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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 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 (statistically significant differences between stage I and stages II, III, or IVA [log rank $p = .003$–$.017$]). 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

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Small cell carcinomas (SmCCs) are high-grade neuroendocrine tumors that emerge from neuroendocrine cells or result from the dedifferentiation of an aggressive nonneuroendocrine 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)[3] 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 isles 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) discarded 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 grays and weekly cisplatin 40 mg/m^2 was started. After completing EBRT, chemotherapy with cisplatin 75 mg/m^2 on day 1 plus etoposide 100 mg/m^2 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

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S.C. and M.R. participated in the conceptualization and methodology of the study and writing of the article. S.C. and M.R. performed the data collection. M.R. performed the data analysis. S.C., M.D., L.V., V.T., M.S., E.C., D.D., G.M., C.M., J.L., S.M.-R.S., and M.R. participated in writing of the article. All authors approved the final manuscript.

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The present study was exempt from institutional board review. Oral and written informed consent was obtained for case publication of the patient reported by our group.

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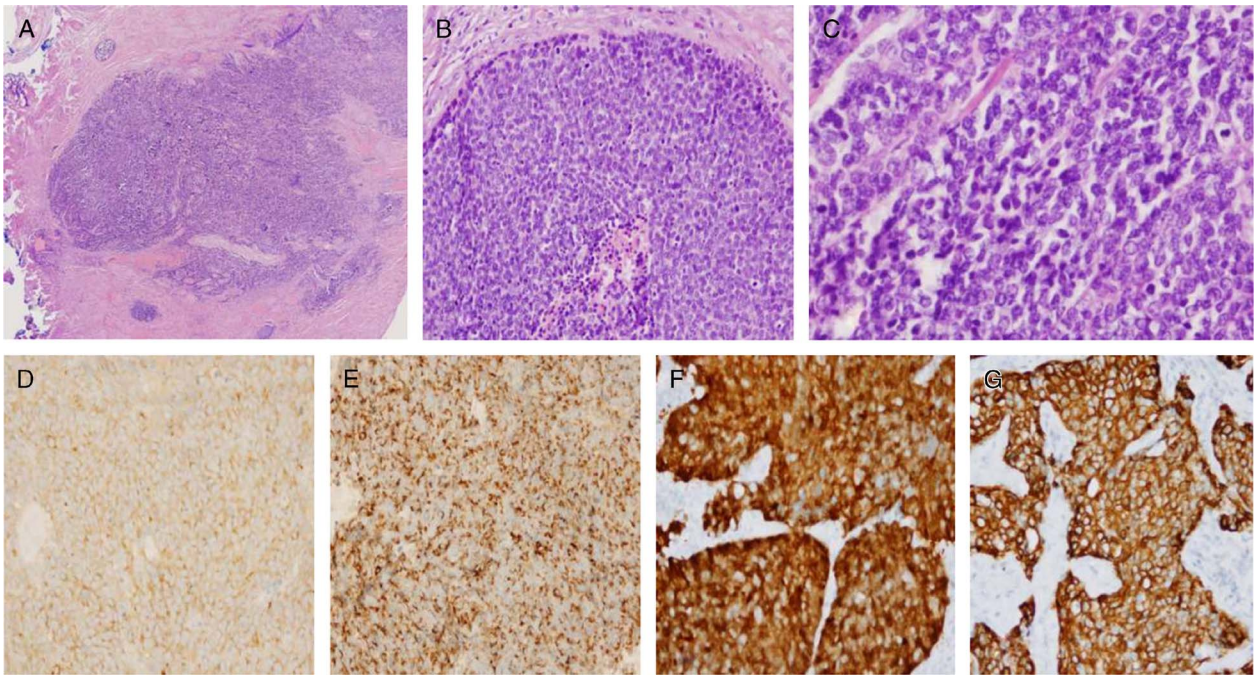

FIGURE 1. Pathological study of vaginal tumor. Histologic examination shows (A) a bluish submucosal proliferation growing in a solid fashion close to the resection margins. Molding and smudging phenomena, especially in the periphery of the lesion and around the vessels, are a distinctive feature (hematoxylin-eosin [H&E], 2×). Diffuse areas and (B) well-defined nests are observed (H&E, 20×). C, A relatively monotonous population of small round cells with finely stippled "salt and pepper" nuclear chromatin, inconspicuous nucleoli, and scant cytoplasm constitutes the lesion. A thin delicate fibrovascular stroma is also noted (H&E, 40×). D, Immunohistochemistry reveals the neuroendocrine nature of the tumor cells with a diffuse membrane expression of synaptophysin. E, The neoplasm is also positive for chromogranin A with a perinuclear dot-like pattern. F, An intense nuclear p16 expression is identified. Cytokeratin positivity was demonstrated with (G) CAM.5, CK7, and CK20 stains.

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/m^2 day 1 plus etoposide 100 mg/m^2 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[5] and the last one was reported in December 2021.[6] 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 Committe 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

Search details: ("carcinoma, small cell"[MeSH Terms] OR ("carcinoma"[All Fields] AND "small"[All Fields] AND "cell"[All Fields]) OR "small cell carcinoma"[All Fields] OR ("small"[All Fields] AND "cell"[All Fields] AND "carcinoma"[All Fields])) AND ("vagina"[MeSH Terms] OR "vagina"[All Fields])

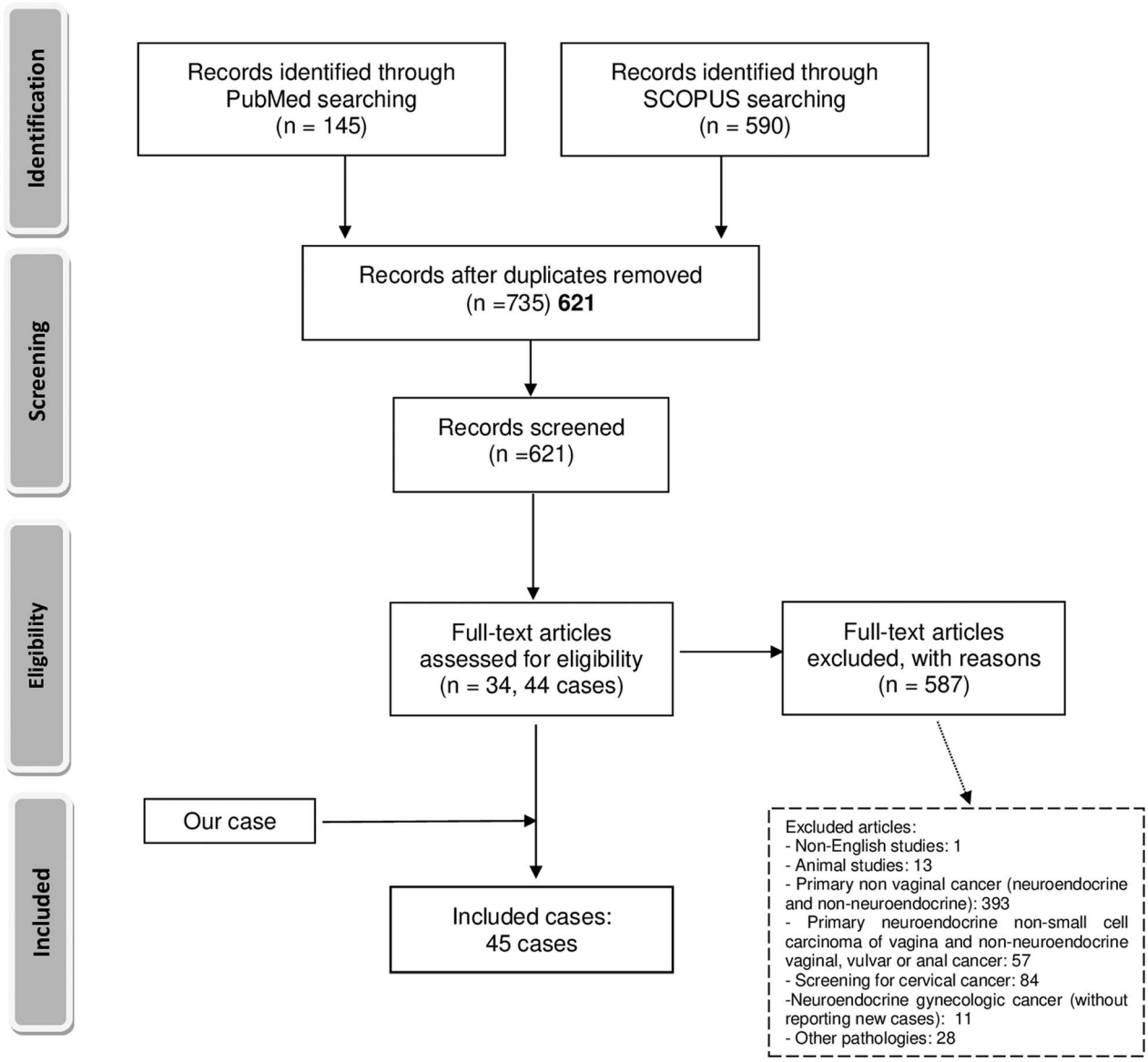

FIGURE 2. Flow chart of studies retrieved and finally included in the meta-analysis.

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.

TABLE 1. Clinical and Pathological Information of Patients Diagnosed With Small Cell Carcinoma of the Vagina

N	Ref	Year	Age, y	Clinical features	Tumor size, cm	Imaging staging	HPV	Lymph M1	Immunohistochemical staining
Stage I FIGO 2009 (n = 9)									
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 5HT
4	[10]	2009	53	Ns	Ns	Ns	Np	No	NS
5	[11]	2013	81	AVB	—	MRI + PET-CT	Np	No	Chr-A and SYN
6	[12]	2016	NS	NS	4.5 × 2.5 × 2	Ns	Np	No	Ns
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
Stage II FIGO 2009 (n = 12)									
10	[15]	1985	61 (m)	Ns	Ns	Ns	Np	No	Ns
11	[15]	1985	61 (m)	Ns	Ns	Ns	Np	No	Ns
12	[16]	1986	32	AVB	3 × 3 × 2	Chest x-ray, 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	—
17	[20]	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	[12]	2016	Ns	Ns	4 × 4 × 1.5	Ns	Np	No	Ns
20	[22]	2018	34	Vaginal mass	1 × 1	PET-CT	Np	Ns	LMW CK and SYN
21	[4]	2019	43	Vaginal mass	—	—	Np	No	Ns
Stage III FIGO 2009 (n = 10)									
22	[15]	1985	61 (m)	Ns	Ns	Ns	Np	Ns	Ns
23	[15]	1985	61 (m)	Ns	Ns	Ns	Np	Ns	Ns
24	[23]	1992	78	Vaginal discharge	3 nodes (1.2–4)	CT scan, chest x-ray	Np	Yes	NSE, PGP 9.5, chr-A, SYN, CD57, and LMW CK
25	[24]	1998	32	Vaginal mass	10 × 8		Np	No	SYN, NSE, neurofilament, CD57, chr-A
26	[25]	2000	57	AVB	8	CT scan	Np	No	NSE and SYN
27	[26]	2004	55	AVB	7 × 3 × 3	CT and bone scan	Np	Yes	TTF-1, LMW CK, chr-A, SYN
28	[27]	2005	50	AVB	—	Ns	Np	Yes	NSE, chr-A
29	[28]	2018	51	Ns	Ns	Ns	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
Stage IVA FIGO 2009 (n = 5)									
33	[15]	1985	61 (m)	Ns	Ns		Np	Ns	Ns

Continued next page

TABLE 1. *(Continued)*

N	Ref	Year	Age, y	Clinical features	Tumor size, cm	Imaging staging	HPV	Lymph M1	Immunohistochemical staining
34	17	1989	68	AVB	—	Chest x-ray	Np	No	Np
35	17	1989	73	Vaginal discharge	Ns	CT scan	Np	Yes	Np
36	26	2004	74	AVB	7 × 5	CT and bone scan	Np	Yes	LMW CK, chr-A and SYN
37	26	2004	38	Rectal pain	10 × 8 × 8	CT and bone scan	Np	No	LMW CK, chr-A and SYN
Stage IVB FIGO 2009 (n = 2)									
38	31	2008	61	AVB+ Cushing syndrome	9 × 3 × 2	CT scan	Np	Yes	LMW CK, chr-A, CEA, SYN, CD56.
39	32	2016	43	Vaginal mass + AVB	2.5 × 1.5 × 1	CT scan	Np	Yes	CK AE1/AE3, vimentin, Ki-67 (50%), SYN, and CD99
40	6	2021	70	Vaginal bleeding	3.8	Yes (ns)	+ (18)	Yes	CK19, CK20, SYN, Chr-A, p16
Stage not specified (n = 5)									
41[a]	33	2011	50	Vaginal mass	1.5 × 1	Chest x-ray and abd US	Np	Ns	NSE, SYN, chr-A
42[a]	34	2013	50	Vaginal discharge	3 × 4	Ns	—	Ns	SYN, CD56
43[a]	35a	1986				Histopathologic study without clinical details			
44[a]	5a	1984				Histopathologic study without clinical details			
45[a]	36a	2018				Histopathologic study without clinical details (detected by cfDNA testing)			

[a]Case was excluded for survival analyses.

5HT indicates serotonin; abd US, abdominal ultrasound; AVB, abnormal vaginal bleeding; Chr-A, chromogranin A; CK, cytokeratins; HSIL, high-grade squamous intraepithelial lesion; LMW, low molecular weight; M1 metastases; m, median; N, number; Np, not performed; Ns, nonspecified; NSE, neuron-specific enolase; PGP 9.5, protein gene product 9.5; Ref, reference; SYN, synaptophysin; TTF-1, thyroid transcriptor factor 1.

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 2021[6] and our case). The 3 cases HPV18+ positive were reported to be p16+ with a diffuse pattern in the immunochemistry study. Moreover, 2 of them[6] 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.T4671) 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.[37] 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,[37] 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 IVA (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

TABLE 2. Treatment and Survival Outcomes of Patients With Small Cell Carcinoma of the Vagina

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 + DXR + 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) conc	CDDP + ETO (4) conc CBP + PTX (2)	CR	No			7 (A)
7	12	Va + BILND	Ns	Ns	CR	Ns			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	5-Fluoracil	15
15	18	—	EBRT + BT (100)	—	CR	Yes	Bony, lung	Palliative EBRT.	11
16	19		EBRT (ns)	CDDP + ETO (5)	P			P-Chemo (ns) (refused CDDP + ETO)	8
17	20	Va + BILND	EBRT + BT (ns)	CDDP + ETO (3)	CR	Yes	Ns	—	6
18	21	—	EBRT + BT (ns)	CDDP + ETO (6)	CR	No			5 (A)
19	12	RH + partial Va + BILND	EBRT + BT (ns)	CDDP + ETO (6)	CR	Ns			Ns (A)
20	22	RH + partial Va + RSO + RPLND	Refused	Refused	CR	Yes	1 pelvic mass (5 mo) 2 retroperit LN + brain (28 mo)	1 TPT + PTX + Bev + IMRT 2 TPT + DTX + Bev	34
21	4	CKC + Va + BILND	—	PTX + CBP (2)	CR	Yes	Ns	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	Ns	14

Continued next page

TABLE 2. *(Continued)*

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	CR	Yes	Vaginal, bone and supraclav LN	CDDP + ETO	4
28	27	Anterior PE + BPLND	—	CDDP + ETO + DXR (ns)	CR	Yes	Para-aortic LN	Ns	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	6	—	RT conc (ns)	Ns (conc)	PR				8 (A)
Stage IVA (n = 5)									
33	15	—	—	—	Ns	Ns		—	12 (md)
34	17	—	EBRT (52)	ADR + CFM (1)	P	—	Lung	Palliative EBRT	5
35	17	—	—	CDDP + MTX (ns)	CR	Yes	Ns		9
36	26	—	EBRT (ns) conc	CDDP + ETO (2.AE)conc	P	—			4
37	26	—	EBRT + BT (ns) conc	CDDP + ETO➔ CDDP (3) only conc	CR	No			15 (A)
Stage IVB (n = 3)									
38	31	—	—	CDDP + ETO (4.AE)	PR	Early P		Epi	8
39	32	—	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)									
41[a]	33[a]	Lump excision	Ns	Ns	Ns	Ns	Ns	Ns	Ns
42[a]	34[a]	Lump excision	Ns	Ns	Ns	Ns	Ns	Ns	Ns
43[a]	35[a]	Histopathologic study without clinical details							
44[a]	5[a]	Histopathologic study without clinical details							
45[a]	36[a]	Histopathologic study without clinical details							

[a]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, docetaxe; 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.

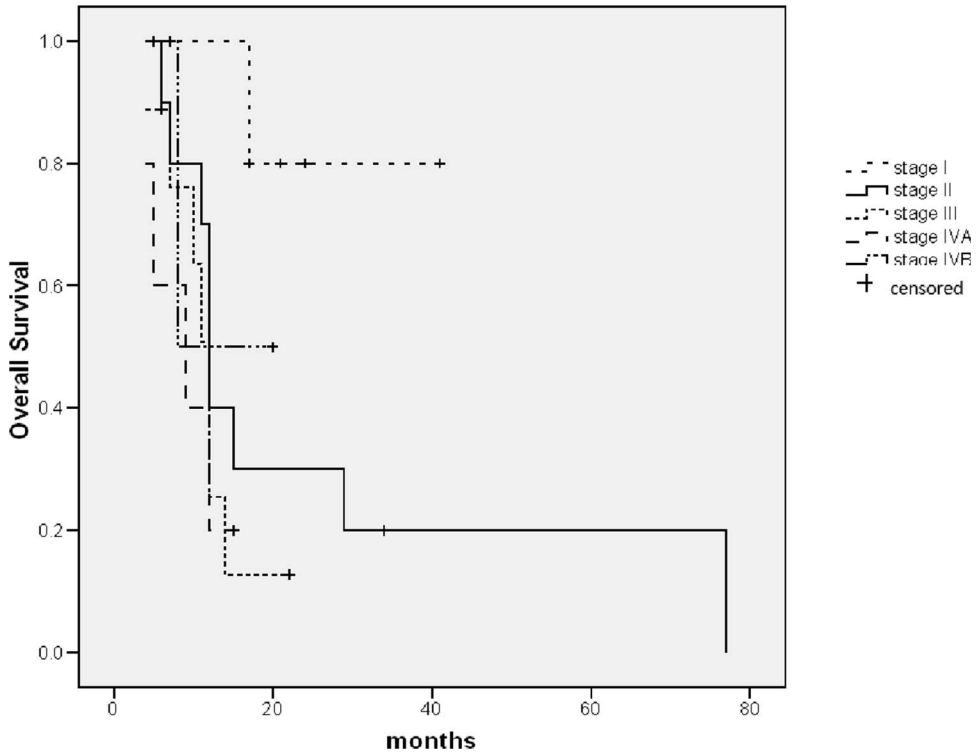

FIGURE 3. Overall survival curve of our series according to the FIGO staging.

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%), 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[26] 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.[31] 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.[22] 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[a], 21, 24[a], 27[a], 28, 40
			II (2)	1		
			III (3)	1		
			IVB (1)	1		
Radiotherapy ± chemotherapy	10	4 (2–10, *n* = 7)	I (2)	2	12	3, 5, 12, 14[a], 15, 16, 18, 25, 30, 34
			II (5)	3		
			III (2)	0		
			IVA (1)	1		
Chemoradiation ± chemotherapy	10	5.6 (2–10, *n* = 9)	I (3)	1	17	2, 6, 9[a], 26, 28, 29, 31, 32, 36, 37
			III (3)	2		
			IVA (2)	1		
			IVB (2)	1		
Surgery plus radiotherapy ± chemotherapy (not concurrent)	4	2.5 (0.5–4, *n* = 3)	I (2)	1	29	1, 4, 13, 17
			II (2)	1		

[a]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.[43,44] 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).[45] 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 stablished 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/m^2 day 1 plus etoposide 100 mg/m^2 days 1–3 every 3 weeks, up to 6 cycles (2 concurrent to radiation).[48] 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,[49,50] we do not recommend prophylactic brain radiation.

Regarding follow-up, the Society of Gynecologic Oncology guidelines[38] 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.[51]

For relapsed SmCCV patients, individualized management would be recommended.[38] For isolated local relapses, salvage

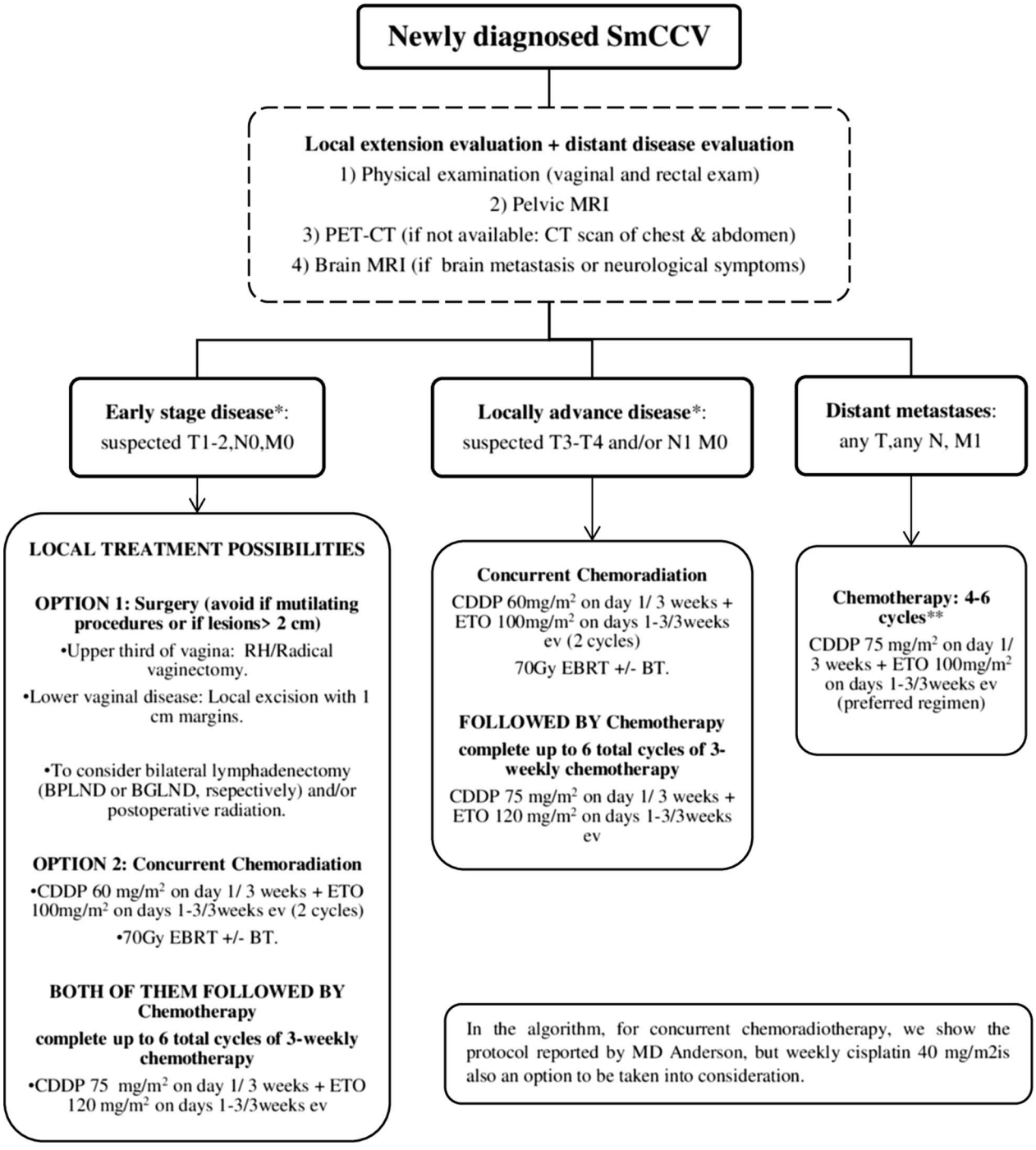

FIGURE 4. Proposal of staging and management algorithm for patients with SmCCV. BGLND, bilateral groin lymph node dissection; BPLND, bilateral pelvic lymph node dissection; BT, brachytherapy; CDDP, cisplatin; EBRT, external beam radiation therapy; ETO, etoposide; IMRT, intensity-modulated radiation therapy; 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.[52] Of note, the combination of topotecan (0.75 mg/m^2 on days 1–3), paclitaxel (175 mg/m^2 on day 1), and bevacizumab (15 mg/kg on day 1 on a 21-day cycle) was associated with a significant improvement in PFS (8 vs 4 months)[52] compared with other regimens in a retrospective analysis of 33 patients with SmCCC treated with primary chemotherapy. Outstandingly, the case 30[22] 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,[53,54] 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,[28] but progression was observed after 6 weeks of treatment. Importantly, HPV-related carcinogenesis 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 SmCLC[58,59] revealed different but convergent pathogenesis[60] 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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