

Case report

Fertility-sparing treatment of locally advanced vulvar squamous cell carcinoma in a young patient

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1. Introduction

Vulvar cancer is a rare gynecologic malignancy primarily affecting elderly women with a median age of diagnosis at 68. ([Cancer Stat Facts, 2021](#)) It comprises 3–5 % of all female genital tract cancers and 0.3 % of all new cancer cases in the United States. ([Cancer Stat Facts, 2021](#)) Although not the most common cancer, between the years of 2009 – 2018, cases of newly diagnosed vulvar cancer and age-adjusted death rates from vulvar cancer increased annually by an average of 0.6 % and 1.7 %, respectively. ([Cancer Stat Facts, 2021](#)) Furthermore, it was predicted in 2021 there would be 6,120 new cases of vulvar cancer diagnosed and 1,550 deaths from vulvar cancer in the United States. ([Key Statistics for Vulvar Cancer, 2021](#)) The most common histologic type of vulvar cancer is squamous cell carcinoma, representing almost 90 % of all vulvar malignancies. ([Alkatout, 2015](#); [Weinberg and Gomez-Martinez, 2019](#))

Treatment of vulvar squamous cell carcinoma (VSCC) largely depends on histology and stage; patients with early stage cancers undergo surgical excision, while those with locally advanced disease undergo

radical surgery with adjunctive radiation and chemotherapy. ([Weinberg and Gomez-Martinez, 2019](#)) In this case, we detail a young woman diagnosed with locally advanced VSCC who underwent treatment including modified radiation therapy to preserve reproductive function. She subsequently delivered a viable healthy infant through in vitro fertilization (IVF) and frozen embryo transfer and she has remained without evidence of disease for more than 5 years after treatment.

2. Case

This is a case of 34-year-old nulliparous female who presented to her primary obstetrician for an annual visit and reported a painful right labial lesion measuring 2 cm that appeared irritated and bled with palpation. Her past medical history was remarkable for a 10-year history of smoking 1 pack per day and newly diagnosed LGSIL on pap smear. Colposcopic biopsies demonstrated CIN 1 with HPV-related changes and endocervical curettage was negative for malignancy. She was initially prescribed antibiotics for her labial lesion without improvement and underwent punch biopsy which returned positive for invasive squamous

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cell carcinoma with involved margins but no depth of invasion on pathology report. She was subsequently referred to a gynecologic oncologist. At that time, her exam was significant for a 4–5 cm lesion along the right posterior vulva without evidence of inguinal lymphadenopathy in an office exam. Her preoperative computerized tomography (CT) scan revealed a visible non-enlarged right pelvic and inguinal lymph node. She underwent radical vulvectomy and bilateral inguino-femoral lymph node dissection. Intraoperatively, the right labial lesion measured 4 × 6 cm comprising the right labium majus as well as minus into the posterior fourchette, extending into the vagina and across midline to involve the left labium minus. An enlarged 3 × 2 cm right inguinal lymph node was also discovered, although not earlier appreciated on CT or in the office. The left inguinal lymph nodes were grossly negative and removed. Her enlarged right inguinal lymph node returned positive with a 0.04 mm focus of metastatic carcinoma. Her final pathology confirmed Stage IIIA invasive, moderately differentiated keratinizing squamous cell carcinoma with a depth of invasion at 11 mm, no lymphovascular invasion, negative margins with the closest margin at 3 mm, 1 out of 5 positive inguinal lymph nodes on the right, and 3 negative lymph nodes on the left (Fig. 1). Given the patient's desire for fertility and childbearing, she was referred to reproductive endocrinology and infertility (REI) and underwent successful oocyte retrieval, freezing a total of 7 embryos. Prior to chemoradiation, she was started on an oral contraceptive. She completed her chemoradiation treatment 6 months after initial vulvar cancer diagnosis for a total of 6 cycles of cisplatin 40 mg/m² weekly and 45 Gy/25fx to the pelvic and inguinal nodes followed by a 5.4 Gy/3fx boost to the right inguinal basin (Fig. 2). The vulva was omitted from the treatment field.

Her postoperative course was complicated by a recurrent rectovaginal fistula that required two separate operations after her

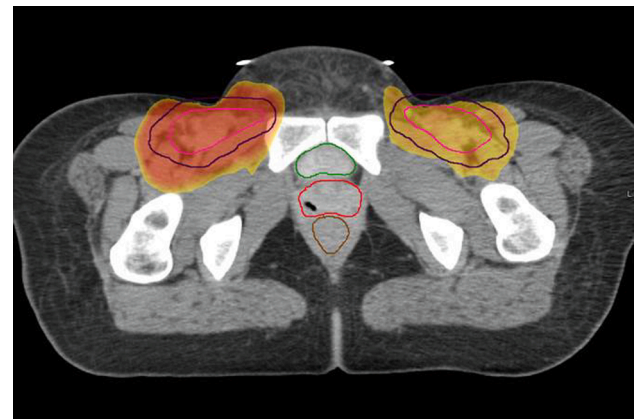


Fig. 2. Green = bladder; Red = vagina; Brown = rectum; Pink = clinical target volume covering both right and left inguinal nodal basins; Purple = planning target volume, a 0.7 cm expansion from the clinical target volume.

chemoradiation treatment, ultimately repaired with sphincteroplasty and Martius flap graft with urogynecology. This complication was a result of the tumor extension into the vagina and small entrance into rectum during radical resection requiring three layer closure of the defect. In addition, she developed a small 1.5 left inguinal abscess that was drained without further complication and a bilateral groin rash that was biopsied for psoriasis and treated successfully with topical steroids. Following full recovery of her rectovaginal fistula, she underwent successful embryo transfer 1.5 years after treatment and delivered a viable term infant via primary low transverse cesarean section. Clinical surveillance for the past 6 years and to date has remained without evidence

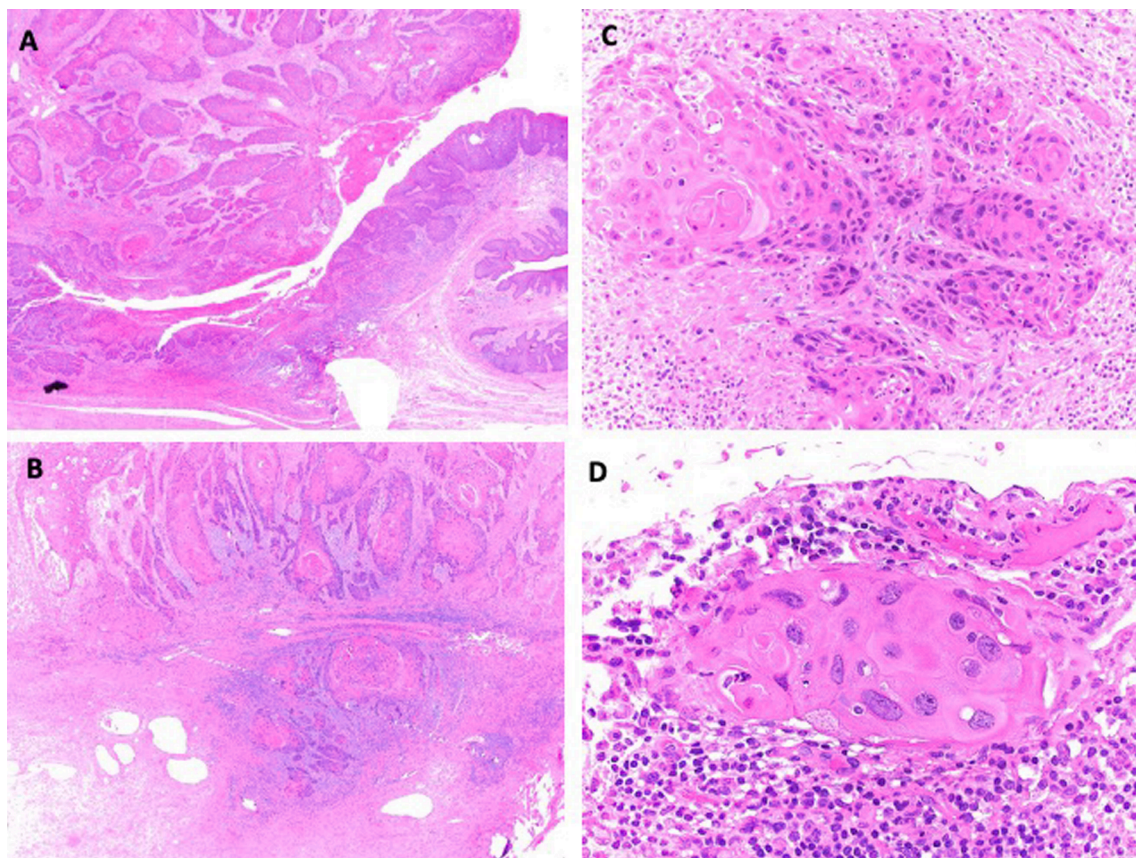


Fig. 1. A. Right vulva showing raised tumor measuring 4.8 cm in largest dimension, 40 × amplification. B. Carcinoma invading underlying stroma to a depth of 11 mm, 100 × amplification. C.. Carcinoma consisting of large polygonal cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei, 200 × amplification. D. Right inguinal lymph node showing metastatic carcinoma, 400 × amplification.

of disease.

3. Discussion

VSCC is commonly appreciated to be a disease of the elderly and diagnosed in early stages. (Akhtar-Danesh et al., 2014; Gaulin et al., 2020; Stroup et al., 2008) Surveillance, Epidemiology, and End Results Program (SEER) and Canadian Cancer Registry (CCR) data reports the average age of VSCC diagnosis at 68 years old, with more than 70 % of diagnosis occurring in individuals above the age of 60. (Akhtar-Danesh et al., 2014; Stroup et al., 2008) A SEER database review by Stroup et al revealed that almost 90 % of VSCC diagnosed was found to be early disease. Known risk factors include older age, lichen sclerosus, squamous hyperplasia, smoking, HPV infection, and an immunocompromised state. (Alkatout, 2015; Dohopolski et al., 2018; Stroup et al., 2008; Weinberg and Gomez-Martinez, 2019) Current survival data predicts the important prognostic factors of VSCC to be age and stage, specifically lymph node involvement. (Akhtar-Danesh et al., 2014; Gaulin et al., 2020; van der Steen et al., 2010) Age was observed to be an independent prognostic factor in Gaulin et al's National Cancer Database (NCDB) review showing improved 5-year overall survival in non-elderly patients (defined as less than 75 years of age) at 78 % when compared to elderly at 43 % and statistically significant survival differences across all stages of diagnoses. Five-year overall survival was found to be approximately 80 % for Stage I, 60 % for Stage II, 50 % for Stage III, and 30 % for Stage IV. In addition to age and stage, degree of nodal involvement is a known prognostic factor and directly observed to impact 5-year disease specific survival in patients, with 1 positive node at 77 %, 2 or 3 positive nodes at 62 %, and 4 or more positive nodes at 28 %. (van der Steen et al., 2010)

The significance of this case is twofold: long-term disease-free interval following treatment of locally advanced VSCC and successful fertility preservation in a young female patient treated with chemotherapy. Our patient was treated in accordance with guideline recommendations for locally advanced VSCC: radical vulvectomy and bilateral inguinal lymph node dissection followed by chemotherapy and radiation. As VSCC typically affects elderly women, there is limited data surrounding treatment of advanced stage VSCC in younger women. Gaulin et al recently reported a 20% risk reduction of death among non-elderly patients treated with chemotherapy and radiation versus those treated with radiation alone. However, the median age of this cohort was 57 and may not represent outcomes associated with a younger patient such as our own.

Following primary treatment of VSCC, overall recurrence rate is 30 %. (Ragupathy et al., 2016) Recurrence data is heterogenous but currently proposes disease association with tumor size, margin status, lymph nodal involvement, precursor lesions, and tumor depth of invasion. (Ragupathy et al., 2016; te Grootenhuys et al., 2019) For node-positive patients, recurrence within the first 2 years after treatment is 32.7 %. (Weinberg and Gomez-Martinez, 2019) A retrospective review by Ragupathy et al suggests late vulvar cancer recurrence, defined as greater than 2 years, confers a better overall survival rate when compared to early recurrence. Specifically with close margins, the risk of local recurrence is unclear. (Alkatout, 2015) A more recent retrospective cohort study by Bedell et al showed data indicating additional treatment for early stage VSCC with close margins, defined as less than 8 mm, did not improve recurrence free survival or overall survival. (Bedell et al., 2019) There is growing evidence to suggest prognostic implications of p16 staining used in proxy for HPV-related disease. VSCC is understood to have 2 distinct disease pathways, HPV-related and non-HPV related, with younger patients more likely to be diagnosed with the former. A retrospective analysis performed in 2018 by Dohopolski et al observed decreased locoregional relapse among women diagnosed with p16-positive tumors when compared to p16-negative tumors following adjuvant radiation therapy, 32.5 % versus 59.1 % respectively. (Dohopolski et al., 2018) Our patient's pathology was p16

positive and with colposcopic pathology reflecting HPV changes that may have contributed to her overall increase in disease-free interval following treatment.

By nature of VSCC typically affecting older women, there is also limited data pertaining to fertility considerations in treatment. Our patient's radiation therapy plan was altered such that midline structures were spared, along with the vulvar resection bed to preserve reproductive function and avoid the rectovaginal fistula. A review of current literature showed radiation therapy may impact fertility by impairing uterine growth potential and altering uterine morphology, typically requiring cesarean section at birth. In addition to fertility, pregnant women who have previously undergone chemotherapy or radiation treatment are more likely to experience pregnancy or birth complications, such as spontaneous abortion, abnormal placentation, preterm birth, low birth weight, stillbirth, and uterine rupture. (Griffiths et al., 2020) To date, there are no clinical studies identifying potential impacts of chemotherapy or radiation therapy exposure to the uterus. (Griffiths et al., 2020) There are very few case reports that document pregnancy outcomes following treatment of vulvar cancers, most of which were diagnosed early stage and not treated with radiation therapy. (Arjona et al., 2011; Dicken et al., 2010) In one of the cases, a young woman was diagnosed with vulvar synovial cell sarcoma and underwent multi-step personalized treatment to preserve fertility, including purposeful localization of radiation, and delivered a full-term infant without complication. (Dicken et al., 2010)

Although current trends reflect VSCC to be a disease of the elderly, both the increasing age of childbearing women and growing number of gynecologic malignancies make fertility considerations a new challenge in treatment of gynecologic cancers. This is especially relevant for vulvar cancers which are historically non-responsive to hormonal treatments as opposed to other gynecologic cancers. (Sherman et al., 1994) This case introduces the possibility of a modified radiation technique as a novel approach and fertility-sparing treatment of locally advanced vulvar cancer.

4. Author Contribution:

NCV wrote the manuscript, NBG provided edits for the manuscript, ZH provided edits for the manuscript, Fig. 2 and explanation, SL provided Fig. 1 and explanation, and TCK provided edits for the manuscript and obtained patient consent. All authors reviewed the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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