

Original Article

Analysis of clinical outcomes of patients with adenoid cystic carcinoma of Bartholin glands

Gun Yoon^{1*}, Hyun-Soo Kim^{2*}, Yoo-Young Lee³, Tae-Joong Kim³, Chel Hun Choi³, Sang Yong Song⁴,
Byoung-Gie Kim³, Duk-Soo Bae³, Jeong-Won Lee³

¹Department of Gynecology and Obstetrics, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea; ²Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; ³Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ⁴Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. *Equal contributors.

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Abstract: Adenoid cystic carcinoma of Bartholin glands (BG-ACC) is a rare, slow-growing but a highly aggressive tumor with remarkable capacity for local recurrence and distant metastasis. The purpose of this study was to elucidate our experiences of the diagnosis and treatment of BG-ACC and to analyze the clinical outcomes and prognosis of patients with BG-ACC. A retrospective chart review was performed to assess the demographic information, chief complaints, pathologic features of tumors, primary treatment, and development of local recurrence or distant metastasis, as well as the patient outcome. All patients received surgical excision as the primary treatment, and the diagnosis of BG-ACC was confirmed histopathologically. Three of four patients whose tumors showed pathologic features indicating a high probability of recurrence received adjuvant radiotherapy. These patients did not develop local recurrence, in contrast, one patient who did not receive adjuvant radiotherapy developed local recurrence and distant metastasis on several occasions. All patients who received primary surgical treatment are alive to date. When patients who are more than 40 years of age and who present with symptomatic BG lesions, BG-ACC should be included in the differential diagnosis and biopsy should be performed for histopathologic confirmation. Radical local excision with sufficient negative margins seems to be beneficial for primary treatment. Adjuvant radiotherapy is a reasonable treatment option for patients with high risk factors after surgery or for patients who develop local recurrence.

Keywords: Bartholin glands, adenoid cystic carcinoma, treatment, surgery, vulvar cancer

Introduction

Primary carcinoma of the Bartholin glands (BG), first documented by Klob [1] in 1864, is a rare malignancy comprising less than 1% of all female genital tract malignancies. Adenocarcinomas and squamous cell carcinomas each account for approximately 40% and adenosquamous carcinomas account for approximately 5% of BG carcinomas [2]. Adenoid cystic carcinoma of BG (BG-ACC) is a rare variant of BG carcinoma, comprising 15% of all BG malignancies [3, 4]. BG carcinoma has no distinguishing clinical manifestations; hence, it is not easy to suspect or diagnose it during clinical practice. As a result, most primary BG carcino-

mas are often misdiagnosed and mistreated as BG cysts or abscesses. Because ACC in particular is even rarer, it is very difficult for clinicians to suspect it. Nevertheless, it is clinically very important since ACC has a high local recurrence rate and a tendency for distant hematogenous metastasis. Additionally, perineural invasion is common in ACC, and it is known to show local recurrence frequently even after securing a negative resection margin [5].

ACC is generally considered as a variant of vulvar cancer; hence, surgical treatment is often performed based on the treatment guideline for primary squamous cell carcinoma of the vulva. Anatomically, however, it arises in tissues that

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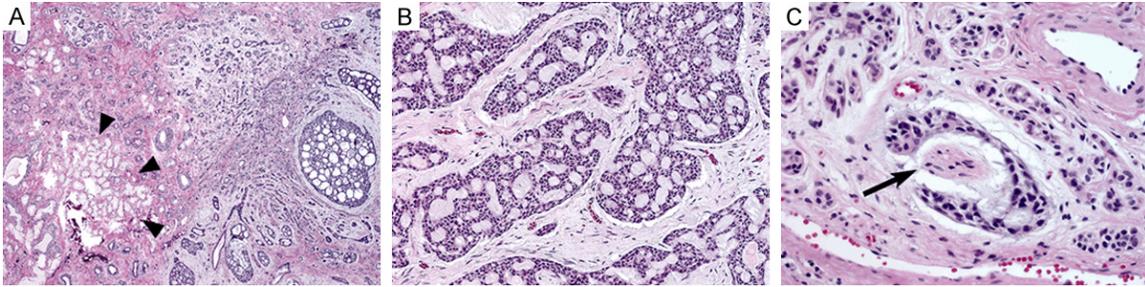


Figure 1. Microscopic findings of BG-ACC. A. At low power magnification, an infiltrated tumor tissue (center and right one-third), the adjacent normal glands and ducts (black arrowheads) were observed. B. BG-ACC exhibited cribriform nests of small uniform tumor cells forming gland-like spaces with basement membrane-like material. C. Note perineural invasion with tumor cell nests surrounding a nerve fiber (black arrow).

are different from the vulva, as the BG is located within the subcutaneous tissue of the posterior labia [6]. Since no prospective and randomized controlled trial for determining the optimal treatment modality for ACC exists, until now there is no consensus on the standard treatment.

The purpose of this study was to elucidate our experiences of the diagnosis and treatment of BG-ACC and to analyze the clinical outcomes and prognosis of BG-ACC patients treated in a single institution.

Patients and methods

Between January 2001 and December 2014, five patients were diagnosed with BG-ACC at the Obstetrics and Gynecology, Samsung Medical Center (Seoul, Republic of Korea). A retrospective chart review was performed to assess the demographic information, chief complaints, pathologic features of tumors, primary treatment modality, the development of local recurrence, the presence of lymph node and/or distant metastasis, performance scale (based on the ECOG/WHO/Zubrod scoring system), and the outcome of patients. As a preoperative work-up, abdomino-pelvic magnetic resonance imaging, chest computed tomography (CT), and/or whole body positron emission tomography-CT scans were performed.

In all cases, the diagnosis of primary or recurrent BG-ACC was confirmed histopathologically. All cases satisfied the diagnostic criteria for both BG carcinoma and BG-ACC. Firstly, the diagnostic criteria for primary BG carcinoma established by Finan et al. [7] were as follows: correct anatomic location of the tumor, with a

primary location deep in the labia, intact overlying skin, the presence of normal glandular elements on histology (**Figure 1A**), and no evidence of a concurrent primary tumor elsewhere [8]. Secondly, the diagnostic criteria for BG-ACC described in the current WHO Classification were as follows: rounded and cribriform islands of uniform epithelial cells present within hyaline stroma composed of basement membrane material [2]. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to their inclusion in this study.

Results

The clinical profiles and pathologic features are described in **Table 1**. The median age at diagnosis was 59 years (range, 50-67 years). The youngest patient was premenopausal. Patient 4 had received right hemicolectomy with left lateral segmentectomy of the liver ten years ago due to ascending colon cancer with hepatic metastasis. After 12 cycles of adjuvant chemotherapy, no recurrence has been reported during the follow-ups to date. Patient 5 had a previous history of marsupialization of BG abscess performed 8 months before the diagnosis of BG-ACC. All patients complained of a palpable mass near the BG area, and 4 patients had accompanying pain. Preoperative imaging studies showed no evidence of inguinal lymph node metastasis or distant metastasis in all patients, indicating that the BG-ACCs were localized lesions at diagnosis.

As the primary treatment, radical local excision (n=4) or radical hemivulvectomy (n=1) was per-

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Table 1. Clinicopathological features and outcomes of 5 patients with a surgically resected BG-ACC

| Patient | Age | Tumor laterality | Tumor size (cm) | Preoperative imaging study | | Primary treatment | Pathologic features | | | Local recurrence | Distant metastasis | Outcome | | |
|---------|-----|------------------|-----------------|----------------------------|--------------------|-------------------|---------------------|-----------------------|---------------------|------------------|--------------------|---------------------|--------|----|
| | | | | Lymph node metastasis | Distant metastasis | | RM status | Lymph node metastasis | Perineural invasion | | | Follow-up time (mo) | Status | PS |
| 1 | 54 | Right | 2.0 | Absent | Absent | RLE+IILND+ARTx | Positive | Absent | Present | Absent | Present | 71 | SD | 1 |
| 2 | 67 | Left | 2.5 | Absent | Absent | RLE+ARTx | Positive | NA | Present | Absent | Absent | 106 | NED | 1 |
| 3 | 50 | Left | 1.0 | Absent | Absent | RHV+IILND+ARTx | Negative | Absent | Present | Absent | Absent | 137 | NED | 1 |
| 4 | 60 | Left | 3.0 | Absent | Absent | RLE | Positive | NA | Present | Present | Present | 224 | PD | 2 |
| 5 | 59 | Right | 4.0 | Absent | Absent | RLE+IILND | Negative | Absent | Present | NA | NA | Recent case | | |

RLE: radical local excision; IILND: ipsilateral inguinal lymph node dissection; ARTx: adjuvant radiotherapy; RHV: radical hemivulvectomy; RM: resection margin; NA: not applicable; SD: stable disease; NED: no evidence of disease; PD: progressive disease; PS: performance scale.

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Table 2. Clinical features of 2 patients with recurrent or metastatic BG-ACC

| Patient | Disease progression | Months after the first surgery | Tumor location | Treatment |
|---------|----------------------|--------------------------------|--|----------------------|
| 1 | Distant metastasis | 7 | Lung | Metastasectomy |
| | Recurrent metastasis | 8 | Lung | Metastasectomy +PCTx |
| 4 | Local recurrence | 24 | Vulva | RLE |
| | Local recurrence | 46 | Vulva | RLE |
| | Local recurrence | 60 | Pelvic peritoneum, vagina, and urethra | RH+PE+BIFLND |
| | Distant metastasis | 71 | Lung | Metastasectomy +PCTx |
| | Distant metastasis | 132 | Liver | CTx+ hemihepatectomy |
| | Recurrent metastasis | 179 | Lung | Conservative |
| | Local recurrence | 182 | Perineal area and pelvic peritoneum | Conservative |
| | Recurrent metastasis | 189 | Lung | Conservative |

PCTx: palliative chemotherapy; RLE: radical local excision; RH: radical hysterectomy; PE: pelvic exenteration; BIFLND: bilateral inguinofemoral lymph node dissection; CTx: chemotherapy.

formed. Ipsilateral inguinal lymphadenectomy was performed in three patients. Average tumor size was 2.5 cm in the longest diameter (range, 1.0-4.0 cm). Microscopically, all cases of BG-ACC exhibited a classical cribriform arrangement of tubules and gland-like elements (**Figure 1B**). We examined the presence of several pathologic features indicating aggressive oncogenic behavior (i.e., high-risk factors), including the involvement of surgical resection margin, inguinal lymph node metastasis, lymphovascular invasion, and/or perineural invasion (**Figure 1C**). Involvement of the resection margin was observed in three patients (Patients 1, 2, and 4). Three patients who received ipsilateral inguinal lymphadenectomy had no lymph node metastasis. Perineural invasion was observed in all patients. Among the four patients who had more than one high-risk factors (Patients 1, 2, 3, and 4), postoperative adjuvant radiotherapy was applied to three patients except for Patient 4. Recurrence of tumor was identified in two patients (Patients 1 and 4).

The outcomes of patients with BG-ACC were also assessed (**Table 1**). The mean survival time except for that in one patient (Patient 5, recent case) was 134.5 months (range, 71-214 months). All patients are alive to date. According to the RECIST classification, two patients (Patients 2 and 3) were classified as having 'no evidence of disease', one (Patient 1) was classified as having 'stable disease', and one (Patient 4) was classified as having 'progressive disease'.

The clinical features of two patients who developed local recurrences and/or distant metastases

are summarized in **Table 2**. Despite showing resection margin involvement Patient 4 did not receive adjuvant radiotherapy. She developed local recurrence in the vulva, perineal area, and pelvic cavity on 4 occasions, and distant metastasis to the lung and liver on 5 occasions both after the first surgery. Especially after the first recurrence, active treatments such as surgery and/or palliative chemotherapy were performed, but local recurrence and distant metastasis occurred subsequently. At present, we are only performing conservative management such as pain control. Patient 1 developed pulmonary metastases twice at 7 and 8 months after radical local excision with adjuvant radiotherapy. Patient 1 received metastasectomy with subsequent chemotherapy (paclitaxel and carboplatin) for the first metastasis, and metastasectomy only for the second metastasis. Regardless of the active treatment similar to that in Patient 4, it was impossible to remove pulmonary lesions completely. However, no local recurrence has occurred to date, and the number and the size of residual pulmonary lesions have not increased.

Discussion

BG-ACC is extremely rare, with only about 80 cases having been reported in the literature [5]. This study reported the highest number of cases of BG-ACC alone at a single institution. Clinical manifestation of BG-ACC is not largely different from that of vulvar cancer, which shows different histology. Patients with a mass around the BG usually complain of an abnormal sensation along with a palpable mass (or cyst)

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with or without pain, pruritus, or skin discoloration etc. It is presumed to be related to perineural invasion, which is a characteristic of BG-ACC but not a unique feature of BG-ACC. Therefore, most symptomatic BG masses are diagnosed as BG cysts or abscesses, and they are managed only by incision and drainage. However, some cases among those, in which only marsupialization was performed, are likely to be of BG carcinoma. In this study, we confirmed that when Patient 5 visited our institution with a BG mass 8 months ago, we suspected it to be a BG cyst and only performed marsupialization without biopsy. We cannot exclude the possibility of the BG mass (which was found 8 months after marsupialization) being a newly developed BG-ACC, but there is a possibility that BG-ACC was misdiagnosed as a BG cyst, which resulted in belated treatment. In this respect, number of researchers have recommended cytologic examination through fine-needle aspiration in women who are 40 years of age or older [9, 10]. However, cytology has low diagnostic value and morbidity related to the procedure increases in case of radical procedure such as BG cystectomy. Thus, it can be considered that in case of a symptomatic BG cyst, incisional or excisional biopsy is necessary to exclude the presence of a hidden carcinoma after draining the cyst.

Because BG-ACC is a slow-growing tumor, it is known to be apt to invade locally. Perineural invasion, which is a histologic characteristic of ACC, is also one of the reasons that explain its frequent recurrences. Moreover, there are reports that even after initial surgical excision, regardless of the existence of resection margin involvement (in other words, after securing a negative resection margin,) it recurs at the end [11]. On the other hand, distant metastasis generally occurs after a long time since the initial diagnosis. When we refer to previous studies, it seems that even after the first recurrence, BG-ACC patients stay alive for a considerable amount of time [12]. The rate of local recurrence and distant metastasis of BG-ACC is estimated to be 30% and 31%, respectively [9]. One study reported that the overall survival rates of patients with BG-ACC for 5 and 10 years range from 71% to 100% and 59% to 100%, respectively [11]. Another study showed that the progression-free survival rate was 47% at 5 years and 35% at 10 years, respectively, and that the overall survival rate was 71% and

59% at 5 and 10 years, respectively [9]. In this study, Patient 4 who did not receive adjuvant radiotherapy showed metastatic lesions in the lung and liver on several occasions, but it did not lead to her death. This proves that BG-ACC is a slow-growing tumor although it shows aggressive behavior, and further investigation on survival is necessary.

The most preferred primary treatment is surgical excision. Various surgical options include local or wide local excision, radical local excision, and radical hemivulvectomy, with or without ipsilateral inguinofemoral lymphadenectomy. An important point about the surgery is that wide excision is crucial in order to secure a pathologically sufficient negative resection margin. The reason for this is that BG carcinoma tends to extend towards the lateral wall of the vagina as well as towards the ischioanal fossa. Thus, partial excision of the levator ani muscle and/or distal vagina may be necessary when we consider various clinical situations. However, radical vulvectomy should not be universally applied because recurrence rates are similar in patients with positive and negative resection margins, explained in part by adjuvant radiation therapy being preferentially proposed in case of inadequate margin status [1]. Accordingly, this study suggests that adjuvant radiotherapy may be beneficial in reducing local recurrence. Three patients who had resection margin involvement and perineural invasion received adjuvant radiotherapy, and no local recurrence was found during the follow-up. Among them, one patient developed pulmonary metastasis. On the other hand, one patient who showed resection margin involvement but did not receive adjuvant radiotherapy developed local recurrence on several occasions, and despite repeated surgery, the tumor extended to the pelvic peritoneum. Eventually, radical hysterectomy and pelvic exenteration was performed, but the tumor recurred again in residual perineal tissues. In the future, researches assessing the efficacy and safety of adjuvant radiotherapy are necessary. However, performing adjuvant radiotherapy in patients who present with pathologic features which indicate aggressive oncogenic behavior is thought to be beneficial in reducing the local recurrence as of now. Rosenberg et al. [8] and Copeland et al. [9] have reported the benefits of postoperative external beam radiation in patients with positive surgical margins. They performed adjuvant

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radiotherapy in 15 patients with BG-ACC, and no local recurrence occurred after the treatment. This study indicates that adjuvant radiotherapy may reduce the incidence of local recurrence.

The frequency of microscopically positive surgical resection margin is relatively high. Therefore, it is reported that approximately 40% of patients need adjuvant radiotherapy after primary surgery [8, 9, 13]. In a previous study, primary radiotherapy or chemotherapy was performed in 10 patients with BG carcinoma [6]. Treatment options included teletherapy combined with a boost to the primary site, regional nodes and/or interstitial brachytherapy. The median follow-up period was 87.2 months (range, 45-142 months). Three- and five-year survival rates were 71.5% and 66%, respectively, comparable to outcomes after surgery and postoperative radiotherapy. This indicates that primary nonsurgical treatment might provide an effective alternative to surgery with preservation of genital function and low morbidity.

No lymph node metastasis was found in this study before and after the primary treatment. It is known that inguinal lymph node metastasis rarely occurs in BG-ACC patients and even if it does, it occurs ipsilateral to the primary tumor. However, the prognostic and therapeutic value of lymphadenectomy is unclear in the literature.

Lung is the most common site of distant metastasis of BG-ACC [5]. In unusual cases, metastasis has been reported to occur in the brain, kidney, and liver [14, 15]. There is not much information on treatment of metastasis and it varies according to the location of the metastasis. In metastatic ACC, chemotherapy has been used; but there are few researches assessing the effectiveness of chemotherapy to date. The aim of the treatment is palliation. Several chemotherapeutic regimens have been evaluated in the literature, but cyclophosphamide, adriamycin, and cisplatin regimen seems to be used relatively frequently. A previous study reported that after the administration of 5-fluorouracil, adriamycin, and mitomycin in a patient with metastatic ACC of the salivary gland, the tumor showed complete remission [16]. In another study, a combination of methotrexate, dactinomycin, chlorambucil, adriamycin, and cyclophosphamide was administered in a patient

with metastatic BG-ACC [11, 13]. In this study, we performed 6 cycles of adriamycin and cisplatin in Patient 1 who developed pulmonary metastasis, and the patient has achieved stable disease status until now. In Patient 4, local recurrence occurred on three occasions and pulmonary metastasis developed subsequently. In the follow-up after surgery, the tumor showed progression; hence, we performed palliative chemotherapy with 6 cycles of cyclophosphamide, adriamycin, and cisplatin. After this, metastasis to the liver occurred; hence, 4 cycles of palliative chemotherapy with ifosfamide as a single agent were performed. However, the effect was not satisfactory.

BG-ACC is a very rare malignancy of the vulva. Local recurrence and distant metastasis have been commonly reported. This study has taken a very small number of patients into account. Nevertheless, when we consider that ACC develops very rarely in the BG, we think that our clinical experience can help to determine its clinical course and prognosis. As in the case of other tumors, a prospective randomized study can provide the most powerful evidence for deciding the optimal treatment. However in reality, it is very difficult to perform such a large study of extremely rare diseases. In this respect, collaborative multicenter data collection is crucial and the accumulated information will provide a strong basis for long-term prognosis, overall and recurrence-free survival rates, and identifiable surgical risk factors. It will also contribute to provide necessary evidence for deciding the optimal treatment modality.

Finally, in order to prevent misdiagnosis and mistreatment, we propose that in case of a symptomatic cyst or mass in the BG area in a patient of age 40 years or older, ACC must be included in the differential diagnosis. A pathological diagnosis through a biopsy is critical. As a primary treatment, radical local excision should be performed for securing a sufficient resection margin. If there are high risk factors, performing adjuvant radiotherapy seems to be the optimal treatment of choice as of now.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jeong-Won Lee, Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of

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Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 135-710, Republic of Korea. Tel: +82-2-3410-1382; Fax: +82-2-3410-0630; E-mail: gardlee1@naver.com

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