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A clinical analysis of small-cell neuroendocrine carcinoma of the gynecologic tract: report of 20 cases

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Abstract

Objective The aim of this retrospective observational study was to analyze the clinical and pathological characteristics of small-cell neuroendocrine carcinoma of the gynecologic tract (SCNCGT).

Methods Twenty patients with SCNCGT were enrolled and their clinic-pathological features were analyzed. All patients were treated at the Beijing Obstetrics and Gynecology Hospital, Capital Medical University, China, and were followed up until December 31, 2017.

Results (1) Patient characteristics: The incidence of SCNCGT was 0.3% (20/6578) of gynecologic cancer in our hospital from January 1, 2007, to December 31, 2017. The average age of the patients was 42.0 ± 11.8 (23–63 years). Out of 20 patients enrolled, seven (35.0%) had lymph node metastasis. Out of 17 patients treated with complete surgery, 14 (82.4%) had lymph-vascular space invasion. (2) Treatment: Eleven out of the 14 patients with small-cell neuroendocrine carcinoma of the cervix (SCNCC) were treated with radical surgery; all the 11 patients received chemotherapy and radiotherapy postoperatively. The remaining three patients received comprehensive chemotherapy and/or radiotherapy instead of radical surgery. The six patients who had one or the other type of SCNCGT (involving the ovary, endometrium, or vagina) were all treated with comprehensive surgery. (3) Prognosis: The follow-up time for the study ranged from 8 to 87 months. Three (15.0%) of the 20 patients were diagnosed with distant metastasis at the beginning of the study. Eight (40.0%) patients died as of December 31, 2017, while the other 12 patients were in follow-up. The average survival time was 43.6 months (16–77 months).

Conclusion SCNCGT is a highly malignant tumor characterized by rare morbidity, a propensity for metastasis, and poor prognosis. Comprehensive treatment may be a good approach to prolong survival in some patients.

Keywords Small-cell neuroendocrine carcinoma · Gynecologic tract · Comprehensive treatment · Malignant tumor

Introduction

Neuroendocrine tumors (NET) occur in a spectrum of malignancies, the most aggressive of which is small-cell cancer. NETs are most commonly observed in the gastrointestinal tract and lungs; they can also occur in the thyroid, liver, cervix, ovary, prostate, and bladder. There is an increased incidence in women compared to men. The annual incidence of NETs has increased from 0.3 cases in 1973 to 1.35 cases per 100,000 in 2004, most likely because of improved techniques of detection [1]. Small-cell neuroendocrine carcinoma of the gynecologic tract (SCNCGT) is a rare disease. Among various types of SCNCGT, the order of incidence (highest to lowest) is as follows: small-cell neuroendocrine carcinoma of the cervix (SCNCC), followed by that of the ovary (SCNCO), endometrium (SCNCE), vagina (SCNCVa), and vulva (SCNCV) [2]. Neuroendocrine tumors primary to the gynecologic tract are rare, and there are only limited prospective data to guide clinical decisions. These tumors tend to metastasize early. Therefore, they are difficult to treat, and the prognosis is poor.

This study included 20 patients with SCNCGT, treated at the Beijing Obstetrics and Gynecology Hospital, Capital

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Medical University, China, in the last 11 years (2007–2017). Their clinical and pathological data were analyzed and summarized to look for specific clinical and pathological characteristics that may be used as a marker(s) for SCNCGT.

Methods

A total of 20 patients, who were initially diagnosed pathologically with SCNCGT and treated in the Department of Gynecological Oncology of the University Hospital from January 1, 2007, to December 31, 2017, were enrolled in this study; the total patients diagnosed with gynecological cancer were 6578 during this time (2977 patients were with cervical cancer, 925 patients were with ovary cancer, 1903 patients were with endometrial cancer, 42 patients were with vaginal cancer, 116 patients were with vulva cancer and 615 patients were with other gynecological cancer). The study retrospectively analyzed the clinical and pathological characteristics (including age, clinical stage, tumor type and size, tumor invasion, lymph node metastasis, treatment, and prognosis). All patients were followed up via an outpatient clinic and via telephone. For a deceased patient, the date of death was considered as the end of her follow-up. Until December 31, 2017, the median follow-up time for all 20 patients was 36 months (8–87 months), and no patient was lost to follow-up.

The International Federation of Gynecology and Obstetrics (FIGO) staging was used for tumor staging [3]. The WHO classification of tumors, Pathology and Genetics of Tumors of the Breast and Female Genital Organs, was used for pathological diagnosis [4]. This retrospective study was approved by the Ethics Committee (EC) from the Beijing Obstetrics and Gynecology Hospital.

Results

Patient characteristics of SCNCGT

The information and symptoms of the patients are summarized in Table 1. The incidence of SCNCGT accounted for 0.3% (20/6578) of gynecologic cancer in our hospital. The average age of the 20 patients with SCNCGT was 42.0 ± 11.8 years (23–63 years). A total of 14 patients were diagnosed with SCNCC which accounted for 0.5% (14/2977) of cervical cancer, three patients had SCNCO which accounted for 0.3% (3/925) of ovary cancer, two patients had SCNCE which accounted for 0.1% (2/1903) of endometrial cancer, and one patient had SCNCVa which accounted for 2.3% (1/42) of vaginal cancer. Out of the 14 patients with SCNCC, 12 (85.7%) experienced irregular bleeding and bleeding after intercourse. Of the three patients with SCNCO, one had irregular bleeding, another had abdominal distention, detected by the patient herself, and one had both irregular bleeding and abdominal distention during a routine gynecological examination. Out of the two SCNCE patients, one had irregular bleeding, and the other one was seen to have an abdominal mass during a routine gynecological examination. The solitary patient with SCNCVa was found to have masses in the vagina during a routine gynecological examination.

The clinical staging of all the 20 patients was determined according to the FIGO 2009 standard. The details of all the patients' clinical and pathological information are shown in Table 1. Of the 14 patients with SCNCC, three had stage IB1 cancer, six had stage IB2, four had stage IIA2, and one had stage IVB. Among the three patients with SCNCO, the first patient had stage IC, the second had stage IIIC2, and the third had stage IV. Of the two patients with SCNCE, one had stage IIIC1 and the other had stage IB. The solitary patient with SCNCVa had stage II.

Small-cell neuroendocrine tumors were diagnosed on the basis of the pathology and morphology of small, oval, polygonal, or fusiform cells with little cytoplasm, deep nuclei, or coarse granular chromatin. Of the 20 patients with SCNCGT, seven patients had lymph node metastasis, confirmed either by histology (4 patients) or by imaging (3 patients) of pathological nodes. The overall percentage of lymph node metastasis (LMN) was 35.0%. A total of 17 patients underwent lymph node dissections. The other three patients did not undergo lymph node dissection because their cancer was at a very late stage; among these three patients, who showed bilateral pelvic lymph node metastasis on a CT examination, one SCNCC patient had stage IIA2 and underwent chemoradiotherapy; another SCNCC patient had stage IB2 and had radio-chemotherapy (instead of radical surgery) and left obturator lymph node biopsy and anterior rectal mass resection to confirm metastasis; and one SCNCO had stage IV and was given chemotherapy. In addition, 14 (82.4%) out of the 17 patients also had lymph-vascular space invasion (LVSI) (See Table 1 for details).

Patient treatment of SCNCGT

Table 2 lists the details of the treatments given to the patients. Of the 14 patients with SCNCC, 11 received radical hysterectomy (three patients with stage IB1; five patients with stage IB2; three patients with stage IIA2), including seven who had adnexectomy at the same time. Prior to the surgery, four patients received chemo- and/or radiotherapy. Among them, one patient received 1 cycle of EP (etoposide/cisplatin) + 2 cycles of TC (paclitaxel/cisplatin) via intravenous (IV) chemotherapy, one patient received 1 cycle of neoadjuvant TC via arterial intervention (AI) chemotherapy, one patient received 2 cycles of neoadjuvant EP via IV chemotherapy, and one patient

Table 1 Patient characteristics of SCNCGT

Age	Parity	Family history of cancer	Symptoms	Stage	Grade	LVSI	LNM
SCNCC							
50	Y	N	N	IB1	G3	Y	N
32	Y	N	Bleeding	IB1	G3	Y	N
54	Y	N	Bleeding	IB1	G3	N	N
49	Y	N	Bleeding	IB2	G3	Y	N
50	Y	N	Bleeding	IB2	G3	Y	N
28	Y	N	Bleeding	IB2[a]	G3	–	Y
44	Y	Y	Bleeding	IB2	G3	Y	N
35	Y	N	Bleeding	IB2	G3	N	N
38	Y	N	Bleeding	IB2	G3	Y	N
33	Y	Y	Bleeding	IIA2	G3	Y	N
43	N	N	N	IIA2	G3	Y	Y
29	Y	N	Bleeding	IIA2	G3	Y	N
59	Y	N	Bleeding	IIA2	G3	–	Y (CT)[b]
24	Y	N	Bleeding	IVB[c]	G3	–	Y (CT)
SCNCO							
41	N	N	Bleeding	IC	G3	N	N
23	N	N	Bleeding; abdominal distention	IIIC2	G3	Y	Y
41	Y	N	Abdominal distention	IV[c]	G3	Y	Y (CT)
SCNCE							
59	Y	N	Mass; diarrhea	IB	G3	Y	N
63	Y	Y	Bleeding	IIIC1	G3	Y	Y
SCNCVa							
43	Y	N	Mass	II	G3	Y	N

SCNCGT Small-cell neuroendocrine carcinoma of gynecologic tract, *SCNCC* Small-cell neuroendocrine carcinoma of cervix, *SCNCO* Small-cell neuroendocrine carcinoma of ovary, *SCNCE* Small-cell neuroendocrine carcinoma of endometrium, *SCNCVa* Small-cell neuroendocrine carcinoma of vagina, *Y* Yes, *N* No, *LSVI* Lymph-vascular space involvement, *LNM* Lymph node metastasis

[a]Rectal wall metastasis; [b]LNM metastasis diagnosed by CT scan; [c]Liver metastasis

received radiotherapy to shrink the tumor. Postoperatively, all 12 patients received chemo- and/or radiotherapies as supplements: two patients received chemotherapy with TC, one received chemotherapy with EP, one received chemotherapy of EP combined with TC, five received chemotherapy with TC + radiotherapy treatment (RT), two received chemotherapy of EP combined with TC + RT, one was treated with pelvic resection of rectal tumor and ovarian biopsy + lymph node biopsy following supplemental chemotherapy with TC and RT. One was treated with concurrent chemoradiotherapy, and one patient with stage IVB with liver metastasis was treated with chemotherapy with TC.

Of the three SCNCO patients, one underwent cytoreductive surgery (CS) for ovarian tumor. Another patient received fertility-sparing cytoreductive surgery (FS-CS), followed postoperatively by supplemental chemotherapy via 5 cycles of BEP (bleomycin/etoposide/cisplatin) + 1 cycle of TC. The third patient, who had stage IV cancer with liver metastasis, received unilateral salpingo-oophorectomy + omentectomy + resection of rectal tumor, and supplemental chemotherapy via 1 cycle of EP and TC postoperatively.

Of the 2 SCNCE patients, one underwent extrafascial hysterectomy + lymph node dissection + adnexectomy, followed by supplemental chemotherapy with 4 cycles of TC. The other patient underwent extrafascial hysterectomy + lymph node dissection + adnexectomy, and supplemental chemotherapy with 3 cycles of TC plus RT.

The single SCNCVa patient underwent a cold-knife conization (CKC) + vaginectomy (vaginal mass resection) with bilateral inguinal lymph node dissection, followed by supplemental chemotherapy with 2 cycles of TC.

Patient prognosis of SCNCGT

Of the 20 patients with SCNCGT, three (15%) were first diagnosed with distant metastasis; two of them had liver metastasis and one had rectal metastasis. The follow-up

Table 2 Patient outcomes of SCNCGT

Date of diagnosis	Stage	Pre OP	OP	Primary treatment post-OP	Recurrence	OS (months)
SCNCC						
01/2011	IB1	N	RH + LN + Ad	TC 2 cycles	Y	83 (Follow-up)
12/2011	IB1	N	RH + LN + Ad	TC 6 cycles + RT	Y	72 (Follow-up)
04/2016	IB1	N	RH + LN + Ad + Pa-LN	TC 2 cycles + RT	N	20 (Follow-up)
03/2014	IB2	N	RH + LN + Ad	TC 6 cycles	Y	45 (Follow-up)
09/2010	IB2	N	RH + LN + Ad	TC 2 cycles	Y	87 (Follow-up)
10/2010	IB2 (rectal wall metastasis)[a]	N	Ovary biopsy + LN biopsy + Rectal wall mass removal[a]	TC 1 cycle + RT	–	42 (Death)
03/2016	IB2	RT	RH + LN + Ad + Pa-LN	TC 2 cycles + RT	Y	18 (Death)
03/2017	IB2	EP 2 cycles (IV)	RH + LN + Pa-LN	EP 2 cycle	Y	9 (Follow-up)
05/2016	IB2	N	RH + LN + Pa-LN	TC 3 cycles + EP 2 cycles	Y (4 months)	19 (Follow-up)
08/2016	IIA2	EP 1 cycles + TC 2 cycle (IV)	RH + LN + Pa-LN	EP 3 cycles + TC 1 cycle + RT	Y	16 (Follow-up)
11/2016	IIA2	TC 1 cycle (AI)	RH + LN + Ad + Pa-LN	TC 2 cycles + RT	N	l3 (Follow-up)
09/2016	IIA2	N	RH + LN + Pa-LN	TC 3 cycles + EP 2cycles + RT	N	15 (Follow-up)
09/2011	IIA2	N	RTC	–	Y	39 (Death)
10/2014	IVB (liver metastasis)	TC 1 cycles	–	–	–	36 (Death)
SCNCO						
07/2013	IC	N	CR	–	N	53 (Follow-up)
03/2011	IIIC2	N	FS-CR	BEP 5 cycles + TC 1 cycle	Y	16 (Death)
10/2010	IV (liver metastasis)	EP 1 cycles (IV)	Ad + OR + Rectal wall mass removal[b]	EP 1 cycle + TC 1 cycle	–	82 (Death)
SCNCE						
08/2007	IB	N	EFH + LN + Ad	TC 4 cycle	Y	39 (Death)
04/2017	IIIC1	N	EFH + LN + Ad	TC 3 cycles + RT	N	8 (Follow-up)
SCNCVa						
03/2011	II	N	CKC + LN + Vaginal mass removal	TC 2 cycles	Y	77 (Death)

SCNCGT Small-cell neuroendocrine carcinoma of gynecologic tract, *SCNCC* Small-cell neuroendocrine carcinoma of cervix, *SCNCO* Small-cell neuroendocrine carcinoma of ovary, *SCNCE* Small-cell neuroendocrine carcinoma of endometrium, *SCNCVa* Small-cell neuroendocrine carcinoma of vagina, *OP* Operation, *OS* Overall survival, *RH* Radical hysterectomy, *EFH* Extra-fascial hysterectomy, *LN* Lymph node resection, *Ad* Adnexectomy, *Pa-LN* Para-aortic lymph node resection, *RTC* Radiotherapy concurrent chemotherapy, *RT* Radiotherapy, *OR* Omentum resection, *CR* Cytoreductive surgery, *FS-CR* Fertility-sparing cytoreductive surgery, *EP* Etoposide/Cisplatin, *TC* Paclitaxel/Carboplatin, *BEP* Bleomycin/Etoposide/Cisplatin, *IV* intravenous, *AI* arterial intervention, *Y* Yes, *N* No

[a]The patient was diagnosed SCNCC who had stage IB2 and received surgery firstly, but during surgery, we perform rectal tumor and ovarian biopsy + lymph node biopsy to confirm rectum and ovary metastasis. The patient was performed chemo-radiotherapy instead of radical hysterectomy finally

[b]Hysterectomy has been performed because of myoma before

time for the 20 patients ranged from 8 to 87 months, during which 8 patients (40.0%) died. The average survival time was 43.6 months (16–77 months). The remaining 12 patients are still being followed up, and seven of these patients (58.3%) had recurrences. Ten patients (six with SCNCC, two with SCNCO, one with SCNCE and one with SCNCVa) were followed up for longer than 3 years, and five (50.0%) of them survived. Five patients (three with SCNCC, one with SCNCO, and one with SCNCVa) were followed up for more than 5 years, and three (60.0%) of them survived.

Discussion

The incidence of small-cell neuroendocrine tumors in the female reproductive system cancer is extremely low, and the result of this study is consistent with this fact which is 0.3%. However, some data published recently showed increasing incidence of these tumors, most likely because of increasing improvement in disease recognition and accuracy of diagnostic techniques [5, 6]. The incidence of SCNCC is 0.06/100 thousand [7], which accounts for 2–5% of cervical cancer cases [8]. Less than 300 cases of SCNCO, a total of 80 cases of SCNCE [9], less than 25 cases of SCNCVa [10], and 15 cases of SCNCV have been reported in the world [11]. With regard to the 20 patients in this study, the incidence of SCNCC was the highest at 0.2% (14/6578), followed by that of SCNCO at 0.05% (3/6578), SCNCE at 0.03% (2/6578), and SCNCVa at 0.01% (1/6578) in the female reproductive system cancer. This is consistent with the literature [10]. The onset or detection of the disease was mainly in the middle age (23–63 years with an average of 42.0 ± 11.8). In this study, most patients had symptoms, such as vaginal bleeding and abdominal mass, when the cancer was detected, with 75.0% (15/20) of them already with the cancer at an advanced stage.

The biological characteristics of SCNCGT are unique, with the tumor showing diffuse interstitial infiltration. Forty–fifty percent of SCNCGT exhibits lymph node metastasis at the early stage, and easily manifests as a distant metastasis, spreading to the liver, lung, bone, brain, and even skin [12]. Distant metastasis was the most common type of recurrence, and the clinical outcome correlated with the initial disease extent. In this 20-patient study, 35.0% of the patients had lymph node metastasis, 82.4% of the patients had combined vascular tumor thrombus, and 15.0% of the patients had distant metastasis at the beginning of study (to the liver in two patients and to the rectum in one patient). Eight patients died, with an average survival time of 43.6 months (16–77 months from the time of detection). Of the 12 patients still alive, seven (58.3%) had recurrences. Postoperatively, the earliest time to metastasis (to the left supraclavicular lymph node) was 4 months. Another previous report found that SCNCGT is characterized by a high mitotic index, necrosis, and frequent lymphovascular space involvement. It has an aggressive clinical behavior, with high propensity to metastasize to the lymph nodes and the distant organs, coupled with a poor prognosis and a high mortality rate [13]. The result of this study is consistent with those reports, and reemphasizes the importance of paying attention to monitoring the increased risk of LVSI and pelvic recurrence.

Most treatments for SCNCGT use a comprehensive approach. Surgery and radiotherapy can control local recurrence. SCNCGT is a rare disease, with the uterine cervix being the most common site of occurrence. Because of the limited number of samples, it is difficult to develop a standard for diagnosis and treatment approach. Some reports of the diagnosis and treatments for SCNCC are relatively standard. Surgery is an option for early-stage cancer, including radical hysterectomy with regional lymphadenectomy as a component of the primary management [10, 14]. For advanced stage, or non-surgical patients, chemoradiation is a reasonable treatment choice [15]. Chemoradiation with EP, concurrent with pelvic radiation is appropriate. Bajaj [16] reported that postoperative chemotherapy with EP was associated with a significant survival advantage. Adjuvant chemotherapy provided a survival advantage for patients, either with or without lymph node metastasis. In 2003, Chan [17] proposed an algorithm for management of small-cell carcinoma of the cervix. For tumors less than 4 cm, radical hysterectomy with lymphadenectomy can be performed, with consideration of EP-based therapies in the adjuvant setting. For tumors larger than 4 cm and limited, using a neoadjuvant approach with systemic platinum-based therapies, followed by a localized treatment-based approach (including surgery) can be considered. Radiotherapy is an integral aspect of definitive chemoradiotherapy for treating cervical cancer and should not be omitted [18]. In this study, ten out of 20 patients with SCNCGT had locally advanced SCNCC. Three of them died (18–42 months), and seven patients are still being followed up (9–87 months). Seven of these ten patients had recurrences, and the tumors of another three patients were reduced after surgery, with supplemental chemoradiotherapy postoperatively. Up to now, there is no specific treatment for SCNCC, cervical cancer was diagnosed by colposcopy directed biopsy, but it is difficult to diagnosed SCNCC directly by biopsy, so for local advanced cervical cancer (LACC), we performed neoadjuvant chemotherapy to shrink the tumor firstly. Recently, NACT has been reported useful in the control of LACC. Early or pre-chemotherapy NACT has been used to reduce tumor volume prior to surgery or radiotherapy. For patients with advanced cervical cancer, 2–3 cycles, NACT can improve the success rate of resection. Previous studies show that NACT can inhibit tumor micrometastases and enhance the resection rate by shrinking tumor volume [19, 20]. A meta-analysis showed that NACT followed by radical hysterectomy can improve the survival rate [21]. We choose the 2–3 cycles as average number of neoadjuvant chemotherapy for LACC. Whether preoperative neoadjuvant chemotherapy can prolong the tumor-free time and total survival still needs further investigation.

It has been reported that the 5-year survival rates of SCNCC were 36.8%, 9.8% and 0% for patients with FIGO stage I–IIA, IIB–IVA, and IVB, respectively [22]. In this

study, three patients with SCNCGT had late-stage cancer, with distant metastasis at the time of detection. Ten patients were followed up for greater than 3 years, and five (50.0%) of them survived. Five patients were followed up for more than 5 years and three (60.0%) of them survived.

One of the limitations of this study is its small sample size. Because SCNCGT is a rare cancer, the study included only 20 patients. No significant difference could be detected for such a small sample size. Future long-term multicenter studies that include more patients at different stages and lesion sites are warranted.

In conclusion, the incidence of SCNGT is low, the degree of malignancy is high, and the prognosis is poor. A comprehensive approach is still the main treatment regimen. A multicenter prospective controlled study is warranted to identify other more specific prognostic factors and to develop better therapeutic strategies.

Author contribution YH: Conceptualization and Resources and Funding acquisition and Writing—original, draft preparation; HZ: Conceptualization and Resources and Writing—original; YMW: Funding acquisition and Supervision and Writing—review; XML: Data curation and Formal analysis; CHY: Supervision and Writing—review.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Ethic Committee (EC) from the Beijing Obstetrics and Gynecology Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Motiwala H, Bansal I, Goyal P, Dorokhova O, Kumar Y, Olsavsky TD et al (2017) Do we really care about incidental lung nodules?—Review of atypical lung carcinoid and a proposal for systematic patient follow up. Transl Lung Cancer Res 6(3):387–392
2. Patibandla JR, Fehniger JE, Levine DA, Jelinic P (2018) Small cell cancers of the female genital tract: molecular and clinical aspects. Gynecol Oncol 149(2):420–427
3. FIGO Committee on Gynecologic Oncology (2014) FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet 125(2):97–98
4. Wee WW, Chia YN, Yam PK (2012) Diagnosis and treatment of vaginal intraepithelial neoplasia. Int J Gynaecol Obstet 117(1):15–17
5. Gadducci A, Carinelli S, Aletti G (2017) Neuroendrocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists. Gynecol Oncol 144(3):637–646
6. McCusker ME, Cote TR, Clegg LX, Tavassoli FJ (2003) Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. Gynecol Oncol 88(3):333–339
7. Chen J, Maedonald OK, Gaffney DK (2008) Incidence, mortality, and prognositic factor of small cell carcinoma of the cervix. Obstet Gynecol 111(6):1394–1402
8. Zhou J, Yang HY, Wu SG, He ZY, Lin HX, Sun JY (2016) The local treatment modalities in FIGO stage I–II small-cell carcinoma of the cervix are determined by disease stage and lymph node status. Cancer Med 5(6):1106–1115
9. Matsumoto H, Takai N, Nasu K, Narahara H (2011) Small cell carcinoma of the endometrium: a report of two cases. J Obstet Gynaecol Res 37(11):1739–1743
10. Gardner GJ, Reidy-Lagunes D, Gehrig PA (2011) Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. Gyencol Oncol 122(1):190–198
11. Sheikh ZA, Nair I, Vijaykumar DK, Jojo A, Nandeesh M (2010) Neuroendocrine tumor of vulva: a case report and review of literature. J Cancer Res Ther 6(3):365–366
12. De Caluwé A, Bowering G, Nichol A, Hsu F (2017) The incidence of symptomatic brain metastases from extra-pulmonary small cell carcinoma: is there a role for prophylactic cranial irradiation in a clinically relevant population cohort? Radiother Oncol 124(1):31–37
13. Silva-Meléndez PE, Escobar PF, Silva Héctor, Gutiérrez S, Rodríguez M (2015) Small cell carcinoma of the uterine cervix: a case report and literature review. Bol Asoc Med PR 107(1):55–57
14. Satoh T, Takei Y, Treilleux I, Devouassoux-Shisheboran M, Ledermann J, Viswanathan AN et al (2014) Gynecologic Cancer Inter Group (GCIG) consensus review for small cell carcinoma of the cervix. Int J Gynecol Cancer 24(9 suppl3):S102–S108
15. Nagao S, Miwa M, Maeda N, Kogiku A, Yamamoto K, Morimoto A et al (2015) Clinical features of neuroendocrine carcinoma of the uterine cervix: a single-institution retrospective review. Int J Gynecol Cancer 25(7):1300–1305
16. Bajaj A, Gopalakrishnan M, Harkenrider MM, Lurain JR, Small W Jr (2018) Advanced small cell carcinoma of the cervix-successful treatment with concurrent etoposide and cisplatin chemotherapy and extended field radiation: a case report and discussion. Gynecol Oncol Rep 23:4–6
17. Chan JK, Loizzi V, Burger RA, Rutgers J, Monk BJ (2003) Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer 97(3):568–574
18. Robin TP, Amini A, Schefter TE, Behbakht K, Fisher CM (2016) Brachytherapy should not be omitted when treating locally advanced neuroendocrine cervical cancer with definitive chemoradiation therapy. Brachytherapy 15(6):845–850
19. Hwang YY, Moon H, Cho SH, Kim KT, Moon YJ, Kim SR et al (2001) Ten-year survival of patients with locally advanced, stage Ib–IIb cervical cancer after neoadjuvant chemo-therapy and radical hysterectomy. Gynecol Oncol 82(1):88–93
20. Cho YH, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH (2009) Comparative study of neoadjuvant chemotherapy before radical hysterectomy and radical surgery alone in stage IB2-IIA bulky cervical cancer. J Gynecol Oncol 20:22–27

21. Eddy GL, Bundy BN, Creasman WT, Spirtos NM, Mannel RS, Hannigan E et al (2007) Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. Gynecol Oncol 106(2):362–369

22. Cohen JG, Kapp DS, Shin JY, Urban R, Sherman AE, Chen LM et al (2010) Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. Am J Obstet Gynecol 203(4):347.e1–347.e6