Small Cell Carcinoma of the Vagina: First Systematic Review of Case Reports and Proposal of a Management Algorithm

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Objectives: Small cell carcinoma of the vagina (SmCCV) is an extremely rare disease. Evidence-based data and specific guidelines are lacking. We conducted the first systematic review of case reports to provide the most overall picture of SmCCV.

Materials and Methods: Literature search in PubMed and Scopus was performed using the terms “small cell carcinoma” and “vagina.” English-language case reports of primary SmCCV up to January 2022 were included.

Results: Twenty-nine articles describing 44 cases met our inclusion criteria. We report a new case of our hospital. The global median overall survival (mOS) was 12.00 months (95% CI = 9.31 – 14.69). The mOS was 17.00 months for stage I, and it was 12.00, 12.00, 9.00, and 8.00 months for stages II, III, IVA, and IVB, respectively (statistically significant differences between stage I and stages II, III, or IVA [log rank p = 0.003 – 0.017]). Thirty-five cases received local treatments (77.8%). The mOS of patients treated with surgery ± complementary chemotherapy, radiotherapy ± complementary chemotherapy, chemoradiation ± complementary chemotherapy, and surgery + radiotherapy ± complementary chemotherapy were 11.00, 12.00, 17.00, and 29.00 months, respectively. The use of adjuvant or neoadjuvant chemotherapy (64.5%, mostly platinum + etoposide) showed longer mOS (77.00 vs 15.00 months). Four of 5 tested cases presented human papillomavirus infection, 3 of them presenting type 18.

Conclusions: Small cell carcinoma of the vagina shows dismal prognosis. Multimodal local management plus complementary chemotherapy seems to achieve better outcomes. Human papillomavirus could be related to the development of SmCCV. A diagnostic-therapeutic algorithm is proposed.

Key Words: neuroendocrine tumors, vaginal cancer, small cell carcinoma, cancer of vagina, human papillomavirus, molecular characterization

Small cell carcinomas (SmCCs) are high-grade neuroendocrine tumors that emerge from neuroendocrine cells or result from the dedifferentiation of an aggressive noneuroendocrine tumor.1 Most commonly, SmCCs arise in the lung (SmCLC),2 and only 5% are extrapulmonary. An SmCC from the female genital tract (usually cervix) constitutes less than 2% of all gynecologic cancers,4 showing poorer prognosis than other carcinomas. A small cell carcinoma of the vagina (SmCCV) is a rare neoplasm with less than 50 cases reported to date (the first in 1984).5 Herein, we report our own case and we present, to our knowledge, the first systematic review of case reports and a diagnostic-therapeutic algorithm.

Case Presentation

A 55-year-old patient was admitted to our hospital in July 2018 for postmenopausal bleeding. She had an active type 2 diabetes mellitus and no family history of malignancy. Her general physical examination was normal and vaginal examination revealed a 2-centimeter polypoid mass depending from the upper third of vagina without involving cervix (1 cm apart). Biopsy of the vaginal polypoid mass showed infiltration of subepithelium by islands of malignant cells with a high nuclear-cytoplasmic ratio, hyperchromatic nuclei, and scanty eosinophilic cytoplasm. Immunohistochemical staining showed positivity for chromogranin A, synaptophysin, and low-molecular weight cytokeratins (CKCAM 5.2, CK7, CK20). The pathologic diagnosis was small cell carcinoma. Type 18 human papillomavirus (HPV) was detected in biopsy specimen, and an intense nuclear p16 expression was observed (see Figure 1).

Gynecologic transvaginal ultrasound scan proved normal and discarded invasive disease in cervix or paracervix. Laboratory results were unremarkable, including tumor markers (cancer antigen 12.5 [CA125], cancer antigen 19.9 [CA19.9], and squamous cell carcinoma[SCC] antigen). A positron emission tomography–computed tomography (PET-CT) disclosed distant dissemination. Thus, the final diagnosis was primary small cell carcinoma of the vagina (SmCCV) stage I, according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) clinical staging system.

Concurrent external beam radiation therapy (EBRT) with 50 gray and weekly cisplatin 40 mg/m² was started. After completing EBRT, chemotherapy with cisplatin 75 mg/m² on day 1 plus etoposide 100 mg/m² on days 1–3 every 3 weeks was continued until completing 6 cycles. An episode of febrile grade 4 neutropenia occurred after administration of cycle 2 and grade 2 radiation-related colitis after cycle 4. Complete response was achieved.

The patient underwent strict follow-up with physical examination and full-body CT every 3 months. Six months after finishing
chemotherapy, mediastinal adenomegalies were observed in full-body CT scan, without signs of local recurrence in the gynecological examination. A fine-needle puncture-aspiration assessment (PAAF) guided by endobronchial ultrasound was conclusive for sarcoidosis.

In January 2020, 14 months after finishing chemotherapy, a vaginal mass of 1 cm in upper vaginal location was detected on physical examination. The biopsy confirmed local recurrence. A PET-CT scan showed the vaginal nodule (maximum standardized uptake value of 5) and 2 infracentimetric pulmonary nodules (located in left lower and right upper lung lobes, both maximum standardized uptake value of 5). A salvage vaginal surgery and an excisional biopsy of the lung nodules, followed by chemotherapy, were planned. The patient underwent laparoscopic-robotic assisted radical hysterectomy with bilateral adnexectomy and upper colpectomy, with an unremarkable postoperative course. Suddenly, world pandemic for COVID-19 started, and thoracic surgery was postponed. The patient started chemotherapy, using cisplatin 75 mg/m² day 1 plus etoposide 100 mg/m² days 1–3 every 3 weeks, and completed 4 cycles. The CT scan after chemotherapy showed stable disease. The excision of the 2 lung nodules was planned in 2 surgical times with 1 month of difference.

The anatomopathological study of both nodules revealed metastatic SmCCV, with margins free of lesion.

In January 2021, she was admitted in hospital because of complete bowel obstruction and intense dorsal pain. Relapse in the peritoneum, liver, and multiple bones was detected. She received palliative decompressing radiotherapy on D5–D6 and began again cisplatin plus etoposide on February 15, 2021. Malignant bowel obstruction resolved, and she was discharged from hospital. She continued chemotherapy up to 6 cycles. Unfortunately, in June 2021, systemic progression occurred, and the patient decided to travel to her homeland and abandoned medical controls.

**SYSTEMATIC REVIEW OF THE LITERATURE AND ANALYSIS**

**Methods**

**Search Strategy, Selection Criteria, Study Design, and Endpoints.** A systematic review of the literature was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed and Scopus were search using the combination of the key words “small cell carcinoma” and “vagina” (see Figure 2). Search ended on January 23, 2022.

Articles had to meet the following inclusion criteria: English manuscripts, human patients diagnosed with primary SmCCV, and original nonduplicated data. Two authors (S.C. and M.R.) reviewed independently the retrieved articles and clarified dubious cases with VT and SM before deciding on the definitive inclusion or exclusion for the review. As expected, only case reports were identified. First reported case dates from 1984 and the last one was reported in December 2021. Data regarding pathological and clinical features, as well as medical management approaches and outcomes, were extracted. Progression-free survival (PFS) was lacking in many reports. Overall survival (OS) was the only outcome that could be measured. Those patients who were staged according to the American Joint Committee on Cancer Cancer staging and Tumor Node Metastases staging system were modified to meet the definitions of the 2009 FIGO clinical staging system.

**Statistical Analyses.** Clinical information is summarized in Tables 1 and 2 according to the FIGO stages. All possible variables were quantified and summarized using percentages, means, or medians when appropriate. We used the Kaplan-Meier method to estimate...
survival curves and the log rank test to compare survival differences. Overall survival was calculated from time of diagnosis until death or last contact alive. Global median OS (mOS), mOS according to the FIGO stage, and mOS according to different therapeutic approaches were analyzed. Analysis was performed using the Statistical Package for Social Science software (IBM SPSS Statistics 15.0; IBM Corp, Armonk, NY) for Windows, and \( p \) values less than .05 were considered statistically significant.

**RESULTS**

Until January 23, 2022, our search identified 29 articles describing 44 different cases that met our inclusion criteria (see Figure 2). All cases, including our own, are summarized in Tables 1 and 2.

**Clinical Presentation**

The mean age at diagnosis was 55.29 years (\( n = 42 \), range 32–81 years). Most commonly, SmCCV presented with postmenopausal vaginal bleeding and an exophytic vaginal polypoid mass. Lymphatic dissemination was reported in 10 cases, affecting groin nodes, pelvic, and/or para-aortic nodes, according to radiological and/or surgical findings. Interestingly, we identified 3 patients with para-aortic dissemination without pelvic or inguinal involvement.
| N  | Ref Year | Age, y | Clinical features | Tumor size, cm | Imaging staging | HPV | Lymph M1 | Immunohistochemical staining |
|----|----------|--------|------------------|--------------|--------------|-----|---------|-----------------------------|
| 1  | 7 1992   | 65     | HSIL             | 0.5          | CT scan, chest x-ray | —   | No      | NSE                         |
| 2  | 8 1997   | 59     | AVB + Cushing syndrome | 3.5 × 3 | CT scan | Np | No      | Negative for ACTH             |
| 3  | 9 2000   | 51     | AVB              | 4 × 3        | MRI, CT scan | Np | No      | CK, NSE, chr-A and SYN       |
| 4  | 10 2009  | 53     | AVB              | 3 × 3 × 2    | Chest x-ray, CT scan, proctoscopy | Np | No      | 5HT                         |
| 5  | 11 2013  | 81     | AVB              | 4 × 3        | Chest x-ray, cystoscopy, sigmoidoscopy | Np | No      | Chr-A                       |
| 6  | 12 2016  | NS     | AVB              | 4.5 × 2.5 × 2 | Ns | MRI + PET-CT | Np | No      | Chr-A and SYN               |
| 7  | 13 2018  | 56     | Vaginal mass     | 3            | PET-CT | + (Other) | No | Ns      |                             |
| 8  | 14 2020  | 51     | AVB              | 0.5          | MRI, CT scan | Np | No      | Chr-A and CD56              |
| 9  | Ours 2021| 53     | AVB              | 2 × 2 × 1    | PET-TC | + (18) | No | LMW CK, chr-A, and SYN      |
| 10 | 15 1985  | 61     | NS               | NS           | NS          | Np | No      | NS                         |
| 11 | 15 1985  | 61     | NS               | NS           | NS          | Np | No      | NS                         |
| 12 | 16 1986  | 32     | AVB              | 3 × 3 × 2    | CT scan, proctoscopy | Np | No      | 5HT                         |
| 13 | 17 1989  | 41     | AVB              | 4 × 3        | Chest x-ray, cystoscopy, sigmoidoscopy | Np | No      | Np                         |
| 14 | 18 1989  | 78     | Tenesmus, malaise | 4            | CT scan | Np | No      | Np                         |
| 15 | 18 1989  | 74     | AVB              | 3            | CT scan | Np | No      | Np                         |
| 16 | 19 1990  | 62     | AVB              | 2            | —        | Np | No      | Np                         |
| 17 | 19 1992  | 34     | Vaginal mass     | 3            | CT scan | Np | No      | Chr-A                       |
| 18 | 21 2013  | 41     | Vaginal discharge | 2 × 2        | MRI       | Np | No      | CK AE1/AE3, CD57, chr-A     |
| 19 | 22 2016  | NS     | NS               | 4 × 4 × 1.5  | Ns | MRI     | Np | No      | Ns                         |
| 20 | 23 2018  | 34     | Vaginal mass     | 1 × 1        | PET-CT | Np | NS      | LMW CK and SYN              |
| 21 | 23 2019  | 43     | Vaginal mass     | —            | —       | Np | No      | NS                         |
| 22 | 15 1985  | 61     | NS               | NS           | NS          | Np | No      | NS                         |
| 23 | 15 1985  | 61     | NS               | NS           | NS          | Np | No      | NS                         |
| 24 | 15 1985  | 61     | NS               | NS           | NS          | Np | No      | NS                         |
| 25 | 24 1998  | 32     | Vaginal mass     | 3 nodes (1.2–4) | CT scan, chest x-ray | Np | Yes | NSE, PGP 9.5, chr-A, SYN, CD57, and LMW CK |
| 26 | 25 2000  | 57     | AVB              | 10 × 8       | —          | Np | Yes | SYN, NSE, neurofilament, CD57, chr-A |
| 27 | 26 2004  | 55     | AVB              | 8            | CT scan | Np | Yes | NSE and SYN                  |
| 28 | 27 2005  | 50     | AVB              | 7 × 3 × 3    | CT and bone scan | Np | Yes | TTF-1, LMW CK, chr-A, SYN    |
| 29 | 28 2018  | 51     | AVB              | 1.5          | MRI, PET-CT | Np | Yes | SYN, CD56, Chr-A             |
| 30 | 29 2018  | 54     | AVB              | 1.5          | MRI, PET-CT | Np | Yes | CD56, CK7                    |
| 31 | 30 2019  | 65     | Vaginal pain     | 7 × 9        | MRI and CT scan | Np | Yes | SYN and CD56                |
| 32 | 6 2021   | 70     | AVB              | 3            | Yes (ns) | + (18) | Yes | CK19, SYN, Chr-A, p16       |
| 33 | 15 1985  | 61     | NS               | NS           | NS          | Np | No      | NS                         |
Two of 42 patients (5%) with clinical information presented central nervous system metastases at diagnosis. Endocrinologic disorders were present in 4 of 42 patients (10%), specifically ectopic Cushing syndrome (n = 2, 5%) and syndrome of inappropriate antidiuretic hormone secretion (n = 2, 5%).

**Pathologic Study**

The only macroscopic pathological description observed “a yellow and hemorrhagic mass” after resection.24 The mean larger diameter of the vaginal masses was 3.15 cm (range = 0.5–10 cm, n = 30). Microscopically, high mitotic rate, extensive areas of necrosis, and frequent lymph-vascular space invasion were usually reported.

Immunohistochemical staining was described in 26 cases (60%, n = 45). Chromogranin A (n = 17, 65%), synaptophysin (n = 17, 65%), low–molecular weight cytokeratin (n = 11, 42%) and neuron-specific enolase (n = 7, 27%) were the most frequently positive markers.

**Human Papillomavirus Infection and Molecular Studies**

Only 5 cases were reported to be tested for HPV: 1 negative,7 1 positive for a high-risk type different to 16–18 (not specified),13 and 3 positive for 18 type (2 cases reported in 202115 and our case). The 3 cases HPV18+ positive were reported to be p16+ with a diffuse pattern in the immunohistochemistry study. Moreover, 2 of them6 were studied by next-generation sequencing analysis of a panel of 60 major cancer-related genes, finding low tumour mutational burden (TMB), low microsatellite instability score, and no TP53 (tumor protein p53) or retinoblastoma gene mutations in both cases. One of them harbored a mutation in NF1 (neurofibromatosis type 1) gene (NF1 p.T467I) and the other case harbored a mutation in AR (androgen receptor) gene (AR p.C327Y).

**Staging and Global Prognosis**

Primary vaginal tumors are clinically staged, but imaging techniques help determine their real local and distant extension.25 Twenty-seven of 45 patients (64.2%) reported information about imaging techniques. Pelvic magnetic resonance imaging (MRI), which is the best technique for evaluating the real tumor size and invasion of neighboring tissues,27 was performed in 6 patients (22.2%). Distant metastatic disease was evaluated with a CT in 18 cases (66.7%) and/or a PET-CT scan in 5 cases (18.5%).

According to the 2009 (FIGO) staging system, 9 patients were stage I (23.7%), 12 stage II (31.6%), 11 stage III (26.3%), 5 stage IV A (13.2%), and 3 stage IVB (5.3%), of 40 cases with staging information.

The median follow-up of the whole series was 12 months (minimum–maximum = 4–77, n = 38; mean = 17.65). Twenty-two deaths were described (59.5%, n = 38), all caused by disease progression. The mOS was 12.00 months (95% CI = 9.31–14.69). The most frequent sites of metastases were lung (n = 5), liver (n = 3), lymph nodes (n = 3), bones (n = 3), brain (n = 1), and occipital scalp (n = 1; see Tables 1, 2). The mOS was not reached for stage I, and it was 12.00, 12.00, 9.00, and 8.00 months for stages II, III, IVA, and IVB, respectively (see Figure 3). Survival differences between stage I and stages II, III, or IVA were statistically significant (log rank p ranging from .003 to .017).

**Primary Treatment and Outcomes**

Treatment approaches were very heterogeneous among the 42 cases with some kind of information regarding management (see Tables 1, 2). Local treatments (surgery and/or radiotherapy) were used in 35 cases (83.3%), chemotherapy alone in 4 cases (10%, with 2 radiological responses described), and best supportive care
| N  | Ref | Surgical treatment | Radiation, Gy | Chemotherapy (no. cycles) | Resp | Recur | Site of recurrence/P | Recur/progress treatment | Survival, mo |
|----|-----|-------------------|---------------|---------------------------|------|-------|---------------------|---------------------------|--------------|
|    |     |                   |               |                           |      |       |                     |                           |              |
| **Stage I (n = 9)** |     |                   |               |                           |      |       |                     |                           |              |
| 1  | 7   | Lump excision     | BT (70)       | Vin + DNR + CFM (6)       | CR   | No    |                     |                           | 24 (A)       |
| 2  | 8   |                   | EBRT (45)conc | CDDP + ETO (1) conc      | CR   | Yes   | Liver               |                           | 17           |
| 3  | 9   |                   | EBRT (ns)     | CDDP + THP + CFM (5)     | CR   | No    |                     |                           | 41 (A)       |
| 4  | 10  | Yes (ns)          | EBRT (50)     | CBP + ETO (4)            | CR   | No    |                     |                           | 36           |
| 5  | 11  |                   | EBRT + BT (63)| No                       | CR   | No    |                     |                           | 20 (A)       |
| 6  | 12  |                   | EBRT + BT (51)| CDDP + ETO (4) conc     | CR   | No    |                     |                           | 7 (A)        |
| 7  | 12  | Va + BILND        | Ns            | CDDP + ETO (4) conc      | CR   | No    |                     |                           | Ns (A)       |
| 8  | 14  | Lump excision     | —             | Irinotecan + CDDP (6)    | CR   | No    |                     |                           | 11 (NED)     |
| 9  | Ours|                   | EBRT (50)conc | Weekly CDDP, then CDDP + ETO (6) | CR   | Yes   | Vaginal, lung       | CDDP + ETO + surgery. P (bones, peritoneum liver) | 26 (A)       |
| **Stage II (n = 12)** |     |                   |               |                           |      |       |                     |                           |              |
| 10 | 15  |                   | —             | Yes (ns)                 | NS   | NS    |                     |                           | 12 (md)      |
| 11 | 15  |                   | —             | Yes (ns)                 | NS   | NS    |                     |                           | 12 (md)      |
| 12 | 16  |                   | EBRT + BT (80)| —                        | CR   | Yes   | Lung and liver      | P-chemo (ns)              | 12           |
| 13 | 17  | Lump excision     | EBRT + BT (90)| —                        | CR   | Yes   | Occipital scalp, bones | Br radiation +CDDP + Vin | 29           |
| 14 | 18  |                   | EBRT (40)     | —                        | CR   | Yes   | Lung, vagina         | S-Fluoracil              | 15           |
| 15 | 18  |                   | EBRT + BT (100)| —                       | CR   | Yes   | Bony, lung           | Palliative EBRT.         | 11           |
| 16 | 19  | EBRT (ns)         | CDDP + ETO (5)| P                        | CR   | No    |                     |                           | 8            |
| 17 | 20  | Va + BILND        | EBRT + BT (ns)| —                        | CR   | Yes   | NS                  |                           | 6            |
| 18 | 21  |                   | EBRT + BT (ns)| CDDP + ETO (3)          | CR   | No    |                     |                           | 5 (A)        |
| 19 | 12  | RH + partial Va + BILND| EBRT + BT (ns)| CDDP + ETO (6) | CR   | No    |                     |                           | Ns (A)       |
| 20 | 22  | RH + partial Va + RPLND| EBRT (ns)| CDDP + ETO (6) | CR   | Yes   | 1 pelvic mass (5 mo) | 2 retroperit LN + brain (28 mo) | 34           |
| 21 | 4   | C/KC + Va + BILND | —             | PTX + CBP (2)           | CR   | Yes   | NS                  |                           | 77           |
| **Stage III (n = 11)** |     |                   |               |                           |      |       |                     |                           |              |
| 22 | 15  |                   | —             | —                        | NS   | NS    |                     |                           | 12 (md)      |
| 23 | 15  |                   | —             | —                        | NS   | NS    |                     |                           | 12 (md)      |
| 24 | 23  | Modified R hemi Va-Vu| —             | —                        | CR   | Yes   | Paravaginal and pararectal | Vu-Va and RR | 10           |
| 25 | 24  |                   | EBRT (ns)     | CDDP + ETO (6)          | CR   | No    |                     |                           | 6 (A)        |
| 26 | 25  | EBRT (54) conc    | CBP + ETO (6) | (AE, low dose, TED)      | CR   | Yes   | Liver, lung         |                           | 14           |

Continued next page
| N  | Ref | Surgical treatment | Radiation, Gy | Chemotherapy (no. cycles) | Resp  | Recur | Site of recurrence/P | Recur/progress treatment | Survival, mo |
|----|-----|------------------|---------------|--------------------------|-------|-------|----------------------|--------------------------|--------------|
| 27 | 26  | Radical Vu + partial Va | Refused       | Refused                  |       |       | Vaginal, bone and supraclav LN | CDDP + ETO              | 4            |
| 28 | 27  | Anterior PE + BPLND   | —             | CDDP + ETO + DXR (ns)    | CR    | Yes   | Para-aortic LN        | —                        | 11           |
| 29 | 28  | —                 | EBRT (ns) conc | CDDP + ETO + PTX (5)     | CR    | Yes   | Lung                 | RRx-001 + CDDP + ETO + Nivolumab | 7            |
| 30 | 29  | —                 | EBRT + BT     | CDDP (5) conc            | CR    | No    | —                   | —                        | 12 (NED)     |
| 31 | 30  | —                 | EBRT + BT (70) conc | PTX + CDDP (1), CDDP + ETO (1), CDDP (2), PTX + CBP (1), CBP + ETO (1) | CR    | No    | —                   | —                        | 22 (A)       |
| 32 | 31  | —                 | RT conc (ns)  | NS (conc)                | PR    |       | —                   | —                        | 8 (A)        |

Stage IVA (n = 5)

| N  | Ref | Surgical treatment | Radiation, Gy | Chemotherapy (no. cycles) | Resp  | Recur | Site of recurrence/P | Recur/progress treatment | Survival, mo |
|----|-----|------------------|---------------|--------------------------|-------|-------|----------------------|--------------------------|--------------|
| 33 | 15  | —                 | —             | —                        |       |       | —                   | —                        | 12 (md)      |
| 34 | 17  | —                 | EBRT (52)     | ADR + CFM (1)            | P     |       | Lung                 | Palliative EBRT          | 5            |
| 35 | 18  | —                 | —             | CDDP + MTX (ns)          | CR    | Yes   | NS                   | —                        | 9            |
| 36 | 19  | —                 | EBRT (ns) conc | CDDP + ETO (2.AE)conc | P     |       | —                   | 4                        |
| 37 | 20  | —                 | EBRT + BT (ns) conc | CDDP + ETO→ CDDP (3) only conc | CR    | No    | —                   | 15 (A)       |

Stage IVB (n = 3)

| N  | Ref | Surgical treatment | Radiation, Gy | Chemotherapy (no. cycles) | Resp  | Recur | Site of recurrence/P | Recur/progress treatment | Survival, mo |
|----|-----|------------------|---------------|--------------------------|-------|-------|----------------------|--------------------------|--------------|
| 38 | 22  | —                 | —             | CDDP + ETO (4.AE)        | PR    | Early | P                    | Epi                      | 8            |
| 39 | 23  | —                 | EBRT + BT (ns) conc | CDDP + PTX (6) | CR    | No    | —                   | 21 (A)       |
| 40 | 6   | TH + BSO + Va     | —             | —                        |       |       | Yes (ns)             | PR No                     | 8 (A)        |

Not specified (n = 5)

| N  | Ref | Surgical treatment | Radiation, Gy | Chemotherapy (no. cycles) | Resp  | Recur | Site of recurrence/P | Recur/progress treatment | Survival, mo |
|----|-----|------------------|---------------|--------------------------|-------|-------|----------------------|--------------------------|--------------|
| 41 | 3a  | Lump excision    | —             | —                        |       |       | —                   | —                        | —            |
| 42 | 4a  | Lump excision    | —             | —                        |       |       | —                   | —                        | —            |
| 43 | 5a  | Histopathologic study without clinical details | — | — | | | | | |
| 44 | 6a  | Histopathologic study without clinical details | — | — | | | | | |
| 45 | 7a  | Histopathologic study without clinical details | — | — | | | | | |

*Case was excluded for survival analyses.

(A) indicates alive at the moment of reporting the case; ADR, adriamycin; AE, adverse effect; Bev, bevacizumab; BILND, bilateral inguinal lymph node dissection; BPLND, bilateral pelvic lymph node dissection; BSO, bilateral salpingo-oophorectomy; BT, brachytherapy; CBP, carboplatin; CDDP, cisplatin; CFM, cyclophosphamide; CKC, cold knife conization; CR, complete response; DTX, docetaxel; DXR, doxorubicin; ETO, etoposide; Epi, epirubicin; IMRT, intensity-modulated radiation therapy; LN, lymph node; md, median; MTX, methotrexate; N, number; ns, nonspecified; P, progression; Pal, palliative; p-Chemo, palliative chemotherapy; PE, pelvic exenteration; PR, partial response; PTX, paclitaxel; R, right; Rad, radical; Recur, recurrence; Ref, reference; Resp, response; RH, radical hysterectomy; RPLND, right pelvic lymph node dissection; RR, rectosigmoid resection; RSO, right salpingo-oophorectomy; seq, sequential; Supraclav, supraclavicular; TED, thromboembolic disease; THP, pirarubicin; TPT, topotecan; Va, vaginectomy; Vin, vincristine; Vu, vulvectomy.
in 3 cases (7.5%). None of them received prophylactic brain radiation. The retrospective nature of data hampers determining the palliative or curative intention of treatment in all cases.

Of the 38 patients with survival information, there were 15, 4, and 3 deaths described for each subgroup. The mOS were 29.00 (95% CI = 5.21–52.79), 9.00 (95% CI = 6.39–11.61), and 12.00 months (95% CI = unavailable because of sample size), respectively. We will describe the first subgroup with more detail.

**Patients Treated With Local Therapies (n = 35).** Among them, best recorded response was complete response in 29 cases, partial response in 3 cases, and progression in 3 cases.

Surgery was performed in 15 cases (42.8%), ranging from lumpectomy to anterior pelvic exenteration. Regional lymphadenectomy was only purposely mentioned in 7 patients. Considering cases with survival information, mOS of operated patients was 77.00 months (95% CI = unavailable because of sample size, n = 11) versus 17.00 months (95% CI = 12.04–21.96, n = 19) in nonoperated patients (log-rank p = .586). Considering patients who underwent surgery with available information regarding adjuvant treatments and follow-up, those who received surgery alone had an mOS of 10.00 months (95% CI = 0.40–19.60, n = 3), whereas those who also received complementary treatments (radiotherapy and/or chemotherapy) had an mOS of 29.00 months (95% CI = 0.00–69.80, n = 7, log-rank p = .374). No surgical complications were reported.

Pelvic radiotherapy was performed in 25 of 42 patients with information management (71.4%), ranging from lumpectomy to anterior pelvic exenteration. Regional lymphadenectomy was only purposely mentioned in 7 patients. Considering cases with survival information, mOS of operated patients was 77.00 months (95% CI = unavailable because of sample size, n = 11) versus 17.00 months (95% CI = 12.04–21.96, n = 19) in nonoperated patients (log-rank p = .586). Considering patients who underwent surgery with available information regarding adjuvant treatments and follow-up, those who received surgery alone had an mOS of 10.00 months (95% CI = 0.40–19.60, n = 3), whereas those who also received complementary treatments (radiotherapy and/or chemotherapy) had an mOS of 29.00 months (95% CI = 0.00–69.80, n = 7, log-rank p = .374). No surgical complications were reported.

Pelvic radiotherapy was performed in 25 of 42 patients with information management (71.4%), only 7 of them also operated. The mean administered grays were 64.11 (SD = 18.284, n = 14), usually by combining EBRT and brachytherapy. Considering cases with survival information, mOS of patients who received radiotherapy was 17.00 months (95% CI = 3.02–30.98, n = 24) versus 11.00 months (95% CI = 0–51.21, n = 7) in those who did not (log-rank p = .951). There were no grade III–IV toxicity associated with radiotherapy reported.

To enable a more detailed analysis, patients with survival information (n = 31) were categorized in 4 subgroups, as shown in Table 3: surgery ± chemotherapy (n = 7, 22.6%), radiation ± sequential chemotherapy (n = 10, 32.2%), surgery followed by radiation ± sequential chemotherapy (n = 4, 12.9%), concurrent chemoradiation ± sequential chemotherapy (n = 10, 32.2%). The mOS of each subgroup were 11.00, 12.00, 29.00, and 17.00 months, respectively, without statistically significant differences among them. Of note, most local relapses occurred among operated patients without postoperative radiation. No one received surgery plus concurrent chemoradiation.

Twenty patients (64.5%) underwent chemotherapy sequentially to local treatments (mean number of cycles 6), whereas 14 patients did not (including 5 patients who only received chemotherapy concurrently to radiation). The mOS was 77.00 (95% CI = unavailable because of limited sample size) versus 15.00 months (95% CI = 9.02–20.98, respectively (log-rank p = .390). Either as systemic treatment alone or used concurrently to radiation, regimens of chemotherapy were mostly platinum based, usually in combination with etoposide (see Tables 1, 2). Only 2 cases reported chemotherapy-related serious adverse events: grade 3 gastrointestinal toxicity in 1 patient receiving cisplatin-etoposide concurrently to radiation and persistent hypomagnesemia and hypokalemia as well as retinal hemorrhages in one patient receiving cisplatin-etoposide as a systemic treatment alone. In both cases, further chemotherapy was discarded. Dosages of cisplatin-etoposide were not described in most cases.

**Recurrent Disease**

Among those who achieved complete response after local therapies (n = 29), 15 relapsed (51.7%). Recurrence site was reported only in 13 patients. Rates of local, local and distant, and distant relapses were 8% (2 of 13), 31% (3 of 13), and 61% (8 of 13), respectively. Both isolated local recurrences identified were treated surgically, and one patient presented afterward distant metastasis. A variety of second-line chemotherapy regimens have been used (see Tables 1, 2).
TABLE 3. Survival Outcomes According to Local Approach Treatment in Patients With Small Cell Carcinoma of Vagina Treated With Radical Intention

| Subgroups of local treatment | No. cases | Mean diameter of primary tumor (min–max), cm | FIGO stages (no. cases) | No. cases who received adjuvant CT | Median OS for the whole subgroup, mo | No. case according to Tables 1–3 |
|-----------------------------|-----------|------------------------------------------|------------------------|-----------------------------------|------------------------------------|----------------------------------|
| Surgery ± chemotherapy      | 7         | 4 (1–7, n = 4)                           | I (1)                  | 1                                 | 11                                 | 8, 20, 21, 24, 27, 28, 40        |
|                             |           |                                          | II (2)                 |                                    |                                    |                                  |
|                             |           |                                          | III (3)                |                                    |                                    |                                  |
|                             |           |                                          | IVB (1)                |                                    |                                    |                                  |
| Radiotherapy ± chemotherapy | 10        | 4 (2–10, n = 7)                          | I (2)                  | 1                                 | 12                                 | 3, 5, 12, 14, 15, 16, 18, 25, 30, 34 |
|                             |           |                                          | II (5)                 |                                    |                                    |                                  |
|                             |           |                                          | III (2)                |                                    |                                    |                                  |
|                             |           |                                          | IVA (1)                |                                    |                                    |                                  |
| Chemoradiation ± chemotherapy | 10   | 5.6 (2–10, n = 9)                         | I (3)                  | 1                                 | 17                                 | 2, 6, 9, 26, 28, 29, 31, 32, 36, 37 |
|                             |           |                                          | III (3)                |                                    |                                    |                                  |
|                             |           |                                          | IVA (2)                |                                    |                                    |                                  |
|                             |           |                                          | IVB (2)                |                                    |                                    |                                  |
| Surgery plus radiotherapy ± chemotherapy (not concurrent) | 4 | 2.5 (0.5–4, n = 3) | I (2) | 1 | 29 | 1, 4, 13, 17 |
|                             |           |                                          | II (2)                 |                                    |                                    |                                  |

*Local relapse.
max indicates maximum; min, minimum.

In one case, a chemosensitivity and radiosensitivity gene-profiling test suggested better response to topoisomerase-1 inhibitors and antifolate therapies than to platinum agents or gemcitabine. Thus, a second line (after savage pelvic radiotherapy) using a combination of topotecan, docetaxel, and bevacizumab was chosen, obtaining 14 months of PFS and 34 months of OS.22

DISCUSSION

An SmCCV is an extremely rare and dismal disease that raises a diagnostic-therapeutic challenge with scarce literature available. In our systematic review based in all English-reported cases of SmCCV in Scopus and PubMed, this entity showed a global mOS of 12 months. Nevertheless, most stage I patients were alive at time of report, while all patients diagnosed of stage II–IVB died from metastatic extension (see Figure 3). Remarkably, we found a case with a stage II disease treated with local therapies and only 2 cycles of carboplatin/paclitaxel that survived 77 months.4 Noticeably, diagnosis was done in a routine gynecologic examination (without prior reported symptoms), and tumor diameter is undescribed.

One hypothesis for this dismal prognosis, accepted for other SmCC, is that subclinical metastatic focus could be present even in apparently stage II disease. Importantly, we identified 3 patients with para-aortic dissemination without pelvic or inguinal nodal involvement (see Tables 1, 2). Therefore, we strongly recommend performing a complete gynecologic examination and a full-body PET-CT scan, also according to general recommendations of the Society of Gynecologic Oncology for gynecologic SmCC.38 Historical data of this review (back to 1984) would explain the low reported percentage of performed PET-CT, as well as of MRI.

A PET-CT also allows to rule out other SmCC primaries with higher incidence, because SmCCV is a diagnosis of exclusion. Neuroendocrine markers, despite not being mandatory for the diagnosis of a neuroendocrine carcinoma in the last 2014 World Health Organization classification, may be also useful. Of note, positivity of CD56, chromogranin A, and synaptophysin could potentially differ from SmCC of the cervix (SmCCC, 18.3%, 63.6%, and 63.6%, vs 90%, 90%, and 90%, respectively) or SmCLC (90%, 90%, and 60%),39 but this issue remains to be fully explored.

Contrary to squamous vaginal cancers, the association of HPV and SmCCV remains largely unexplored. In this review, 3 cases presented HPV18 and another case presented a high-risk nonspecified subtype. Noticeably, high-risk HPV type infection in SmCCC ranges 50% to 100%, being the HPV18 the more prevalent type.40–42 Considering that HPV 18 presents highest affinity for glandular and neuroendocrine cells, its hypothetical etiological relationship with SmCCV warrants further research.

According to our results, both surgery and radiation positively impact on OS, and multimodal local approaches seem to be associated with longer survival than any of them alone. Remarkably, mOS of those who received surgery plus radiation was 29 months and, for those who received concurrent chemoradiation, 17 months. On the contrary, those patients treated with one only local approach, either surgery or radiotherapy, ranged 11–12 months (see Table 3). These observations are consistent with literature: chemoradiation has classically shown its superiority to radiation alone in other SmCC and locally advanced squamous cervical carcinomas, and recent reports of SmCCC showed that postoperative radiation seems to achieve better outcomes compared with surgery alone.33,44 In addition, lower locoregional failure and higher OS rates (5-year >78%) have been described for SmCCC patients who received primary chemoradiation in comparison with primary surgery (5-year OS 46%), except for tumors less than or equal to 2 cm and no lymph-vascular space invasion (5-year OS of 89% with primary surgery).31 However, the role of postoperative radiation in gynecologic SmCC, particularly when there is a negative lymphadenectomy, remains to be defined.

We found that complementary platinum-based regimens seem to improve OS in locally treated SmCCV, consistent with the well established role of complementary/adjuvant chemotherapy in other SmCC.46–47 Particularly cisplatin plus etoposide. This regimen was, in fact, the most frequently used in this series, also concurrently to pelvic radiation (similarly to schemas used for concurrent chemoradiation in SmCLC). However, gastrointestinal toxicity is the most relevant adverse event to take into consideration when evaluating pelvic chemoradiation with this schema. Although very few reports included in this review specified dosages, MD Anderson’s protocol for gynecologic SmCC consists...
of cisplatin 60 mg/m² day 1 plus etoposide 100 mg/m² days 1–3 every 3 weeks, up to 6 cycles (2 concurrent to radiation). Figure 4 summarizes authors’ recommendations regarding diagnostic and treatment of SmCCV, integrating our findings and information from other SmCC. Because only 6% of patients in this series presented central nervous system metastases (n = 3) compared with 20%–60% of SmCLC patients, we do not recommend prophylactic brain radiation.

Regarding follow-up, the Society of Gynecologic Oncology guidelines for gynecologic SmCC emphasize the importance of a close surveillance, including vaginal, cervical, rectal, inguinal, and supraclavicular examinations, as well as body imaging (CT or PET-CT scan). We think that HPV test could be recommended if it was positive at diagnosis.

For relapsed SmCCV patients, individualized management would be recommended. For isolated local relapses, salvage

**FIGURE 4.** Proposal of staging and management algorithm for patients with SmCCV. BGLND, bilateral groin lymph node dissection; BPLND, bilateral pelvic lymph node dissection; BT, brachytherapy; CDDP, cisplatin; EBRT, external beam radiation therapy; ETO, etoposide; IMRT, intensity-modulated radiation therapy; M, metastases; N, ganglionar status; RH, radical hysterectomy; T, tumor. *The FIGO 2009 stage. **If possible 6 cycles of chemotherapy.
surgery and/or radiotherapy could be considered, always followed by systemic treatment. Unfortunately, most relapsed patients will eventually die because of distant progressions. Regarding systemic treatment, after progression to platinum or if it is not an option (i.e., in case of renal impairment), single agents used in SmCLC such as topotecan, paclitaxel, or docetaxel can be considered, despite their poor outcomes.25 Of note, the combination of topotecan (0.75 mg/m² on days 1–3), paclitaxel (175 mg/m² on day 1), and bevacizumab (15 mg/kg on day 1 on a 1:2-day cycle) was associated with a significant improvement in PFS (8 vs 4 months)25 compared with other regimens in a retrospective analysis of 33 patients with SmCCC, treated with primary chemotherapy. Outstandingly, the case 3022 of this review used a similar combination (topotecan, docetaxel, and bevacizumab) in a relapsed patient, based on a gene-profiling test, obtaining a PFS of 14 months.

Improving the efficacy of systemic treatments is a priority for all SmCC. Currently, immunotherapy is being intensively investigated in this area,3,5,34 also for recurrent gynecological SmCC.55 In our study, we identified a report on RRx-001 (a M2-to-M1 macrophage stimulating agent) as maintenance after cisplatin/etoposide as first line,26 but progression was observed after 6 weeks of treatment. Importantly, HPV-related congenital could be the rational to further develop immunotherapy.

A comprehensive molecular characterization of SmCCV would also be of interest to discover potential druggable targets. The first communicated attempt analyzed 2 HPV18-related SmCCV with a limited next-generation sequencing panel and found mutations only in NF1 gene (case 1) and AR gene (case 2) and showed TMB-low and microsatellite stability in both cases.6 On the contrary, molecular studies of limited series of SmCCC found driver mutations in MAPK, PI3K/AKT/mTOR, TP53, ATRX, ERBB4, and BRCA pathways.56,57 On the other hand, the partial molecular profile overlap found between SmCCC and SmCLC58,59 revealed different but convergent pathogenesis60 and strongly supports the development of similar therapeutic strategies for both entities.

We recognize some important limitations of our study, mainly, the retrospective and historical nature of case reports and the small sample size, which reduce the statistical robustness of our analysis. In addition, all reported cases exhibit great heterogeneity in management, and unknown confounding factors could exist. Despite limitations, our analysis provides the most complete overall picture of SmCCV to date, and the unlikely performance of prospective randomized studies on SmCCV boosts the importance of our conclusions.

CONCLUSIONS

Improving the outcome of patients with SmCCV is an uncovered medical need. Multimodal local approaches seem to obtain the best outcomes, but results are still modest. Defining the role of postoperative radiation and optimizing systemic treatments are potential areas for improvement. Characterizing the tumor biology and its potential association with HPV remain open. Research in these fields could enable to find potential therapeutic targets and even to impact on prevention. Biomarker-driven trials for patients with extrapulmonary SmCC are urgently required.

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