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High-dose density chemotherapy followed by simple trachelectomy: full-term pregnancy

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Abstract. Robova H, Pluta M, Hrehorcak M, Skapa P, Rob L. High-dose density chemotherapy followed by simple trachelectomy: full-term pregnancy. *Int J Gynecol Cancer* 2008;18:1367-1371.

We report five patients with early-stage cervical cancer who do not fulfill criteria of fertility-sparing surgery (tumor more than 2 cm in the biggest diameter or infiltrating more than half of stroma). Five patients received three cycles of dose density neoadjuvant chemotherapy (NAC) at a 10-day interval: cisplatin plus ifosfamide in squamous cell cancer or plus doxorubicin in adenocarcinoma with good tolerance. After NAC, they underwent laparoscopic pelvic lymphadenectomy and vaginal simple trachelectomy. Two patients had no residual tumor, two had only microscopic residual disease, and one had macroscopic residual disease. Two women became pregnant 5 and 8 months after surgery, one delivered in term healthy baby and one is now in the second trimester of pregnancy without any complications. NAC followed by fertility-sparing surgery seems to be feasible treatment for women with tumor bigger than 2 cm or infiltrated more than half of the stroma.

KEYWORDS: neoadjuvant chemotherapy, pregnancy, sentinel lymph node biopsy, simple trachelectomy.

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Increasing age at time of the first delivery brings with it certain problems. There are more women with cervical cancer who wish to be pregnant and an increasing number of oncogynecologic departments perform



fertility-sparing surgery. The most common procedure is radical vaginal trachelectomy; an alternative is simple trachelectomy or radical abdominal trachelectomy⁽¹⁻⁴⁾. Oncologic outcomes are normally very good if the tumor does not exceed 2 cm in diameter at its largest point or if it does not infiltrate more than half of the stroma. Five-year survival is more than 95% in these cases with good prognosis. Pregnancy outcome is very good in women after radical vaginal trachelectomy or simple trachelectomy, but not so good after radical abdominal trachelectomy^(2,5-7). Adequate free margins are essential for the safety of trachelectomy (7 mm is a minimum). The preservation of an adequate amount of stromal tissue is fundamental for good pregnancy outcome; at our department, 10 mm is considered a minimum requirement. Fertility-sparing surgery is usually performed in nulliparous women who quite often have a very small cervix, and thus, trachelectomy can be a serious problem when performed on tumors that are about 20 mm. In such cases, it is not possible to save a sufficient amount of stroma. It makes little sense to perform fertility-sparing surgery if we do not believe in successful pregnancy results. The literature confirms that neoadjuvant chemotherapy (NAC) works well in stage IB2 cervical cancer before performing Wertheim radical hysterectomy⁽⁸⁾. NAC can decrease the volume of a tumor before surgery to achieve adequate margins without too much loss of cervical stroma. Based on the results of our cervical cancer studies ("Simple trachelectomy in cervical cancer IA1 and small IB1" and "Neoadjuvant chemotherapy in cervical cancer IB2"), the ethical committee approved the study protocol regarding NAC and fertility-sparing surgery in January 2005. All women under the age of 40 years with a desire to be pregnant and who have cervical cancer involving more than half of the stroma but no more than two thirds or a tumor larger than 2 cm were included in the study. The surgical procedure has been described earlier⁽⁶⁾. All women signed an informed consent form that radical hysterectomy should be performed in the event of positivity of lymph nodes or inadequate margins. The treatment protocol is depicted in Figure 1.

Case reports

Case 1

Invasive squamous cell cancer grade 2 with lymphovascular invasion (LVSI) was diagnosed in a 25-year-old nulliparous woman by punch biopsy. Colposcopic findings showed an exophytic tumor 20 × 20 mm. Magnetic resonance imaging (MRI) diagnosed tu-

mor 20 × 20 × 10 mm which involved more than half of the cervical stroma, vaginal ultrasonography (US) confirmed MRI. The patient received three cycles of dose density chemotherapy in a 10-day period (cisplatin 75 mg/m² and ifosfamide 2 g/m²). She presented thrombocytopenia grade 3 and leukopenia grade 2 after a third course of chemotherapy. No other toxicity was observed. Sentinel lymph node (SLN) biopsy and laparoscopic lymphadenectomy were performed 44 days after initiation of the chemotherapy. A frozen section of two SLNs was negative and final histopathology of 16 pelvic nodes also proved negative. Simple trachelectomy was undertaken 1 week after the lymphadenectomy. Histopathology showed only degenerative and regenerative changes: no tumor or precancer lesion was found. The patient is without evidence of disease 27 months later. As of this writing, the patient does not plan pregnancy.

Case 2

Large loop excision of transformation zone was performed on a 26-year-old nulliparous woman. This procedure revealed endometrioid adenocarcinoma grade 3 with massive LVSI. MRI showed a residual tumor 44 × 36 × 19 mm which infiltrated two thirds of the cervical stroma and US showed tumor 31 × 28 × 24 mm.

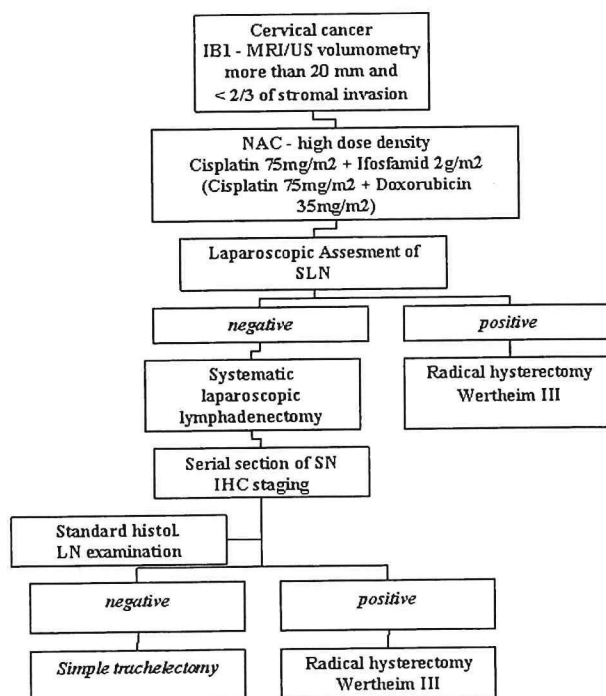


Figure 1. NAC-sentinel lymph node mapping and conservative surgery. LN, lymph node; IHC, immunohistochemistry.

The patient received three cycles of platinum 75 mg/m² and doxorubicin 35 mg/m² in a 10-day interval. She had no hematologic or other toxicity. After the third course of chemotherapy, the patient decided to undergo radical hysterectomy as opposed to conservative surgery. We therefore performed radical hysterectomy. Histopathology did not reveal any cancer in the specimen, but it did show some necrotic changes. Totally, 29 lymph nodes were negative.

Case 3

Adenocarcinoma mucinous endocervical type grade 1 with LVSI was diagnosed in a 30-year-old nulliparous woman by excisional biopsy (20 × 15 mm). Colposcopy detected a 15-mm exophytic tumor on a very small cervix. MRI showed a residual tumor (17 × 11 × 5 mm), which involved two thirds of the cervical stroma (US confirmed MRI findings). Three cycles of the dose density chemotherapy were applied (cisplatin + doxorubicin). We did not observe any serious toxicity. SLN biopsy and laparoscopic lymphadenectomy were performed after 37 days from the beginning of chemotherapy. A frozen section of two SLNs was negative as were all 22 pelvic lymph nodes. Simple trachelectomy was indicated: a residual tumor (0.5 mm) and necrotic tissue were found. The woman was treated with antibiotics 3 weeks after surgery for inflammatory lymphocyst. She became pregnant 8 months after surgery. No complications occurred during her pregnancy and she delivered in the 39th week of gestation a spontaneously healthy boy weighing 3620 g. She is without evidence of disease 23 months after the surgery.

Case 4

Punch biopsy diagnosed squamous cell cancer grade 3 with LVSI in a 24-year-old nulliparous woman. Colposcopy detected a 30 × 25-mm tumor and MRI confirmed the diagnosis from the colposcopy (tumor 30 × 23 × 10 mm); US showed a 20 × 10 × 10 mm tumor. Three cycles of platinum plus ifosfamide were applied. The patient had grade 2 gastrointestinal toxicity. After the third course, grade 2 thrombocytopenia and neutropenia were noted. Surgery was done 40 days from the first course of chemotherapy. Two SLNs were perioperatively negative as was the final histopathology of the pelvic lymph nodes. The residual tumor measured 2 mm. Stenosis of the endocervical canal occurred 9 months after surgery, which led us to perform dilatation of the cervix. A Papanicolaou smear proved negative, but high-risk human papillomavirus are still positive.

Case 5

A 31-year-old nulliparous woman showed evidence of squamous cell cancer grade 3 with LVSI as diagnosed by excisional biopsy. Colposcopy indicated that the exophytic cancer was 25 mm in diameter. MRI showed that a residual tumor (24 × 17 × 15 mm) infiltrated more than half but not more than two thirds of the cervical stroma (US confirm MRI results). Three cycles of platinum plus ifosfamide chemotherapy were administered. The patient showed no toxicity after chemotherapy. The interval between the surgery and the first course of chemotherapy was 40 days. SLNs were negative as were all 22 pelvic lymph nodes. The residual tumor was 13 × 6 mm. This patient is without evidence of disease 9 months postsurgery. She became pregnant 5 months after completion of therapy with no indications of pathology.

Discussion

The oncologic outcomes of fertility-sparing surgery in cervical cancers that infiltrate more than half of stroma or are bigger than 2 cm are classified as unsatisfactory^(9–11). The inclusion criterion in most centers is that the largest diameter of the tumor must be less than 2 cm. In the present study with young patients, the tumor volume and the amount of infiltrated stroma are more important determinants than the biggest diameter because they usually have a very small uterine cervix not bigger than 25 mm in longitudinal axis. We performed tumor volumetry by MRI and vaginal US in all these patients in order to evaluate how much of the stroma is involved. Before starting with the NAC protocol, all women with tumor infiltrated more than half of the cervical stroma or there existed a tumor bigger than 2 cm underwent radical hysterectomy Wertheim, type III.

The lymphovascular space involvement is also a very important prognostic factor in early-staged cervical cancer⁽¹²⁾. Some authors exclude patients with LVSI from conservative protocols. In our department, LVSI is not considered an exclusion criterion^(6,7). Massive LVSI was diagnosed in all women from our group with NAC.

There is a question regarding safety of the simple trachelectomy in patients with SLN and other negative pelvic nodes. We consider SLN mapping as a safe method, even after NAC, because the SLN specific side detection rate in cervical cancer stage IB2 after NAC is high (90.4%) when we use a combination of blue dye and ⁹⁹Tc⁽¹³⁾. The lymphatic channels are often close to the uterine artery in the parametrium and thus cannot be removed by radical vaginal trachelectomy; rather,

laparoscopy or abdominal trachelectomy has to be employed. In these cases, some authors recommend abdominal radical trachelectomy. The parametria, including the uterine artery, are resected during the abdominal procedure, as this approach seems to increase safety. When we perform the SLN procedure, we remove blue afferent lymphatic channels or nodes from the parametrium; these specimens are then sent separately to the histopathology. Thus, the surgical procedure has the same safety as radical abdominal trachelectomy. Abdominal trachelectomies do not have good pregnancy outcome though the oncologic results are very good⁽²⁾. For good pregnancy outcome, the crucial factor is the amount of remaining stromal tissue. However, the safe margins have to be the same in abdominal as in vaginal procedures and the same amount of cervical stroma has to be removed. Another factor for poor pregnancy results is that the important nerves for tubal motility are completely severed during abdominal radical trachelectomy.

NAC followed by radical hysterectomy is used in Europe in stage IB2 bulky cervical cancer as an alternative treatment to chemoradiotherapy, but no data exist about NAC followed by radical hysterectomy in stage IB1 cervical tumor. NAC reduces tumor volume and number of positive lymph nodes. Our results are very good if we use NAC in dose density regimens with short intervals between courses⁽⁸⁾. Our experience with high-dose density NAC is adapted from bulky stage IB2 cervical cancers that we used from 1998 without any serious adverse events⁽¹⁴⁾. NAC can be an opportunity for patients who wish to preserve fertility without increasing the risk of recurrence. The tumor volume reduction after NAC permits less radical removal of the cervical stroma, which therefore improves the chance for successful pregnancy^(15,16). The incision is performed approximately in the level of proximal border of the original tumor (before NAC). Without NAC, we are not able to obtain safe margins with preserving of sufficient amount of cervical stromal tissue. Two of our patients had no residual tumor (after NAC one patient decided to have radical hysterectomy), two had only microscopic residual disease, and one had macroscopic residual tumor, but the volume in that tumor was reduced by 50%. No inadequate tumor margins were seen in our group of patients. No radical hysterectomy was performed till this time from indication of positive lymph nodes or positive margins. In our patient group, we had two spontaneous pregnancies (one delivery in term and one ongoing pregnancy) and no recurrence.

The use of an alkylating agent in women in reproductive age can result in impairment of the ovarian

function. In the past, we have had good experience with cyclophosphamide in high-risk malignant gestational trophoblastic disease with no impact on ovarian function. In our patients, we use 2 g/m² of ifosfamide and no more than a cumulative dose of 3 g per one cycle, which means that the cumulative dose is no more than 9 g. All our patients had regular menstrual cycles within 3 months.

Because of toxicity and mutagenicity of chemotherapy, we typically recommend pregnancy 1 year after the end of chemotherapy. One woman from our group became pregnant 8 months after the conclusion of chemotherapy. The first trimester screening was normal and the second trimester screening and US in the 20th week of pregnancy were within the normal range. She delivered in term a healthy baby. Another woman became pregnant 5 months after chemotherapy treatment. This patient has shown normal pregnancy in the second trimester.

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Therapy-related myelodysplasia and acute myeloid leukemia following paclitaxel- and carboplatin-based chemotherapy in an ovarian cancer patient: a case report and literature review

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Abstract. Yeasmin S, Nakayama K, Ishibashi M, Oride A, Katagiri A, Purwana IN, Iida K, Nakayama N, Miyazaki K, Ishikura, H. Therapy-related myelodysplasia and acute myeloid leukemia following paclitaxel- and carboplatin-based chemotherapy in an ovarian cancer patient: a case report and literature review. *Int J Gynecol Cancer* 2008;18:1371–1376.

Alkylating agents have strong leukemogenic potential. There are a number of recent acute myeloid leukemia (t-AML) cases related to previous paclitaxel exposure. These leukemias tend to be of aggressive subtypes with long-latency periods. Unlike previously reported cases, the present case was of the secondary acute megakaryoblastic myeloid leukemia (AML M7) subtype. Additionally, it did not harbor a translocation in chromosome 19. A 73-year-old woman was diagnosed with t-AML M7 with antecedent myelodysplasia. Leukemia followed a second induction of paclitaxel- and carboplatin-based chemotherapy for recurrent ovarian cancer. Her second induction began 25 months after completion of her first course of chemotherapy. The increased incidence of postpaclitaxel leukemia suggests a probable role for paclitaxel as a leukemogenic agent. It highlights the importance of assessing for leukemia risk factors prior to beginning paclitaxel therapy.

KEYWORDS: myelodysplasia, paclitaxel, secondary leukemia.

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Improvements in chemotherapy have significantly increased the life expectancy of many cancer patients. Understanding the long-term complications of these drugs is now a priority. The most serious long-term complication of chemotherapy is the development of a second malignancy, particularly acute myeloid leukemia^(1,2). Therapy-related acute myeloid leukemia