadenectomy after NACT in LACC with good accuracy and safety.

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Introduction

At the present time, the standard treatment for women affected by locally advanced cervical cancer (LACC) is concomitant radio-chemotherapy [1].

Neo-adjuvant chemotherapy (NACT) followed by radical surgery has become one of the alternative treatment options [2]. Nowadays the results of multicentric randomized trial SNAP01 and SNAP02 confirmed that regimen of paclitaxel, ifosfamide and cisplatin (TIP) is one of the most active neo-adjuvant chemotherapeutic regimens although with a considerable associated hematologic toxicity [3,4]. Possible advantages of neo-adjuvant chemotherapy prior to surgery include the potential for reducing tumor volume, increasing resectability and helping to control micro-metastatic disease [5–7].

Minimally invasive surgery has been performed in early stage cervical cancer without adverse effect on patient's prognosis and survival [8]. Our experience indicates that total laparoscopic radical hysterectomy can be performed not only in early stage cervical cancer but also in locally advanced cervical cancer after neo-adjuvant chemotherapy, with less blood loss and less intra-operative and postoperative short term complications [9]. The development of robotic technology has

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facilitated the application of minimally invasive techniques in gynecologic oncology [10], and also the feasibility of this procedure in locally advanced cervical cancer after neo-adjuvant chemotherapy, has been investigated [11].

The current multicenter study sought to evaluate and confirm the feasibility and morbidity of total robotic radical hysterectomy (TRRH) with pelvic lymphadenectomy in patients with locally advanced cervical cancer after NACT.

Material and methods

This multi-institutional study has involved patients from two oncological institutions: European Institute of Oncology of Milan and the "Regina Elena" National Cancer Institute of Rome.

Study design and data collection

From February 2008 to April 2013, patients with histologically confirmed locally advanced cervical carcinoma (International Federation of Gynecology and Obstetrics (FIGO) stages IB2–IIB) [12] with clinical response after 3 courses of NACT were eligible for the study and underwent TRRH using the Da Vinci Si Surgical System® (Intuitive Surgical Inc®, 1266 Kifer Road, Building 101 Sunnyvale, CA).

Pre-treatment evaluation included: medical history collection, physical examination, vaginal-pelvic examination, chest X-ray, pelvic magnetic resonance imaging (MRI) scans and Positron emission tomography scan (PET-CT). Cystoscopy and/or proctoscopy were performed in case of suspicious involvement of the bladder or of the rectum, respectively. Further eligibility criteria included: ECOG performance status of 2 or less, adequate bone marrow reserve (absolute granulocyte count $\geq$2000/mL, platelet count $\geq$100,000/mL); and adequate renal, hepatic, and cardiac functions. Patients that were not considered candidates for the robotic approach underwent abdominal radical hysterectomy (ARH). Previous abdominal surgery was not considered a contraindication for the TRRH. Approval to conduct the study was obtained independently from an internal review board at each participating institution. Informed consent to neoadjuvant chemotherapy, clinical evaluation and robotic surgery, was obtained from all patients in accordance with local and international legislation (declaration of Helsinki) [13]. All the patients who underwent TRRH were informed that the procedure could have been converted to laparotomy if necessary.

Clinical patient characteristics including age, body mass index (BMI), clinical stage according to the FIGO classification, histopathologic subtype, and tumor grade were recorded. Intra-operative parameters including blood loss and complications were recorded as well blood transfusions were performed if Hb value was $\leq$7 g/dL. Postoperative parameters included short term (within 30 days of the procedure), and long term complications (more than 30 days after the procedure), length of hospitalization, time to recovery of normal bladder function, median follow-up duration, recurrence, disease-free survival (DFS), and overall survival (OS). Complications were defined according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [14]. Moreover, status of the surgical margins, status and number of removed pelvic lymph nodes, length of dissected vagina and width of bilateral parametrium were evaluated.

Neo-adjuvant chemotherapy and evaluation of clinical response

TIP (paclitaxel 175 mg/m^2 + ifosphamide 5 g/m^2 + cisplatin 75 mg/m^2) [3] regimen was chosen as neo-adjuvant chemotherapy for squamous cervical carcinoma and TEP regimen (paclitaxel 175 mg/m^2 + epirubicin 80 mg/m^2 + cisplatin 75 mg/m^2) [15] for cervical adenocarcinoma. Clinical objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors criteria [16]. Pathological responses were defined as follows: optimal response (OPR) included complete pathologic response (PCR) with complete disappearance of tumor in the cervix and negative nodes, or a residual disease with <3 mm stromal invasion including in situ carcinoma (pPR1); and suboptimal response (SOR) consisted of persistent residual disease with >3 mm stromal invasion on surgical specimen (pPR2). After clinical evaluation and radiological of response, before and after NACT, all patients underwent TRRH 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 chemo-radiation).

Surgical procedure

Patients were placed in the lithotomy position with the arms tucked at each side. After creation of a pneumoperitoneum to 12 mmHg with a trans-umbilical Veress needle, a 12-mm trocar was placed at 5 cm cranial to the umbilical. Three 8-mm trocars, specific for the Da Vinci robotic systems (Intuitive Surgical) were placed: one (arm 1) on the right side of the abdominal wall, medial and cranial to the right anterior upper iliac spine, and two on the left side of the abdominal wall, the first (arm 2) on the left lowest rib and the second (arm 3) medial and cranial to the left anterior upper iliac spine on the same line of the right trocar, and fastened to the robotic arms. An assistant 10-mm trocar was placed on the right side of the abdominal wall, 7–10 cm laterally, from the supra-umbilical trocar. After we obtained the Trendelenburg position (30 grade), the Da Vinci robotic column was positioned near the operating table between the patient's feet and docked. The instruments were introduced: a bipolar grasper and a PK grasper on the left robotic trocars (arms 2 and 3, respectively), and a monopolar scissor on the right robotic trocar (arm 1). A 30 grade Surgical Intuitive endoscope was used during all operations. No uterine manipulator was used in any patient, 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 [17]. The robotic aortic lymphadenectomy was reserved to patients with pelvic nodes disease at intra-operative examination or bulking nodes identified at the time of surgery [18]. In case of positive aortic nodes at intra-operative examination, hysterectomy was not performed; patients were excluded from the protocol and were referred to the radiotherapist.

In the third step Class C1 TRRH according to Querleu and Morrow classification [17] was performed. After a careful control of hemostasis, to minimize the risk of port site metastases, the vagina prior to removal of the ports and all the port sites are irrigated with 5% povidone–iodine solution prior to the completion of the surgery [19].

In all patients the urine catheter is removed 3 days after operation and patients are instructed to do intermittent self catheterization for voiding until the post-voiding residual is less than 100 mL.

Results

Sixty patients were included in the study and underwent TRRH and pelvic lymphadenectomy after NACT (Table 1).

Chemotherapy toxicity

All women were evaluated for toxicity and response to chemotherapy. Ifosfamide was discontinued in three patients due to allergic

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