

Case Report

Neoadjuvant chemotherapy followed by vaginal radical trachelectomy in bulky stage IB1 cervical cancer: Case report

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Abstract

Background. We present 3 young women with bulky stage IB1 cervical cancer treated with neoadjuvant chemotherapy followed by laparoscopic pelvic node dissection and vaginal radical trachelectomy.

Cases. In the last year, we have treated 3 young women with large cervical lesions who wished to preserve fertility with induction chemotherapy followed by fertility-sparing surgery. They all had lesions measuring 3 to 4 cm and felt to be too big to safely undergo a radical trachelectomy. Three cycles of platinum-based combination chemotherapy were given and were well tolerated. The 3 patients had a significant clinical response to chemotherapy. A complete pathological response was confirmed by the absence of residual invasive cancer in the three trachelectomy specimens. There has been no recurrence so far and no pregnancy yet.

Conclusion. Neoadjuvant chemotherapy followed by a fertility-sparing surgery may become a valuable option for young women with bulky stage IB1 cervical cancer who wish to preserve their fertility potential.

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Introduction

More and more emphasis is placed on the long-term effects of cancer treatments on the quality of life of cancer survivors. Fertility preservation stands out as a major component of quality of life in young women who undergo cancer treatment. Indeed, the psychosocial impact of cancer-related infertility in women treated for gynecologic malignancies is such that a high proportion of these women experience feelings of depression, grief, stress and sexual dysfunction [1]. Women faced with loss of fertility from gynecologic cancer treatments often felt

deprived of choice and, sadly, felt that medical professionals tended to minimize the sense of loss [2].

In recent years, several publications have demonstrated that the fertility-preserving vaginal radical trachelectomy procedure is a valuable option for young women with early-stage cervical cancer. Reports on oncologic outcome are accumulating and indicate that in well selected cases, the overall survival rate is excellent with a 5-year disease survival of 95% [3]. Obstetrical data also confirm that the majority of pregnancies following a radical trachelectomy reach the third trimester, and of those, most will make it to term [4]. Good results are also accumulating following the abdominal radical trachelectomy procedure [5].

One of the current limitations for this fertility-preserving surgery is that it is usually limited to women with small lesions,

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preferably measuring less than 2–2.5 cm, as the anticipated outcome of the surgery is excellent and adequate surgical margins can usually be obtained. However, several patients are denied this fertility-preserving option because the size of their lesions exceeds those limits. We thus applied the concept of induction chemotherapy to reduce the size of the cervical tumors with the hope of rendering the patients surgically eligible for a radical vaginal trachelectomy.

Case report

Case #1

Ms. F was a 26-year-old G0 woman who was found to have a bulky lesion on the cervix in September 2004. Although the cytology suggested an adenocarcinoma, the biopsy confirmed a grade 3 squamous cell carcinoma without vascular space invasion. Clinically, the lesion was confined to the cervix and measured 4 × 4 cm. Since the FIGO staging system is primarily based on clinical examination, it was classified as a FIGO stage IB1. Tumor markers were all within normal range. The patient desperately wanted to maintain her fertility potential, so we offered her the option of upfront chemotherapy after extensive counseling. She thus received 3 cycles of platinum-based multiagent chemotherapy with the following intravenous regimen: Paclitaxel 175 mg/m² on day 1, Cisplatin 75 mg/m² on day 2 and Ifosfamide 5 g/m² over 24 h with Mesna 5 g/m² on day 2 and 3 g/m² on day 3 with continued hydration. Cycles were repeated every 3 weeks. The first treatment was given October 15th 2004. The treatments were well tolerated except that the patient was hospitalized after the first cycle for an episode of febrile neutropenia even though she had received injections of Neupogen (Amgen, Mississauga) at a dose of 300 µg s.c. per day. The dose of Neupogen was increased to 480 µg and started earlier for the last two cycles and they were uneventful. Clinical examination done prior to the 2nd chemotherapy treatment demonstrated a 50% tumor reduction and following the third cycle, there was no macroscopic evidence of residual tumor although the cervix maintained a pronounced reddish appearance.

She underwent surgery on December 12th 2004. A laparoscopic sentinel node mapping was done first and frozen section on the sentinel nodes were negative. We completed a bilateral pelvic lymphadenectomy followed by a radical vaginal trachelectomy. On final pathology, all the lymph nodes were negative (0/21) and there was residual high-grade dysplasia only, without evidence of invasive cancer in the trachelectomy specimen. The patient has had an uneventful postoperative recovery and left the hospital on day 3. She developed a urinary tract infection postoperatively. She has resumed a completely normal menstrual pattern 4 months after surgery. She is now 1 year post-surgery and her follow-ups have been completely normal.

Case #2

Ms. Z was a 36-year-old G1P0A1 woman who was diagnosed with a stage IB1 moderately differentiated squamous

cell carcinoma measuring 3 × 3 cm in March 2005. There was no vascular space invasion on the cervical biopsy. The lesion was mostly localized to the anterior lip of the cervix (Fig. 1A). Based on clinical examination and MRI, it was felt that the endocervical margins would not be cleared if we did a trachelectomy then. In order to preserve her fertility potential, we offered her the option of neoadjuvant chemotherapy. She received 3 cycles of the regimen described above with Neupogen injections. The treatments were well tolerated. She had a significant tumor response with no evidence of visible tumor on the cervix after 3 cycles (Fig. 1B). After the second cycle, she became amenorrheic and her LH and FSH levels were elevated in the menopausal range.

She underwent surgery on May 17th 2005. Again, the sentinel nodes were negative on frozen section so a complete laparoscopic pelvic lymphadenectomy was completed followed by a radical vaginal trachelectomy. On final pathology, all the lymph nodes were negative (0/18) and there was no residual disease in the trachelectomy specimen. She left the hospital on day 3 and there was no complication except for the need to do bladder catheterization for 2 weeks. Her menses have resumed normally 4 months after surgery and her LH/FSH levels have normalized.

Case #3

Ms. P was a 35-year-old G1P1 woman diagnosed with cervical dysplasia at the time of her first pregnancy. The lesion

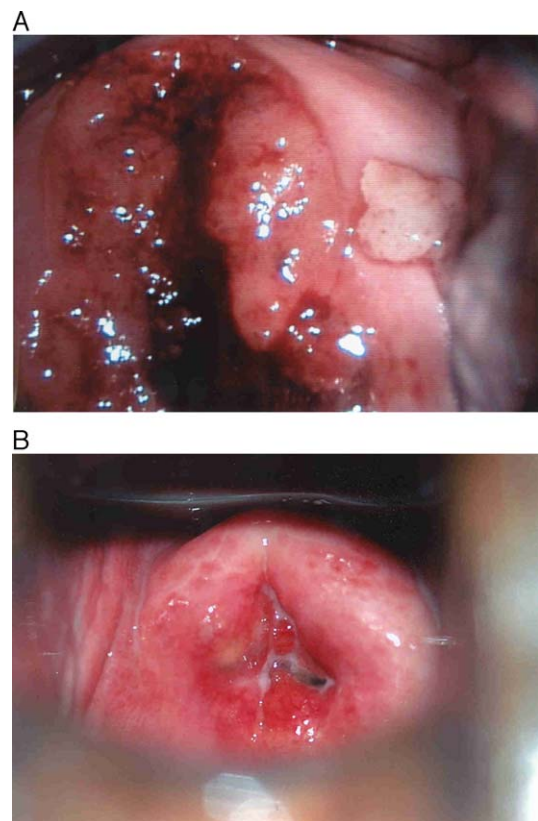


Fig. 1. (A) Mrs. Z. Cervical appearance before chemotherapy. (B) Mrs. Z. Cervical appearance after chemotherapy.

was biopsied in December 2004 and was followed conservatively thereafter. She delivered vaginally April 17th 2005. At her first postpartum visit June 14th 2005, a colposcopy-directed biopsy confirmed the presence of an invasive squamous cell carcinoma of the cervix and the lesion clinically measured 2 cm. An HPV DNA test confirmed an HPV-18 subtype. On July 6th, she had a pelvic MRI which showed a 2 × 2.4 cm lesion on the right side of the cervix. It was described as involving the right vaginal wall and extending into the right parametrium.

Since the patient and husband strongly wished to have other children, she was sent to us for consideration of a radical trachelectomy. She was seen on July 25th 2005, and on clinical evaluation, the lesion occupied the whole right side of the cervix, measuring at least 3 cm in size and was felt to extend laterally almost to the vaginal fornix (Fig. 2A). The right parametrium appeared free, however. Clinically, this was a stage IB1 lesion. The squamous cell carcinoma (SCC) antigen level was 4.1 µg/L (normal range < 1.5 µg/L). Again, we felt we could not clear the margins with a trachelectomy at this point. Given that the patient already had a healthy child, we offered her a radical hysterectomy but the couple strongly wished to retain the possibility to have other children. The option of neoadjuvant chemotherapy was offered with emphasis on the fact that we could not predict tumor response and that chemotherapy could affect her ovarian function permanently.

Nevertheless she pursued with 3 cycles of chemotherapy as described above. The treatment was well tolerated. She was

placed on Neupogen prophylactically. She had hot flashes, elevated LH/FSH and amenorrhea during the chemotherapy treatment. The MRI done after 3 cycles indicated minimal tumor response which was surprising since clinically the lesion appeared to have improved significantly (Fig. 2B) and the repeat SCC marker had normalized (0.6 µg/L). In retrospect, she had several Nabothian cysts on the cervix which had probably been misinterpreted as persistent tumor on the MRI.

She underwent surgery on October 4th 2005. The sentinel node being negative on frozen section, a complete pelvic lymphadenectomy was performed followed by the radical vaginal trachelectomy. The patient left the hospital on post-operative day 2 and developed a urinary infection only postoperatively. On the final pathology report, all the lymph nodes were negative and there was only residual focal carcinoma-in-situ in the trachelectomy specimen. She has not yet resumed regular menses but her LH/FSH levels have normalized.

Discussion

This is the first published report on the use of neoadjuvant chemotherapy (NACT) followed by a radical vaginal trachelectomy as an attempt to preserve fertility in women with bulky stage IB1 cervical cancer.

Generally, the radical trachelectomy procedure has been reserved for patients with small lesions usually measuring less than 2–2.5 cm as it is harder to clear safe endocervical margins with larger lesions. It has been shown that lesion size greater than 2 cm is associated with a higher risk of recurrence [3,6]. Some authors have argued that an abdominal radical trachelectomy can be performed on larger size lesions as the extent of parametrial resection can potentially be more radical [5]. However, the recent report of a pelvic recurrence within 6 months of the abdominal trachelectomy for a 3.8-cm exophytic lesion would suggest that larger lesions remain at greater risk of recurrence [7].

We report 3 women who showed a complete pathological response to neoadjuvant chemotherapy after a rapid sequence of 3 cycles of treatment. Typically, the time between the first cycle of chemotherapy and surgery was approximately 2 months. Treatment was uneventful in all cases with bone marrow support using Neupogen injections. Two patients had residual dysplasia only and one had no residual disease at all on the trachelectomy specimen. Longer follow-up will obviously be needed to confirm the long-term safety of this approach. Similarly, it is premature to know reproductive outcomes considering that 2 of our patients were >35 years old. However, besides reproductive endpoint, preservation of ovarian function in and by itself may be a worthwhile contribution of this approach considering the impact of premature menopause on the overall quality of life of young women treated with standard pelvic radiation therapy in addition to the effects of radiation therapy on sexual function and bone density.

Our experience was adapted from the pioneering work of an Italian group lead by Maneo et al. and they deserve the credit for it. Their work was presented at the International Gynecologic Cancer Society (IGCS) meeting in Edimburg, in October 2004. (We have not seen it published in the English literature). They

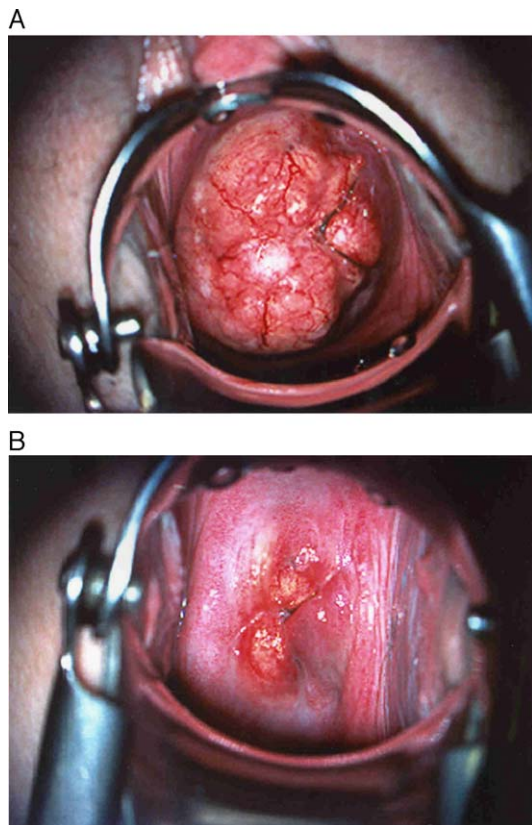


Fig. 2. (A) Mrs. P. Cervical appearance before chemotherapy. (B) Mrs. P. Cervical appearance after chemotherapy.

used neoadjuvant chemotherapy followed by a conisation alone and pelvic lymphadenectomy in young women with cervical cancers (lesions < 3 cm). Their choice for the chemotherapy regimen (Paclitaxel–Ifosfamide–Cisplatin) was based on the protocol developed by the Monza group [9]. Of the 18 patients they treated, 7 (39%) had either no residual disease or only in situ disease, 7 (39%) had minimal residual disease measuring <3 mm in depth and 4 (22%) had residual lesion between 3 and 10 mm deep. No patients progressed on chemotherapy. Following treatment, 8 women attempted to conceive and 5 succeeded for a total of 6 babies [8]. So clearly, cervical cancer is chemosensitive and complete responses have been reported allowing pregnancies to occur post-chemotherapy.

Alkylating agents such as Ifosfamide and Cisplatin are notably detrimental to the ovarian follicles and are associated with ovarian fibrosis which can ultimately lead to premature ovarian failure. Avoiding the Ifosfamide would thus make the chemotherapy regimen much less gonadotoxic. In the future, less toxic combination chemotherapy should be evaluated. For instance, a combination of Carboplatin and Paclitaxel might be more tolerable and much easier to administer as an outpatient regimen. Response rate of 40–60% have been reported with this combination regimen in advanced and recurrent cervical cancer [10,11]. Duenas-Gonzalez et al. have also used this combination in 43 patients with locally advanced cervical cancer (IB2–IIIB), and reported a 95% clinical response rate and a 37% complete or near complete pathological response after 3 cycles [12]. A combination of Carboplatin and Paclitaxel is thus certainly worth exploring and may become the treatment of choice in the future.

Fertility preservation is definitely possible after induction chemotherapy and fertility-sparing surgery but obviously, long-term results are needed before conclusions can be drawn as to the safety, efficacy and reproductive outcome of this approach. Although very preliminary, our results and those of Maneo et al. open the way to a new concept in the management of locally advanced cervical cancer in young women wishing to preserve fertility.

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