



Glassy cell carcinoma of cervix: an analysis for 20 cases and literatures review

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Background: Glassy cell carcinoma (GCC) of the cervix is defined as a rare subtype of adeno-squamous cell carcinoma (ASC) with poor prognosis. We presented our clinical data of patients with cervical GCC and reviewed the outcomes in recent years.

Methods: From 2011.1 to 2019.7, 20 cases of cervical GCC diagnosed and treated in our institution were reviewed for clinicopathologic features, treatment strategies, and outcomes.

Results: (I) Twenty cases confirmed as cervical GCC were selected and represented 1.8% of all invasive cervical cancer diagnoses. The median age of all cervical GCC patients was 46 years (range from 33 to 69 years). The main clinical symptoms were abnormal vaginal bleeding and postcoital bleeding. The incidence of stage I, stage II, stage III was 75%, 20% and 5%. (II) Human papillomavirus (HPV) prevalence in cervical GCC was 44.4% (4/9). Of the HPV-positive tumors, HPV genotyping was variable. Tumors of 3 cases were found infected by HPV-18. Another tumor was infected by HPV-16 and HPV-31. Multiple infections were found in 1 case. (III) The disease-free survival (DFS) of early stage cervical GCC cases was 93%, and DFS of advanced stage cervical GCC cases was 67%. DFS of all cases was 85%. The median follow-up interval for surviving patients was 28 months. Three patients recurred, leading to an overall recurrence rate of 15% (3/20). One of 3 recurred cases was from multimodal treatment group who had one high risk factor (pelvic lymph node metastasis) and three intermediate risk factors lympho-vascular space involvement (LVSI), deep stromal invasion, and large tumor size (3.5 cm). Other 2 cases recurred were from radio-chemotherapy group.

Conclusions: Cervical GCC is associated with high-risk type HPV infection, especially HPV 18. The prognosis of GCC was not poor as depicted in previous studies. Early-stage GCC patients should receive multimodal treatment which reduced recurrence rate and improved survival rate. With the limitation of small sample size, we speculated surgery might play a key role in curing GCC. Patients whose pathology features includes at least two intermediate high risk recurrence or one high risk factor should accept adjuvant treatment after complete surgical management.

Keywords: Glassy cell carcinoma (GCC); cervical cancer; multimodal treatment

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Introduction

Glassy cell carcinoma (GCC) of cervix is a rare subtype of adeno-squamous cell carcinoma (ASC), which was reported by Cherry and Glucksmann first as an aggressive

subtype of cervical carcinoma with poor prognosis (1). It accounts for 0.2% to 9.3% of all cervical cancers, and 2% to 30.2% of cervical adenocarcinomas (2-4). The tumor of GCC can present as a cervical polyp or as a microinvasive

Table 1 General data statistics of patients

| Variable | Number |
|---|--------------|
| Age, median [range], years | 46 [33–69] |
| Abnormal bleeding /discharge or postcoital bleeding | 100% |
| Abnormal pap smear | 54.5% (6/11) |
| HPV infection rate | 44.4% (4/9) |
| HPV-18 | 75% (3/4) |
| HPV-16 | 25% (1/4) |
| HPV-31 | 25% (1/4) |

HPV, human papillomavirus.

lesion, and may grow into the endocervical canal in a barrel-shaped fashion (5). A few studies had indicated that GCC was strongly associated with high-risk type human papillomavirus (HPV) infection although the information of HPV genotyping detection for GCC patients are limited accounting for the lack of retrospective studies (6).

For the rarity of this disease and lack of prospective studies, management of cervical GCC has not been specifically defined. For now, the treatment of cervical GCC still follows the management of squamous cell carcinoma. Multimodal treatment seems to play an important role in improving prognosis of cervical GCC patients. Thus, it is significant to find out risk factors related recurrence to guide multimodal treatment for cervical GCC. Our aim was to analyze the clinical-pathological features of cervical GCC patients admitted in our institution and verify the importance of multimodal treatment for prognosis improvement of cervical GCC.

Methods

A review of cervical carcinoma diagnosed and treated in our institution was performed from the years 2011 to 2019. The study was approved by institutional ethics board of Tianjin Central Hospital of Gynecology Obstetrics and informed consent was taken from all the patients. All patients received the same stage-specific therapy. Cervical GCC was diagnosed if over 50% of the tumor cell type displayed glassy cell features. Twenty cases with a final diagnosis of cervical GCC were selected out after a review of all slides of biopsies and cone specimens by the same gynecologic pathologist. The charts of these patients were reviewed for age, parity, clinical symptoms, Thinprep cytologic test

(TCT), HPV genotype test, stage, nodal status, adjuvant therapy, tumor size, morphology of tumor, depth of invasion, lympho-vascular space involvement (LVSI), lymph node metastasis, disease recurrence, interval to recurrence, mortality, and follow-up interval. All Follow-up data were obtained by review of medical records and telephone calls to primary providers.

Results

Twenty GCC patients with a final diagnose of GCC were found from all the cervical carcinoma patients with an overall incidence of 1.8%. General data statistics of 20 patients were displayed in *Table 1*. The median age of 20 GCC patients was 46 years (range from 33 years to 69 years) which is three years younger than that of common subtype of cervical carcinoma. With the exception of one patient, all were multiparous, but no one was in pregnancy. The main clinical symptoms were abnormal vaginal bleeding or postcoital bleeding; 40.0% (8/20) of all patients had vaginal discharge before abnormal vaginal bleeding. Only 55.0% (11/20) had liquid-based cytology test, while 54.5% (6/11) of all had abnormal results. In our study, HPV prevalence in cervical GCC was 44.4% (4/9). Of the HPV-positive tumors in GCC, HPV genotyping was variable. Tumors of 3 cases were found infected by HPV-18. Another tumor was infected by HPV-16 and HPV-31. Multiple infections were found in 1 case. In our study, the disease-free survival (DFS) of patients received multimodal treatment was 93%, and DFS of patients received chemoradiotherapy was 67%. DFS of all patients was 85%. The median follow-up interval for surviving patients was 28 months.

The stage distribution and prognosis are shown in *Table 2*. Different treatment modalities and outcomes were depicted in *Table 3*. Radical hysterectomy and pelvic lymphadenectomy were performed in 14 patients with stage IB. According to risk factors found in tumor pathology, 10 of 14 patients were given adjuvant treatment after radical hysterectomy, in form of pelvic external beam radiation (EBRT) and monthly combined chemotherapy with paclitaxel and cis-platinum (4 circles). One of 10 patients suffered relapse. Two of 14 patients received radical surgery as sole treatment and 2 of 14 patients were given pelvic EBRT, none of them recurred. Five advanced stage cervical GCC patients and 1 early stage cervical GCC (stage IB) were given radiotherapy and combined chemotherapy. Of these patients, 1 patient with stage IB and 1 patient with stage IIB suffered relapse.

Table 2 Stage distribution and prognosis

| Stage | No. [%] | Recur [%] | DFS (%) |
|-------|----------|-----------|---------|
| IB | 15 [75] | 2 [13] | 87 |
| IIB | 4 [20] | 1 [25] | 75 |
| IIIB | 1 [5] | 0 | 100 |
| Total | 20 [100] | 3 [15] | 85 |

DFS, disease-free survival.

Table 3 Treatment modalities

| No. | Treatment | Recur, n [%] | DFS (%) |
|-----|---------------------|--------------|---------|
| 10 | RH + Chemo + EBRT | 1 [10] | 90 |
| 2 | RH + EBRT | 0 | 100 |
| 2 | RH | 0 | 100 |
| 6 | EBRT + ICBT + Chemo | 2 [33] | 67 |

RH, radical hysterectomy; Chemo, chemotherapy; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; DFS, disease-free survival.

Table 4 Tumor characteristics (N=14)

| Variable | Number |
|------------------------|-------------|
| Tumor size ≥ 3 cm | 50% (7/14) |
| Exophytic | 71% (10/14) |
| Endogenous | 14% (2/14) |
| Mild erosion | 14% (2/14) |
| Depth of invasion | |
| Deep 1/3 | 36% (5/14) |
| Middle 1/3 | 29% (4/14) |
| Inner 1/3 | 29% (4/14) |
| LVSI | 36% (5/14) |
| Pelvic LN(+) | 7% (1/14) |

LVSI, lympho-vascular space involvement; LN, lymph node.

Detailed evaluation of tumor characteristics was intensively depicted among 14 cervical GCC who underwent surgical treatment in *Table 4*. At the time of diagnosis, 7/14 patients had gross tumor of which the diameter is greater or equal to 3 cm, meanwhile 11/14 had exophytic tumors. Of 14 patients, 9 had deep or moderate stromal invasion ($\geq 1/3$ of stroma). LVSI was found in 5 patients. Pelvic lymph node metastasis was discovered in

only one patient. Seven patients of operation group had at least two intermediate risk factors—LVSI, deep or moderate stromal invasion, and/or large tumor size (>3 cm). The recurred patient in operation group had three intermediate risk factors: LVSI, deep stromal invasion, and large tumor size (3.5 cm). In addition, pelvic lymph node metastasis was found in pathology. Surprisingly, the patient with stage IB received radio-chemotherapy suffered relapse.

Discussion

GCC is a rare neoplasm with rapidly aggressive behavior that occurs frequently in uterine cervix and was reported once arising in vagina (7). Cervical GCC was recognized as a rare histological entity associated with poor prognosis since the report from Cherry and Glucksmann (1). The incidence of GCC in our cases series was 1.8%, which was closely in line with previous reports, Seltzer's (1.2%) (8), Littman's (1.3%) (4), Tsukahara's (1.3%) (9). The 2014 World Health Organization classification system considers GCC malignancy lying within the spectrum of adenosquamous carcinoma (10). It was reported that cervical GCC might be associated with pregnancy; however, we couldn't confirm this in this report. Patients of cervical GCC are younger (median age: 46 years; mean age: 47 years) comparing to all cervical carcinoma patients who diagnosed in our institution (median age: 49 years). The clinical symptoms being the first complaint of cervical GCC are semblable to invasive cervical carcinoma, such as abnormal vaginal bleeding and discharge. In our study, about half of cervical GCC patients had liquid-based cytology test. Colposcopy biopsy would be performed instead of liquid-based cytology test when gross lesions were noticed at the patient's first visit. This result might be consistent with rapidly aggressive behavior of cervical GCC.

TCT applying in screening cervical cancer elevated the detecting rate of cervical abnormal cells. However, the diagnostic accuracy in cytology of cervical GCC was low accounting for the lack of differentiation and its low incidence. Sharp cytoplasmic margins have been considered as an important cytomorphological and histopathological characteristics of GCC meanwhile cytoplasmic molding and distinct intercellular windows were reported helpful to diagnose cervical GCC, especially in liquid-based preparations (11).

The prognosis of cervical GCC was deemed to be poor in previous studies. In 1976, Littman *et al.* (4) reported an unfavorable overall survival rate of 31% in 13 patients with

cervical GCC. Tsukahara *et al.* (9) reported that 13 out of 14 patients with GCC were died within 25 months. A meta-analysis of 292 cases with GCC indicated that recurrence rate was high when patients treated with radical surgery alone and median overall survival (OS) for all cases was 25.0 months and the 5-year OS was 54.8% (3). However, this poor outcomes might be associated with under-staged diagnosis of cervical GCC patients (12) which could explain the poor response of this subtype tumor to radiation and surgical therapy when compares to other subtypes of cervical carcinomas (13,14). Recent years, this grim outlook of cervical GCC has been changed with the improvement in diagnostic technology and multimodal treatment gradually used on this aggressive disease. Multimodal treatment for early stage cervical GCC was recommended by Piura *et al.* (15) which includes primary surgery with radical hysterectomy and lymphadenectomy followed by pelvic radiotherapy given concurrently with cisplatin-containing systemic chemotherapy. Effectiveness of multimodal therapy has been proved. Koufopoulos *et al.* (16) believed the prognosis has been improved by multimodal treatment in relatively early-stage (FIGO stage I or II) cervical GCC patients, but not in higher stage disease. In our present study, the stage I patients received primary radical hysterectomy followed by pelvic radiotherapy and monthly combined chemotherapy (paclitaxel and cisplatinum) and the DFS of stage I was 93% with 28 months median follow-up intervals. It is worth noting that a relapse happened on one of stage I patients who received pelvic radiation and combined chemotherapy instead of surgery because of her fundus lesions. With the limitation of small sample size, we speculated that surgical treatment might play an important role to cure this tumor. The DFS of GCC patients in advanced-stage received concurrent chemoradiotherapy was 67%. Surprisingly, Yoon *et al.* (17) reported an unexpected excellent result in which three patients with stage IIB tumors who accepted concurrent chemoradiotherapy survived for more than 8 years without tumor recurrence or metastasis. Further studies are needed to investigate the reason of this big different response of advanced stage cervical GCC patients. Other studies proposed that neoadjuvant intraarterial chemotherapy which could provide operation choice for advanced-stage patients had a good effect (18,19). This might indicate the status of surgical treatment from the other side.

Risk factors for recurrence have been extracted. Cervical GCC patients who had at least one high or intermediate risk factor should receive adjuvant treatment. High risk

factors include: large lesion; metastases to lymph nodes; involvement of parametrium; and insufficient surgical margin (20). Intermediate risk factors include: lympho-vascular space invasion; deep stromal invasion; and tumor size >3 cm (2). Gray *et al.* (2) found 4 patients who suffered recurrence had at least two or more intermediate histopathologic risk factors known to predict a higher rate of relapse after radical hysterectomy and all of them could not receive sufficient adjuvant after primary radical surgery. In our study, there were 7 patients who had at least two intermediate risk factors received radiation therapy and combined chemotherapy after radical surgery and there was only one patient recurred within 28 months of median follow-up period. The pathologic features of this recurrent patient included one high risk factor (pelvic lymph node metastasis) and two intermediate risk factors. Gray *et al.* (2) believed poor prognosis in the GCC subset was independent of lymph node metastases. However, pelvic lymph node metastasis should not be neglected when we focused on the only one recurrent patient in present study. Additionally, paclitaxel-carboplatin chemotherapy was reported be effective in recurrent patients (21).

A main factor leading to cervical cancer had been identified as HPV infection (22). Thus, we tried to found out the association between HPV infection and cervical GCC which would disclose the nosogenesis guiding following therapy and prevention measures. In our series, the HPV prevalence was 44.4% which was a bit higher than that of previous study (34.8%) (12). A few studies have indicated that there is a strong association existed between GCC and high-risk HPV infection (6,12). HPV type 18 has been reported as the most common type detected in previous studies (12). Similarly, we found HPV type 18 was the major infection type which was detected in 3 (75%) patients. It was reported that HPV type 18 infection was more frequent than HPV type 16 which leading to an argument that GCC favored glandular tumors (12). However, HPV type 18 was not specific to glandular tumors which is also associated with high-grade neuroendocrine carcinomas (23). Therefore, what we could conclude is the ability of HPV type 18 to differentiate cells in variable directions (24). For all that we had 20 cases sample size, the rate of HPV detection (45%) was low in our study which was a limitation to do a full HPV infection evaluation. Meanwhile, the sample size of other previous studies reported HPV infection were also small. Thus, further studies are expected for evaluating the HPV infection status in cervical GCC.

Conclusions

Cervical GCC is associated with high-risk type HPV, especially HPV type 18. Multimodal therapy indeed improved DFS of cervical GCC. The outcome of cervical GCC was not poor as depicted in previous studies, but with the increase of staging, the prognosis is worse. Patients whose pathology features includes at least two intermediate high risk recurrence or one high risk factor should receive adjuvant treatment after complete surgical management. With the limitation of small sample size and relatively short follow-up period, further studies are need to explore more effective therapy for cervical GCC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.35>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by institutional ethics board of Tianjin Central Hospital of Gynecology Obstetrics (No. 2020KY023). The patient provided written informed consent for the publication of any associated data and accompanying images.

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