



## Oncological and pregnancy outcomes after high-dose density neoadjuvant chemotherapy and fertility-sparing surgery in cervical cancer



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### HIGHLIGHTS

- Prospective study on neoadjuvant chemotherapy in cervical cancer larger than 2 cm before fertility sparing surgery, oncologic and fertility results.
- Evaluation of oncological results: adverse events, response for neoadjuvant chemotherapy, recurrence rate.
- Evaluation of pregnancy results after neoadjuvant chemotherapy followed by laparoscopic pelvic lymphadenectomy and simple trachelectomy.

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### ABSTRACT

**Objective.** 28 women under 35 years with early-stage cervical cancer and strong desire for fertility preservation that do not fulfil standard criteria for fertility-sparing surgery (tumour larger than 2 cm or with deep of infiltration more than half of stroma) were included in prospective study.

**Methods.** Dose-dense neoadjuvant chemotherapy (NAC) was performed on all 28 patients in 10-day intervals: cisplatin plus ifosfamide in squamous cell cancer (15 women—53.6%) or cisplatin plus doxorubicin in adenocarcinoma (13 women—46.3%). Patients underwent laparoscopic lymphadenectomy and vaginal simple trachelectomy after NAC. Patients with positive lymph nodes or inadequate free surgical margins underwent radical hysterectomy.

**Results.** No residual disease was found in 6 women (21.4%), microscopic disease was observed in 11 women (39.3%) and macroscopic tumour in was observed in 11 women (39.3%). Ten women (35.7%) lost fertility. Four women (20%) after fertility-sparing surgery recurred, two died of the disease (10%). Fertility was spared in 20 (71.4%) women and 10 of them became pregnant (50%). Eight women delivered ten babies (6 term and four preterm deliveries). There were two miscarriages in second trimester (in one woman) and one in first trimester. One woman underwent four unsuccessful cycles of IVF, one failed to become pregnant and one recurred too early. Two women underwent chemoradiotherapy for recurrence and lost chance for pregnancy.

**Conclusions.** Downstaging by NAC in IB1 and IB2 cervical cancer before fertility-sparing surgery is still an experimental procedure, but shows some promise. Long-term results in relation to oncological outcome for this concept are still needed.

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### Introduction

The mean age of women at the time of first delivery has increased in the past decade, which, inadvertently, has led to an increase in the number of women with cervical cancer who wish to preserve their reproductive potential to achieve pregnancy in the future. Vaginal radical trachelectomy (VRT), abdominal radical trachelectomy (ART) or simple

trachelectomy are safe fertility procedures for the treatment of women with lymph node-negative early-stage cervical cancer. One of the limitations of fertility-preserving surgery is deep stromal invasion and a tumour larger than 2 cm [1,2]. The recurrence rate in women with a tumour larger than 2 cm is 20.8% after VRT and 20% after ART [3]. Cervical cancer is usually chemosensitive on a platinum-based combination of agents. Some centres use neoadjuvant chemotherapy (NAC) in “bulky” cervical cancer to downstage tumour before radical surgery. The response rate of NAC in advanced cervical cancer is between 60 and 95% [4–6]. NAC can decrease tumour volume before surgery, which enables the complete removal of the tumour with negative margins whilst

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preserving an adequate amount of cervical tissue. Such a procedure improves the chances for successful pregnancy. This is a prospective study of women with early-stage cervical cancer with tumours that exceeded 2 cm in the largest diameter or infiltrated more than half of the cervical stroma and who had undergone high-dose density neoadjuvant chemotherapy.

## Material and methods

Patients with previously untreated histologically confirmed invasive squamous cell carcinoma, adenocarcinoma or adenosquamous cervical carcinoma IB infiltrating more than half and less than two thirds of the cervical stroma and larger than 2 cm in the largest diameter were eligible. All (small and large cell) neuroendocrine or adenocarcinoma with neuroendocrine components were excluded. All women were in fertility age (40 years and younger) and expressed a strong desire to spare their fertility. All women underwent magnetic resonance imaging (MRI) and vaginal ultrasonography (US) examination to evaluate tumour size and volume as well as to assess pelvic lymph node status. Patients with clinically (MRI or US) positive lymph nodes and with tumour that infiltrated more than two thirds of cervical stroma were excluded from the study. In addition, a chest radiograph, blood count and biochemistry (liver function, creatinine clearance and ionogram) were performed. The study was approved by the local ethical committee. Informed consent was obtained from each patient before the initiation of study procedures.

The patients were treated with three cycles of dose-dense NAC using an interval of 10–14 days. A combination of cisplatin (75 mg/m<sup>2</sup>) and ifosfamide (2 g/m<sup>2</sup>, maximal total dose 3 g) was used in squamous cell carcinoma and cisplatin (75 mg/m<sup>2</sup>) plus doxorubicine (35 mg/m<sup>2</sup>) in all adenocarcinomas. Blood count and biochemistry were done before each cycle of chemotherapy and before surgery. Adverse effects of chemotherapy were graded with the WHO classification. US or MRI, or both were performed after a 3rd cycle of chemotherapy to evaluate response to chemotherapy.

Laparoscopy with sentinel lymph node (SLN) mapping was performed in all patients. SLNs were sent for frozen section analysis. If the sentinel nodes were negative on frozen section, laparoscopic pelvic lymphadenectomy was completed. If the definitive histopathological evaluation after 7 days did not detect metastases in the lymph nodes, simple trachelectomy was performed. At least two thirds of cervical stroma was removed by simple trachelectomy in all cases (8–10 mm of cervical stroma was preserved). Frozen section was not performed during trachelectomy to identify close margins. Ultramicrostaging of SLNs and standard evaluation of other nodes were performed. In case of positive SLNs or closed margins (less than 8 mm of tumour free tissue) in the trachelectomy specimens radical hysterectomy type C2 with pelvic and low paraaortal lymphadenectomy was performed. A pathologist with experience in oncogynaecology evaluated all histopathological specimens.

The patients remained on a regular follow-up every third month that included clinical examination colposcopy and Pap smear and every six months HPV-HR testing was performed. In addition, vaginal US and MRI were performed every six months and if any abnormalities were detected, MRI is indicated.

## Results

Written informed consent was signed by the 28 women between April 2005 and December 2013. Nine patients previously published were included into study and pregnancy data was actualised [4]. Of these 28 women, 26 were nulliparous. The mean age of the women was 28.6 years (range 15–34 years). Fifteen women (53.6%) were diagnosed with squamous cell cancer and 13 (46.4%) were diagnosed with adenocarcinoma. Lymphovascular space involvement (LVSI) presented in 11 women (39.3%), negative LVSI in 7 (25%) and in 10 (37.7%) LVSI

was not possible to determine because only punch biopsy was done as the means of diagnosis. Of the 28 women, 21 had stage IB1 cervical cancer (75%) and 7 had stage IB2 cancer (25%) that infiltrated no more than two thirds of the cervical stroma. The average interval between the first day of chemotherapy and surgery was 42.7 days (range 36–53 days). Grade 3 neutropenia was found in five women (17.9%); no other haematological toxicity grade 3 and 4 was diagnosed. Grade 3 neutropenia occurred in all women after the third course of chemotherapy and thus it was not necessary to postpone chemotherapy. Grade 4 alopecia was found in all women with a regimen of doxorubicin. No other toxicity grade 3 or 4 was seen. Within 6 weeks after surgery, one patient developed inflammatory lymphocyst that was accompanied by fever, elevated C-reactive protein and procalcitonin. She was treated conservatively by antibiotics. Further, one woman had lymph oedema of the legs. Stenosis of the cervical canal after trachelectomy was diagnosed in 5 women of 20 (25%). All of these women underwent dilatation of the cervical canal under general anaesthesia because it was impossible to take an endocervical Pap smear during follow-up. All women had regular menstruation period within four months from last cycle of chemotherapy. No hormonal treatment was necessary.

Median follow-up was 42 months (range 5–103). Complete response (no residual disease after NAC) on the definitive histopathological examination was presented in six women (21.4%) and microscopic residual disease (tumours smaller than 3 mm in the largest diameter) was noted in 11 women (39.3%). Macroscopic residual disease after NAC was diagnosed in 11 women (39.3%). Twenty women (71.4%) retained their fertility. Analysis of frozen sections of SLNs was positive in two women (7.1%), who immediately underwent radical hysterectomy type C2. Positive or close margins on trachelectomy specimens were found in six women (21.4%) with negative lymph nodes. These six women underwent radical hysterectomy. Eight women that underwent radical hysterectomy were excluded from study. The recurrence rate was 20% (4 of 20 women in whom fertility was preserved). Local recurrence in the cervix was diagnosed in three patients. One of these patients underwent radical hysterectomy and she is without evidence of disease. The other two underwent chemoradiotherapy: one is without evidence of disease and one died of disease. Distant recurrence (ovary) was diagnosed in one woman, who later died of disease. The mortality rate was 10% (2 of 20 women with preserved fertility), both of whom had squamous cell cancer. Two women with successfully treated recurrence had adenocarcinoma (Table 1).

Our fertility-sparing procedure was completed in 20 women and ten of them (50%) became pregnant (Table 2). Eight women (40%) delivered ten babies. There were four premature deliveries: one occurred during the 24th week of pregnancy, one during 28th week of pregnancy and two, two were between 34 and 36 weeks of pregnancy. In all four premature deliveries the cause was premature rupture of the membrane (PROM) due to infection. All babies are healthy. Any disability like mental, motoric, hearing lost or vision impairment was not diagnosed in premature delivered babies. One woman had a missed abortion in first trimester. One woman miscarried twice in second trimester, and in both cases intrauterine infection was the cause of the abortion. One woman underwent unsuccessful in vitro fertilisation on four occasions and three women went on to become pregnant. Three women underwent some of the assisted reproduction methods (two women had undergone successful intrauterine insemination and one unsuccessful in vitro fertilisation). Two women recurred and underwent chemoradiotherapy and lost chance for pregnancy. For different reasons (age, partner), 4 women had no plans to become pregnant.

## Discussion

The recurrence rate after fertility-sparing surgery without NAC in tumours exceeding 2 cm is 20% after ART and 20.8% after VRT [2]. When a tumour is larger than 2 cm and completely removed with adequate free margins, there is usually enough stromal tissue remaining

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