Mandić et al. Scr Med 2022 Sep;53(3):265-70. DOI:10.5937/scriptamed53-39686
CASE REPORT

Simple Trachelectomy Following Neoadjuvant Chemotherapy in Cervical Cancer Over 2 cm in Size - a Case Report and Review of Literature

Aljoša Mandić,[1, 2] Bojana Gutić,[1, 2] Miona Davidović-Grigoraki,[3] Đorđe Petrović,[1, 4] Nenad Šolajić,[1, 2] Gabrijel-Stefan Nađ[2]

1. Medical Faculty, University of Novi Sad, Novi Sad, Serbia.
2. Oncology Institute of Vojvodina, Novi Sad, Serbia.
3. Private Gynaecological Clinic Miona Davidovic-Grigoraki, Athens, Greece.
4. Clinic for Obstetrics and Gynaecology, Clinical Centre of Vojvodina, Novi Sad, Serbia.

Correspondence:
ALJOŠA MANDIĆ
E: mandic.aljosa@onk.ns.ac.rs

Abstract

In the past few decades fertility preservation has emerged as a treatment modality for cervical cancer patients. Different surgical methods have been described, such as open or minimally invasive trachelectomy and gross cervical conisation combined with laparoscopic lymphadenectomy. A thirty-year-old nulliparous woman with uterine cervical cancer FIGO stage IB2 (classification from 2009) underwent neoadjuvant chemotherapy. After three cycles of chemotherapy with cisplatin and iphosphamide there was no colposcopic findings of cervical invasion, therefore a conservative surgery was performed. The patient underwent laparoscopic pelvic lymphadenectomy, cervical amputation and the endocervical curettage. The histopathology confirmed a complete response to chemotherapy.

Key words: "Bulky" cervical cancer; Fertility sparing surgery; Neoadjuvant chemotherapy.

ARTICLE INFO
Received: 17 August 2022
Revision received: 25 August 2022
Accepted: 26 August 2022

Introduction

Of all surgically treated stage IB cervical cancers around 45 % occur in women younger than 40.[1] Key factors that make a patient a candidate for radical trachelectomy are: patients younger than 40 years of age, strong motivation to preserve fertility, no history of infertility, tumours smaller than 2 cm in diameter, FIGO stages IA2-IB, that the upper part of the endocervical canal is not involved and no evidence of metastasis to the regional lymph nodes.[2] A radical trachelectomy is an operation to remove most of the cervix with parametria and the upper part of the vagina such as in standard radical hysterectomy but the uterus is left in place with utero-vaginal anastomosis. Approach for this operation could be abdominal or vaginal. Some authors have proposed more conservative treatments with the same oncologic outcomes as radical trachelectomy. The proposed treatments are cervical conisation or simple trachelectomy, followed by pelvic lymphadenectomy in cases of low-risk patients (tumours less than 2 cm in size, no lymphovascular invasion and a negative lymph nodes.[3] Results comparing these two techniques show some differences in pregnancy outcomes however both success rates are acceptable.[2, 4-7]

Case History

A thirty-year-old nulliparous woman with uterine cervix cancer FIGO stage IB2 underwent neoadjuvant chemotherapy. After her routine

This article should be cited as follows: Mandić A, Gutić B, Davidović-Grigoraki M, Petrović Đ, Šolajić N, Nađ GS. Simple trachelectomy following neoadjuvant chemotherapy in cervical cancer over 2 cm in size - a case report and review of literature. Scr Med 2022 Sep;53(3):265-70.

gynaecological exam at the September of 2017 gynaecologist took a PAP smear. PAP smear was high-grade squamous intraepithelial lesion (H SIL) and as examination showed suspicious clinical lesion multifocal gynaecologist did the punch biopsy and cervical squamous carcinoma, G2 was diagnosed (Figure 1).

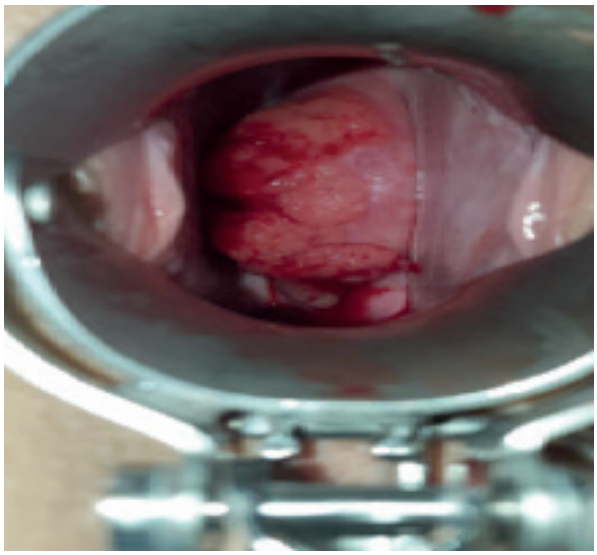

Figure 1: Gynaecological exam before neoadjuvant chemotherapy treatment

The lesion was measured at 30 mm in maximal diameter and the proliferation index was not assessed. Magnetic resonance (MR) of the pelvis and abdomen that was performed, as well (Figure 2). Based on the results patient was sent to the Gynaecological Oncology Tumour Board at the Oncology Institute of the Vojvodina. The standard operative radical surgery was proposed with preservation of the ovaries. A strong desire to preserve fertility was expressed by the patient and she refused the treatment that could jeopardise fertility, such as radiotherapy.

The patient was informed about neoadjuvant chemotherapy treatment as not standard of care, that only a few such cases have been reported in recent literature and that no randomised trials have been conducted among these high-risk patients that could confirm the benefits of fertility preserving treatment in this setting. After counselling the patient about the procedure and algorithm of the treatment she signed the informed consent about fertility preserving. Due to lack of the experience in laparoscopy and sentinel node detection was not initially performed. However, the patient insisted on fertility preservation.

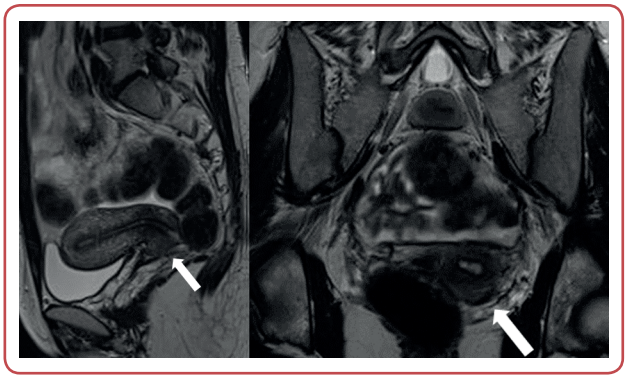

Figure 2: T2W sagittal and paraxial magnetic resonance tomograms on cervix (arrow) hyperintensity zone of infiltration on anterior part of the cervix, diameter 25x29 mm, stomal invasion about 8 mm in depth. Infiltration of parametria was not found and cervical ring was without disruption.

After informing patient about the chemotherapy protocol and receiving informed consent, neoadjuvant chemotherapy (NACT) was administered. The performance status was 0. Medical history showed no other malignancy.

Chemotherapy protocol

Patient received three cycles in 10-12 day interval chemotherapy protocol of cisplatin (75 mg/m^2) and iphosphamide (1800 mg/m^2), in accordance with the Prague protocol for squamous carcinoma,[8] during the October 2017. This protocol was chosen because paclitaxel-based regimens for cervical cancer are not covered by national health insurance in Serbia. A clinical exam along with an MR evaluation was performed three weeks after the last chemotherapy cycle (Figure 3 and 4).

Due to complete response, the patient had surgery four weeks after the last NACT cycle, 16 November 2017. A simple trachelectomy followed by laparoscopic pelvic lymphadenectomy was performed. The surgery lasted four hours with no intra- or postoperative complications. Total blood loss was up to 100 mL. No samples were sent for a frozen section examination.

Final pathological findings resulted in only H-SIL, no cancer was found. There were no metastases in any of the 21 harvested lymph nodes (Figure 5).

The patient was discharged 7 days after operation. The first follow up was one month after operation and showed an adequate length of the uterine cervix over 2 cm. After six months the first a PAP test showed no intraepithelial lesions of malignancy (NILM) and patient had follow up

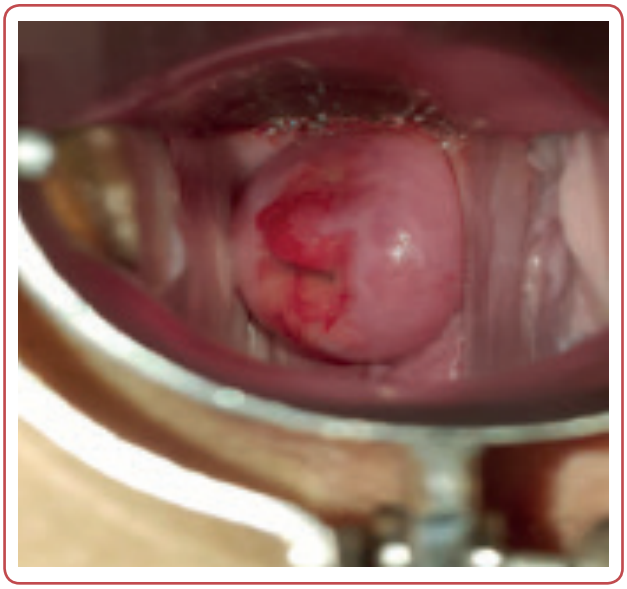

Figure 3: Two weeks after III cycle of neoadjuvant chemotherapy treatment

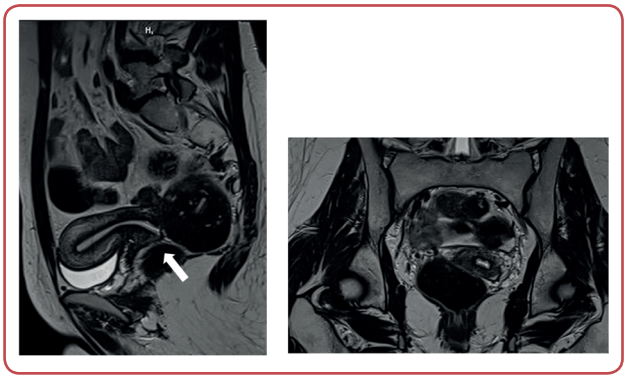

Figure 4: T2w sagittal and paraxial MR tomograms of small pelvis (no pathological findings). Complete therapeutic response (arrow) after III cycles of chemotherapy.

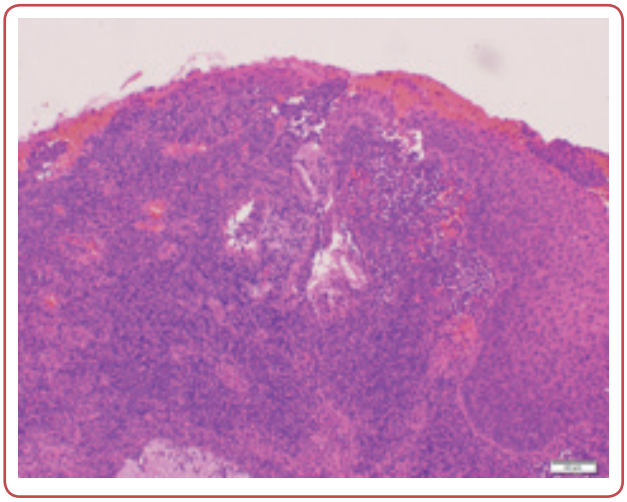

Figure 5: Highly dysplastic cervical squamous epithelium after neoadjuvant chemotherapy. There is a brisk stromal inflammatory response. No tumour stromal infiltration. Haematoxylin and eosin, 100 x.

exams every two months. A pregnancy was diagnosed one year after surgery and a healthy male child was delivered via Caesarean section at 38 gestation week. The pregnancy was followed by obstetrician and no needed for cerclage. Patient was followed in standard 3-4 months interval after delivery with gynaecological examination and PAP smear. The latest follow up in August 2022, 56 months, has shown a NILM PAP smear and imaging with no evidence of disease.

Discussion

Good oncologic and reproductive outcomes have been published in the last three decades with fertility sparring treatment in the early cervical cancer setting.[2, 7] Various surgical approaches have been described, ranging from vaginal and open to minimally invasive surgery. Adequate oncologic and obstetric outcomes have been reported with all approaches. For low risk, early lesions even more conservative treatments plans can show promising results.[9] There is still a subset of patients with a tumours larger than 2 cm in size that have a strong desire to preserve fertility. A key goal for gynaecologic oncologists is to trial fertility sparring approaches for these patients to drive a better balance of oncologic and obstetric outcomes.

Many papers have reported a good chemotherapy response rate for cervical cancer. NACT not only reduces tumour volume, which might lead to less challenging surgery, but also lowers lymph node positivity. Also, a good response to chemotherapy leads to disease downstaging which offers certain subsets of patients an option for fertility sparring treatment.[10] Seven patients with large FIGO IB – IIA-1 tumours (diameter 30 to 45 mm) were presented by Marchiole et al and all patients were treated with neoadjuvant chemotherapy followed by laparoscopic pelvic lymphadenectomy and vaginal radical trachelectomy (VRT). After NACT, all patients were evaluated by clinical examination, colposcopy and MRI. A 50 % reduction of tumour volume was shown in 5 of 7 patients (71 %) and a partial response (40 % volume reduction) was noted in the remaining two cases. All 7 patients underwent VRT. No signs of relapse shown in the follow up period with a median of 22 months (range 5-49 months).[11] A large

Table 1: Neoadjuvant chemotherapy and different techniques of fertility sparing surgery in literature

	Cervical cancer ≥ 2 cm	NACT protocol	Conservative surgery	Optimal pathological response (CR+PR1) No (%)	Recurrences No	Pregnancy No
Marchiole et al[11]	7	TIP (or TEP for Ad Ca)	VRT+PL	4/7 (57 %)	0/7	1/7
Robova et al[12]	15	IP+(Dox for Ad Ca)	ST+PL	9/12* (75 %)	3/12	7/12
Maneo et al[13]	8	TIP (or TEP for Ad Ca)	Conisation + PL	6/6& (100 %)	0/6	NR
Plante et al[14]	3	TIP	VRT+PL	3/3 (100 %)	0/3	3/3
Palaia et al[15]	1	TIP	ST+PL	1/1 (100 %)	0/1	0/1
Kobayashi et al[16]	1	BOMP	Conisation	1/1 (100 %)	0/1	1/1

NACT: neoadjuvant chemotherapy; TIP: cisplatin, iphosphamide, paclitaxel; Ad Ca: adenocarcinoma; BOMP: bleomycin, vincristine, methotrexate, cisplatin; VRT: vaginal radical trachelectomy;

series of 15 patients was published by Robova et el which included tumours larger than 2 cm treated with NACH followed by vaginal trachelectomy. The Prague protocol was used, 3 cycles of cisplatin (75 mg/m^2) and iphosphamide (2 g/m^2) in case of squamous cancer and cisplatin (75 mg/m^2 and doxorubicin (35 mg/m^2) in case of adenocarcinoma every 10 days. That was followed by simple vaginal trachelectomy with laparoscopic lymphadenectomy. Complete response was obtained in 5 patients on the final histopathological report, while 6 patients had microscopic residual disease and 4 had macroscopic residual disease. A relapse occurred in the 3 cases with suboptimal response, all 3 patients in question were diagnosed with adenocarcinoma. A patient affected by ovarian relapse died, while two patients presented with endocervical recurrence but are alive without evidence of disease. In terms of obstetric outcomes, there were 7 reported pregnancies resulting in 7 children, 2 of which were preterm (26 and 35 weeks of gestation).[12] Table 1 presents thirty cases of patients reported in the literature diagnosed with cervical cancer larger than 2 cm in size that were treated with NACT followed by fertility sparing surgery.

Different approaches in young cervical cancer patients were also published. Lanowska et al initiated treatment with laparoscopic lymphadenectomy and after confirming no lymph node metastasis neoadjuvant chemotherapy was administered. Sentinel lymph node detection was performed in all patients. Neoadjuvant chemotherapy was comprised of 2-3 cycles of paclitaxel/iphosphamide/cisplatin regimens. That was followed by radical vaginal trachelectomy. Twenty patients were enrolled with a mean tumour size of 3 cm. Radical vaginal trachelectomy was performed in 18 patients. Complete response was noted in 9 cases, while chemoradiation was recommended in 2 cases due to an insufficient response. One relapse was reported in the mean follow up of 23 months. In terms of obstetric outcomes there were 5 patients reported 7 pregnancies. The authors concluded that the approach of laparoscopic lymphadenectomy followed NACT and RTV in the node negative subset could be adequate in terms of oncologic and obstetric outcomes.[17]

While NACT followed by surgical treatment is performed in some centres, it must be noted that there is no standard in terms of chemotherapy protocols and surgical approaches are even more variable. An acceptable approach with NACT and fertility sparring surgery in the setting of bulky cervical cancer was identified by these three small studies. An oncological safe approach was presented by Lanowska et al for patients at high risk of lymph node metastasis.[17] They used SLN detection or complete pelvic lymphadenectomy to identify candidates for NACT and fertility sparring surgery. Developing a sentinel node detection procedure, this approach will become more acceptable. As mentioned, a further aspect that is not standardised is chemotherapy. Most protocols are double or triple combinations that are based on platinum agents. The paclitaxel/cisplatin is reported to be the most promising regiment and should be the basis for future studies. According to some authors a dose dense NACT interval (12-14 days) has shown a better therapeutic response.[12]

One further important aspect that requires consideration is ovarian function after chemotherapy. Is an examination of ovarian reserve before treatment necessary or is a normal pregnancy outcome expected? An expected normal outcome seems more likely, but further research is warranted. At the recent review article by Buda et al, authors reviewed a total of 20 articles and 114 women with IB2 disease, possible candidates for NACT prior to FS. In this review they found that uterine conservation was achieved only in 76.7 % of them. An optimal pathological response to NACT was achieved in 60.9 % of cases. A TIP protocol (cisplatin, iphosphamide and paclitaxel) regime was related to the best response. Authors notice that suboptimal response to NACT appeared to be an independent negative prognostic factor. Besides, up to 9.2 % of patients recurred with a median 7.4 months and 4.6 % of patients died of disease. In conclusions authors notice that NACT prior to FS surgery could be an option, but the literature about this issue is still weak and FS should be carefully discussed with patients.[18]

Squamous carcinoma is the most frequent cervical malignancy. However, cervical adenocarcinoma has increased incidence in the younger woman and is responsible for 20 to 25 % of all cervical cancers.[19, 20] The histological type of tumour should not influence a decision for surgery based on recent clinical recommendations, with exceptions of rare histological types such as small and neuroendocrine cervical cancer.[2] Both squamous cell and cervical adenocarcinoma receive the same standard treatment, some research has shown that adenocarcinoma has a negative impact on survival in the setting of both early and advanced-stage disease.[21-23]

The diameter of the tumour has been shown as a very important prognostic factor, too. Gil-Ibañez at al presented a total of 111 patients were included, 82 (73.9 %) with tumours < 2 cm and 29 (26.1 %) with tumours 2–4 cm. Authors concluded that the tumour size over 2 cm is the most important negative prognostic factor in this multicentre cohort of patients with early cervical cancer and who underwent fertility spearing surgery in Spain.[24]

Further studies are warranted, both with a larger patient census and a longer follow up to validate this more conservative approach and to best define subsets of patients with bulky cervical cancer that can have the most benefit from this type of treatment. The clinical trial named CONTESA hope will answered on some questions. Trial design is pre-menopausal women diagnosed with stage International Federation of Gynaecology and Obstetrics (FIGO) IB2, 2–4 cm cervical cancer who wish to preserve fertility will receive three cycles of platinum/paclitaxel chemotherapy. Patients with complete/partial response will undergo fertility-sparing surgery. Patients will be followed for 3 years to monitor outcome. Patients with suboptimal response (residual lesion ≥ 2 cm) will receive definitive radical hysterectomy and/or chemoradiation. Authors expected complete accrual in 2022 with presentation of results by 2025.[25]

Acknowledgements

None.

Conflict of interest

None.

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