

Delayed pelvic recurrence in adenoid cystic carcinoma of the Bartholin's gland

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1. Introduction

Adenoid cystic carcinoma (ACC) of the Bartholin's gland is rare and constitutes only 0.1 to 7 % of vulvar carcinomas, and 10–15 % of all Bartholin's gland carcinomas. (Verta et al., 2022; Wang et al., 2022) The mean age at diagnosis is 47 to 50 years. The most common symptoms are vulvar pruritis and pain, which can occur long before a palpable mass becomes evident. (Verta et al., 2022; Hsu et al., 2013) ACCs of the Bartholin's gland are typically slow-growing, locally invasive tumors with a tendency for perineural and lymphatic invasion. (Verta et al., 2022) Histologically, the tumor has a cribriform glandular-like cystic pattern, often surrounding an acellular gap that is filled with PAS-positive substances or granular basophilic substances. (Wang et al., 2022) Microscopic diagnosis of ACC requires the presence of both pseudocystic and true glandular cavities. (Wang et al., 2022).

To date, the optimal treatment strategy for ACCs of the Bartholin's gland is unclear. Typical management is surgical excision followed by adjuvant radiotherapy, which mirrors the treatment strategy for more common head and neck ACCs. (Bernhardt et al., 2018) ACCs of the Bartholin's gland are characterized by multiple local relapses and a tendency for delayed recurrence and metastasis after initial treatment. (Bernhardt et al., 2018) The most common metastatic site is the lungs, however metastases to the bones, liver, and brain have been reported. (Verta et al., 2022) Here we report a rare case of ACC of the Bartholin's gland with a late recurrence in the pelvis.

2. Case

This patient is a 50-year old postmenopausal woman with a remote history of left Bartholin's gland adenoid cystic carcinoma treated with partial radical vulvectomy followed by whole pelvic radiation for positive resection margins in 2001. Prior to radiation, she underwent ovarian transposition. She remained without evidence of disease, but suffered from multiple post-radiation complications including neurogenic bladder requiring self-catheterization, recurrent urinary tract infections, rectal prolapse, and fecal incontinence. Notably, she had a hysterectomy for cervical dysplasia in 2009 and resection of melanoma in 2013. In October 2023 after transferring care to our institution, the patient was referred to Gynecologic Oncology due to sexual dysfunction in relation to her prior surgery and radiation therapy. A pelvic exam was unremarkable aside from post-surgical and post-radiation changes. Despite being asymptomatic, the patient requested imaging to assess for cancer recurrence. Computed tomography (CT) of the abdomen and pelvis showed a 5.5 cm soft tissue lesion in the left hemipelvis thought to be a left iliac node versus a left adnexal mass. Positron emission tomography (PET) scan showed a metabolically active mass in the left pelvic side wall (SUV 5.4) and mildly prominent left axillary lymph nodes (Fig. 1). A CT-guided biopsy of the pelvic mass was consistent with adenoid cystic carcinoma metastatic to a pelvic lymph node, high-risk human papillomavirus (HPV) negative by RNA in situ hybridization (RNA-ISH). The left axillary lymph node was biopsied and was negative

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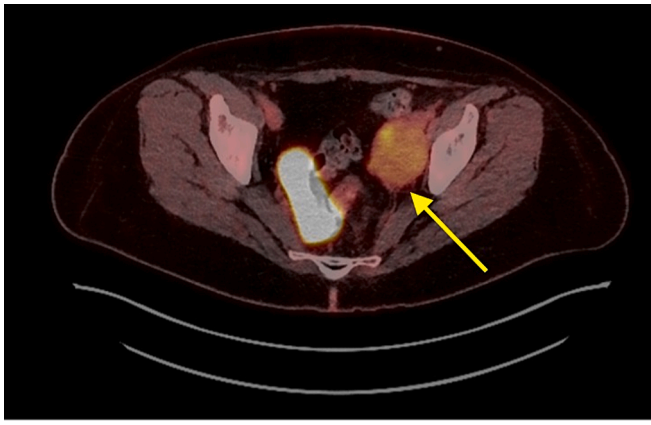


Fig. 1. PET CT axial view-FDG avid mass along the left pelvic sidewall.

for carcinoma, and a diagnostic mammogram was negative. She elected to proceed with surgical management and underwent a robotic-assisted bilateral salpingo-oophorectomy, resection of left pelvic sidewall mass, left pelvic lymphadenectomy, and peritoneal biopsies in December 2023. Final surgical pathology demonstrated a 6 cm left pelvic side wall mass and a lymph node positive for carcinoma (Fig. 2). Next generation sequencing of the tumor revealed a MYB:NFIB fusion mutation which is consistent with adenoid cystic carcinoma, as well as pathogenic variants in ERCC2 and RASA1. (Chae et al., 2015) The patient remains without clinical evidence of disease based on postoperative PET CT and MRI. Her postoperative course was unremarkable aside from a short-term hospital stay four weeks postoperatively for an infected lymphocele and was treated with antibiotics. She is currently disease free four months after her surgery and doing well without complaints.

3. Discussion

We describe a rare case of adenoid cystic carcinoma of the Bartholin's gland with a late recurrence in the pelvis. We present one of the first documented recurrences that was managed using minimally invasive surgery. In this case, our patient experienced the longest reported recurrence-free interval to date of 22 years. (Verta et al., 2022) Verta et al. reviewed 30 cases of Bartholin's gland ACC and found that local recurrence was observed after 9 to 54 months, with a mean recurrence-free interval of 29.6 months. Distant metastasis was reported to occur after 7 to 71 months, which illustrates a mean of 37.7 months.

The ideal primary treatment of Bartholin's gland ACC remains unknown, and no specific treatment guidelines exist. Most literature report simple or radical vulvectomy with negative margins as the choice of

treatment. (Alsan et al., 2011) In a review by Yang et al., wide local excision resulted in a positive margin rate of 48 % and a recurrence rate of 68.9 %, while radical vulvectomy led to a positive margin rate of 30 % and a recurrence rate of 42.9 %. (Wang et al., 2022; Yang et al., 2006) Similar rates were calculated by DePasquale et al., who found a recurrence rate of 61 % after local excision and 50 % after radical vulvectomy. (DePasquale et al., 1996).

It has been hypothesized that the prognosis is related to surgical margins, though data have been inconsistent. In a review by Alsan et al., recurrence was seen in 35 % of patients with positive margins and 10 % of patients with negative margins, regardless of simple versus radical vulvectomy. (Alsan et al., 2011) In contrast, Lelle reported a series that included five patients with local recurrence, four of whom had had negative surgical margins. (Lelle et al., 1994) Yang et al. reported recurrence rates of 52.9 % in the group with positive margins and 52.1 % in the group with negative margins—however, half of the positive margin group received adjuvant radiation which could explain the similar recurrence rates.

The therapeutic and diagnostic value of lymph node dissection remains unknown. (Yang et al., 2006) Metastases to the ipsilateral inguino-femoral lymph nodes have been reported in up to 10 % of patients, while metastases to the contralateral lymph nodes have not been reported. (Lelle et al., 1994; Alhashemi et al., 2023) Several studies reported performing ipsilateral or bilateral inguino-femoral lymphadenectomy. (Verta et al., 2022; Wang et al., 2022; Bernhardt et al., 2018; Chang et al., 2020; Pellizzon, 2018), without consensus as to which patients would benefit the most from this practice. Patient-specific factors and knowledge of the lymphatic spread of vulvar tumors should be considered when counseling patients preoperatively, including size and laterality of tumor, preoperative imaging, and medical comorbidities which could increase surgical risk.

There is little evidence regarding the role of systemic therapy in Bartholin's gland ACC. Chemotherapy has been administered in cases of distant metastasis or as palliative therapy in recurrent disease. Studies have described using a combination of cyclophosphamide, Adriamycin, or cisplatin; other agents include paclitaxel, methotrexate, doxorubicin, 5-fluorouracil, and dactinomycin. (Verta et al., 2022) Outcomes data is scarce, but several patients were able to achieve stable disease for months to years. (Hsu et al., 2013; Yang et al., 2006) In a few case reports, cisplatin or irinotecan were administered in the adjuvant setting with concurrent radiation, and recurrence free intervals ranged from 3 months to 24 months. (Verta et al., 2022; Hsu et al., 2013; Yang et al., 2006).

Prognostic factors such as positive resection margins and perineural spread have been an indication for postoperative radiotherapy in Bartholin's gland ACC, although most data are from head and neck ACCs. (Bernhardt et al., 2018) In Verta et al.'s literature review, of 28

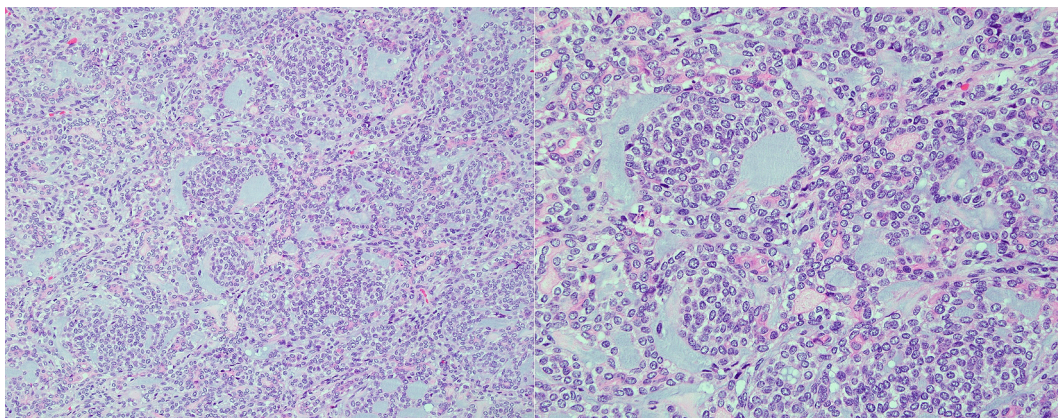


Fig. 2. Surgical pathology specimen. Lymph node infiltrated by ductal and myoepithelial cells growing in a cribriform pattern with basement membrane material within the intraluminal spaces (low power on left, high power on right).

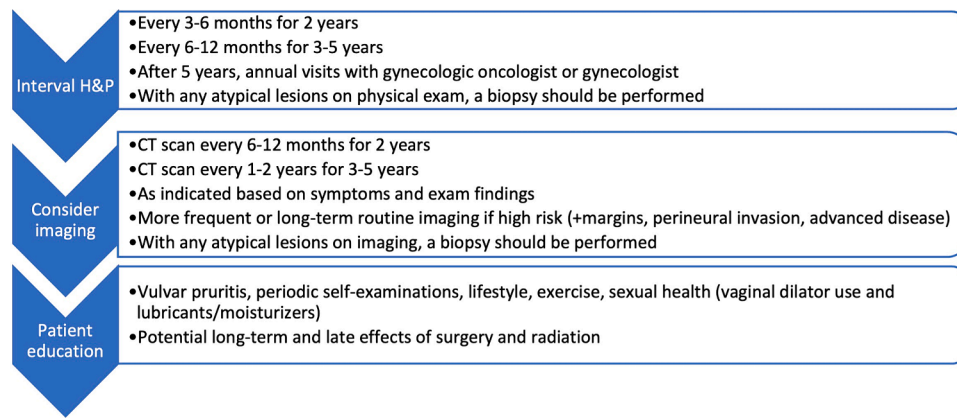


Fig. 3. Proposed survivorship care for patients with a history of adenoid cystic carcinoma. (NCCN, 2024a).

Bartholin's gland cases that had undergone primary surgery, 18 cases (64 %) received adjuvant radiation. (Verta et al., 2022) In 5 cases, the resection margins were negative or unknown, but the remainder 13 cases had positive resection margins. Several authors found that external beam radiation allows for local control of the tumor in patients with positive resection margins, and the recurrence rate was lower than in patients without adjuvant radiotherapy. (Pellizzon, 2018; Rosenberg et al., 1989; Copeland et al., 1986) In this case, our patient developed an isolated pelvic recurrence after adjuvant pelvic radiotherapy following her initial surgery. Given the successful surgical resection of her isolated recurrence likely within the previously irradiated field, decision was made to observe the patient instead of pursuing more radiation or systemic therapy.

Few studies have reported survival outcomes in this disease. According to Copeland et al., patients with ACC have a 5-, 10-, and 15-year progression-free survival of 47 %, 38 %, and 15 %, respectively. The 5-, 10-, and 15-year survival rates are 71 %, 50 %, and 51 %, respectively. (Copeland et al., 1986) According to Johnson et al., patients have a 59–100 % survival rate for 10 years. (Johnson et al., 2017) In the metastatic scenario, case series of head and neck ACCs suggest that the median survival is about 3 years, but some patients survive longer than 10 years. (Bernhardt et al., 2018) Given the potential for long-term survival and recurrence rates as high as 69 %, identification of recurrent disease is important to guide treatment. (Verta et al., 2022; Yang et al., 2006; DePasquale et al., 1996) Recurrent Bartholin's gland ACC may be asymptomatic, and even if symptomatic can be nonspecific. There may be a role for routine imaging, as well as continued surveillance indefinitely. We favor a surveillance plan based on the National Comprehensive Cancer Network (NCCN) guidelines for vulvar cancer, which emphasizes routine physical exams and incorporates cross-sectional imaging to evaluate for distant recurrences, even if clinically the recurrence seems to be local (Fig. 3). (NCCN, 2024a) Similarly, NCCN guidelines for head and neck ACCs favor physical exams every 1–8 months in the first five years, then annually thereafter. In head and neck ACCs, there are no consensus guidelines on the frequency and modality of routine post-treatment imaging in the asymptomatic patient, but PET CT may be the most sensitive and annual imaging may be indicated to evaluate for distant metastasis. (NCCN, 2024b) In this case, our patient's asymptomatic recurrent disease was fortunately identified on imaging and diagnosed with a biopsy to allow for prompt surgical resection.

Despite promising results from prior studies showing adjuvant radiation can lower recurrence rates in patients with positive margins, our patient's disease recurred 22 years after whole pelvic radiation, likely within the radiated field. Although there are no established treatment guidelines on locally isolated recurrent ACC, the recommended treatment strategies should focus on local control with either surgical resection or targeted radiotherapy.

4. Conclusion

Bartholin's gland ACC has a high recurrence rate ranging from 30 % to 69 %, with most recurrences occurring within 5 years after initial diagnosis. However, duration of surveillance and treatment of recurrent disease is not well established. This case demonstrates evidence of a recurrence > 20 years from initial treatment, highlighting the need for long-term surveillance in survivors of this rare vulvar malignancy.

CRedit authorship contribution statement

Chrissy Liu: Writing – review & editing, Writing – original draft, Conceptualization. **Kelsey Roof:** Writing – review & editing. **Alaaeddin Alrohaibani:** Visualization, Project administration. **Krisztina Hanley:** Visualization, Supervision. **Sarah Dilley:** Writing – review & editing, Conceptualization.

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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