Gynecologic Oncology Reports 24 (2018) 27–29

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Oncofertility in the setting of advanced cervical cancer - A case report

Catherine Gordon[a], Joseph C. Carmichael[b], Krishnansu S. Tewari[a,*]

[a] Department of Obstetrics & Gynecology, University of California, Irvine 333 City Blvd, West, Suite 1400, Orange, CA 92868, United States
[b] Division of Colon and Rectal Surgery, Department of Surgery, University of California, Irvine 333 City Blvd, West, Suite 850, Orange, CA 92868, United States

ARTICLE INFO

Keywords:
Cervical cancer
Oncofertility
Radical trachelectomy
In vitro fertilization

ABSTRACT

Objective: To consider fertility options in women with advanced cervical cancer.
Design: Case report.
Setting: Large tertiary care center.
Patient: A 30-year-old nulligravida woman diagnosed with FIGO Stage IB_1 squamous cell carcinoma of the cervix that had metastasized to a pelvic lymph node.
Interventions: Robotic radical trachelectomy with pelvic lymphadenectomy and cerclage placement, followed by ovarian stimulation with oocyte retrieval and in vitro fertilization. Subsequent therapy included adjuvant chemoradiation and embryo transfer to a surrogate mother.
Main outcome measures: Cervical cancer remission, live birth from surrogate pregnancy.
Results: 33-year-old woman in her third year of remission from advanced cervical cancer with healthy twin girls.
Conclusions: Fertility options may exist for patients even in the setting of metastatic cervical cancer. Early involvement of a reproductive endocrinologist is imperative. This case emphasizes the importance of cross-specialty communication.

1. Introduction

Approximately 500,000 cases of cervical cancer are diagnosed worldwide each year, during which time 250,000 women die needlessly from this disease (Willows et al., 2016). Screening programs in developed countries have reduced incidence and mortality rates, however many young women are still diagnosed each year and face the possibility of losing fertility with a hysterectomy. Radical trachelectomy with lymphadenectomy has emerged as a viable option for select women with early stage cancers who strongly desire childbearing. In this case we present the oncofertility challenges of a woman with presumed early stage cervical cancer who is ultimately found to have a lymph node metastasis.

By 1950, radical hysterectomy with lymphadenectomy was embraced as primary treatment for early stage cervical cancer (i.e., FIGO IA_2-IB_1). The primitive vaginal approach pioneered by the Austrian surgeon Frederick Schauta during the 1890s was soon abandoned in favor of the abdominal approach developed by his pupil, Ernst Wertheim. Today, variations on the radical hysterectomy include minimally invasive approaches, nerve-sparing techniques, and sentinel lymph node identification. With the introduction of laparoscopy to dissect lymph nodes, the principles of the vaginal approach were resurrected by the French surgeon Daniel Dargent during the mid-1990s. Dargent developed radical vaginal trachelectomy with laparoscopic lymphadenectomy for fertility preservation. In its Cervical Cancer Treatment Guidelines, the National Comprehensive Cancer Network lists the procedure as Category 2A for women with early stage disease and a tumor diameter $< 2\,cm^2$. The relatively easier abdominal approach has again supplanted the vaginal approach, and in some centers, minimally invasive radical trachelectomies are being performed today.

This case report was approved by the University Institutional Review Board and the patient has also granted permission to her surgeon (author KST) to publish her story.

2. Case history

A 30 year old, asymptomatic, nulligravida, married, Caucasian intensive care unit nurse from a regional community hospital had a February 2014 Pap smear containing abnormal glandular cells of undetermined significance. Colposcopic-directed biopsies demonstrated carcinoma in situ, an endocervical curettage was negative, and an endometrial biopsy was insufficient. A subsequent large loop excision of the transformation zone revealed a moderately differentiated squamous cell carcinoma (SCCA) involving the endocervical and radial margins to a depth of 4.5 mm and width of 9 mm, respectively. Lymphovascular space invasion (LVSI) was also present. She was referred to Gynecologic

* Corresponding author.
E-mail addresses: cgordon1@uci.edu (C. Gordon), jcarmich@uci.edu (J.C. Carmichael), ktewari@uci.edu (K.S. Tewari).

https://doi.org/10.1016/j.gore.2018.03.001
Received 6 December 2017; Received in revised form 16 February 2018; Accepted 1 March 2018
Available online 02 March 2018

Oncology at our University for consideration of fertility-preserving surgery.

A directed 14-point review of systems was negative and there was no evidence of abdominopelvic masses or peripheral lymphadenopathy on physical examination. Upon speculum examination, there was no evidence of tumor on the ectocervix or cervical expansion. A bimanual and recto-vaginal examination revealed the cervix to be mobile, with no parametrial induration, sidewall extension, or rectal infiltration. Pathology review of her original slides confirmed the histologic diagnosis of invasive carcinoma, and a PET/CT was noteworthy for SUV 12 at the cervix and no evidence of loco-regional spread or distant metastases. Her cancer was assigned as occult FIGO IB_1 SCCA of the cervix with LVSI.

Following detailed counseling the patient provided written informed consent to undergo robotic-assisted laparoscopic radical trachelectomy with bilateral pelvic lymphadenectomy and cerclage placement. The patient was also referred to a reproductive endocrinologist/infertility specialist, and then underwent fertility-preserving surgery without complications in June 2014. Intraoperative frozen section of the proximal (i.e., endocervical) margin was negative. Final pathology revealed moderately differentiated SCCA with LVSI, cervical intraepithelial neoplasia III, widely negative distal (i.e. vaginal) margins, negative parametria, and a metastasis in one out of nine right pelvic lymph nodes. Following multidisciplinary tumor board presentation, the patient was counseled to receive chemoradiation, plus vaginal brachytherapy. In anticipation of pelvic radiotherapy, the patient received two cycles of ovarian stimulation followed by oocyte retrieval which ultimately resulted in 19 good-quality frozen embryos. Subsequent robotic-assisted bilateral salpingectomy and lateral ovarian transposition in August 2014 to prevent radiation-induced ovarian failure was technically challenging due to the presence of large, hyperstimulated ovarian cysts. From September to October 2014, the patient received weekly cisplatin-based ($40\ mg/m^2$ intravenously) chemoradiation to a total dose of 45 Gy, followed by 30 Gy of high-dose-rate brachytherapy using iridium-192.

Unfortunately, ovarian transposition failed due to cumbersome cysts, and ovarian function was compromised by radiation therapy. She required hormone therapy for menopausal symptoms, and developed radiation proctitis with a sigmoid stricture. She was initially told she would require a colectomy with ileostomy, but after 40 hyperbaric oxygen treatments, she was able to undergo laparoscopic sigmoidectomy without ostomy in July 2015. Once she was disease free for one year, she and her husband made the decision to move forward with attempting pregnancy. The high costs of ART with IVF were mitigated by charitable donations and her sister agreed to serve as a surrogate. In July 2016, the patient and her husband welcomed two healthy twin girls to their family. Through breast pumping and medical prolactin induction, the patient was able to breastfeed both babies adequately. Serial vaginal cytology and PET/CT scans, as well as a detailed review of systems, peripheral lymph node survey, and pelvic examinations have remained without evidence of disease recurrence for three years since diagnosis.

3. Discussion

Radical trachelectomy should be considered when future childbearing is desired (Koh et al., 2015). Recurrence rates in lesions < 2 cm after radical trachelectomy are < 5%, with mortality rate under 3% (Dursun et al., 2007). Given a similar recurrence rate for hysterectomy, our patient was counseled towards radical trachelectomy for fertility preservation.

The live birth rate following radical trachelectomy is approximately 64–67%, with a conception rate of approximately 85–90% (Willows et al., 2016; Bentivegna et al., 2016). Most reported pregnancies involved ART with intrauterine insemination or in-vitro fertilization. A review of sixteen studies examining pregnancy outcomes after radical trachelectomy demonstrated that 21% of pregnancies resulted in a first trimester loss, 8% in a second trimester loss, and 20% in a preterm delivery (< 36 weeks) (Boss et al., 2005). Authors suggested the reasons for infertility include cervical stenosis, decreased cervical mucous, and decreased vasculature to the uterus. Increased risk of loss and preterm delivery are due to shortened cervix and increased risk of preterm premature rupture of membranes. More importantly, the presence of metastatic disease reduces her likelihood of being cured and therefore the patient's overall prognosis must also be considered and placed in context of any discussion of fertility preservation.

Since 2013 the American Society for Reproductive Medicine has deemed oocyte cryopreservation a useful means of ART given equivalent fertility rates as compared to fresh oocytes, and with no increased risk of chromosomal abnormalities or birth defects (Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology, 2013). Ovarian transposition is a good option for attempts to preserve fertility, but up to 50% of women can still experience loss of hormonal function (Willows et al., 2016). The American Society of Clinical Oncology argues that the care of all cancer patients with reproductive potential should include a discussion on possible infertility with early referral to reproductive specialists (Lee et al., 2006). Close discussion between teams is important so as not to cause too much of a delay between fertility preservation procedures and adjuvant oncological treatment.

Twenty-eight percent of early stage cervical cancers will have LVSI and up to 8% may have nodal metastases (Beiner and Covens, 2007). The latter may be discovered by pre-operative imaging, intraoperative sentinel node identification, or postoperatively upon final pathologic evaluation. Because lymphatic spread warrants adjuvant chemoradiation, pre-operative referral to a reproductive endocrinologist for all patients considering radical trachelectomy is ideal in order to begin the dialogue concerning assisted reproductive technology. Treatment plans are ultimately predicated on surgical pathology, and may require coordination of care to allow for ovarian stimulation, oocyte retrieval (prior to initiation of radiotherapy), embryo cryopreservation and subsequent transfer, hormone replacement therapy, and lactation induction.

There are many charitable organizations that offer financial assistance to oncology patients desiring fertility (see Acknowledgement). These programs assist with the costs of IVF for patients whose treatment for cancer would otherwise render them infertile. Such programs however do not cover the cost of surrogate pregnancy. Even though our patient's sister was a surrogate, the couple still paid nearly $60,000 as the law requires attorney involvement and payment for lost wages and other medical expenses.

Because FIGO staging does not incorporate nodal status, not every woman with FIGO stage I cervical cancer (even those with a tumor diameter < 2 cm) will be able to subsequently conceive and carry a pregnancy. To date, the literature has been silent on whether fertility options exist in the setting of lymphatic metastases. To our knowledge our case constitutes the first report of a woman with advanced disease who pursued fertility and was successful in her endeavor. Through a combination of sheer determination and force of will, this patient fought back against odds that were seemingly insurmountable at the time and ultimately benefitted from ART and is now cancer-free for three years, raising a pair of healthy children carrying a complement of her own genetic material.

Conflict of interest statements

Catherine Gordon: I have no conflicts of interest to disclose.

Joseph C. Carmichael: I have no relevant conflicts of interest with the material presented in the case report. However, I do disclose that I am a consultant to and have participated in product development for Medrobotics and Johnson and Johnson. I am on the speaker's bureau for Johnson and Johnson, Medtronic and Novadaq.

Krishnansu Tewari: I have no relevant conflicts of interest with the material presented in the case report. However, I do disclose that I am a consultant to and have participated on advisory boards of Genentech/Roche, Clovis, Caris, Cue, Astra Zeneca, Regeneron, Vermillion, and Pfizer and that I am on the speaker's bureau for Genentech/Roche, Clovis, Astra Zeneca, Vermillion, Merck, and GlaxoSmithKline. I have received research funding from the NIH, Genentech, Atra Centara, Astra Zeneca, Clovis, Ortho Biotec, Johnson & Johnson, Abvie, Pfizer, Amgen, Intuitive, and Tesaro.

Acknowledgement

We would like to acknowledge the efforts of the Lance Armstrong Livewell Foundation and Walgreens WINFertility Program in supporting our patient to reach her fertility goals in the setting of her cancer diagnosis. We would also like to recognize additional programs available such as Fertile Action, Verna's Purse, and Banking on the Future for their continued philanthropic support of men and women struggling with cancer and the oncofertility consequences.

References

Beiner, M.E., Covens, A., 2007 Jun. Surgery insight: radical vaginal trachelectomy as a method of fertility preservation for cervical cancer. Nat. Clin. Pract. Oncol. 4 (6), 353–361.

Bentivegna, E., Maulard, A., Pautier, P., Chargari, C., Gouy, S., Morice, P., 2016 Oct. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil. Steril. 106 (5), 1195–1211.e5.

Boss, E.A., van Golde, R.J., Beerendonk, C.C., Massuger, L.F., 2005 Dec. Pregnancy after radical trachelectomy: a real option? Gynecol. Oncol. 99 (3 Suppl 1), S152–6.

Dursun, P., LeBlanc, E., Nogueira, M.C., 2007 Oct. Radical vaginal trachelectomy (Dargent's operation): a critical review of the literature. Eur. J. Surg. Oncol. 33 (8), 933–941.

Koh, W.J., Greer, B.E., Abu-Rustum, N.R., Apte, S.M., Campos, S.M., Cho, K.R., Chu, C., Cohn, D., Crispens, M.A., Dorigo, O., Eifel, P.J., Fisher, C.M., Frederick, P., Gaffney, D.K., Han, E., Huh, W.K., Lurain 3rd, J.R., Mutch, D., Fader, A.N., Remmenga, S.W., Reynolds, R.K., Teng, N., Tillmanns, T., Valea, F.A., Yashar, C.M., McMillian, N.R., Scavone, J.L., 2015 Apr. Cervical cancer, version 2.2015. J. Natl. Compr. Cancer Netw. 13 (4), 395–404.

Lee, S.J., Schover, L.R., Partridge, A.H., Patrizio, P., Wallace, W.H., Hagerty, K., Beck, L.N., Brennan, L.V., Oktay, K., American Society of Clinical Oncology, 2006 Jun 20. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J. Clin. Oncol. 24 (18), 2917–2931.

Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, 2013 Jan. Mature oocyte cryopreservation: a guideline. Fertil. Steril. 99 (1), 37–43.

Willows, K., Lennox, G., Covens, A., 2016 Oct 21. Fertility-sparing management in cervical cancer: balancing oncologic outcomes with reproductive success. Gynecol. Oncol. Res. Pract. 3, 9.