Ultrasonographic Diagnosis of Rare Primary Cervical Cancer

Jiaoling Li (doctorlijiaolin@126.com)
Guangzhou Women and Children's Medical Center https://orcid.org/0000-0002-8343-1310
Congmin Gu
Guangzhou Women and Children's Medical Center, Guangzhou Medical University
Haiqing Zheng
Guangzhou Women and Children's Medical Center, Guangzhou Medical University
Xiaofang Liu
Guangzhou Women and Children's Medical Center, Guangzhou Medical University
Xiuping Geng
Guangzhou Woman and Children's Medical Center, Guangzhou Medical University
Haiying Wu
Guangzhou Woman and Children's Medical Center, Guangzhou Medical Universityi

Research article

Keywords: adenocarcinoma of the cervix, adenosquamous carcinoma of the cervix, clear-cell carcinoma of the cervix, small-cell carcinoma of the cervix, squamous cell carcinoma of the cervix, ultrasonography

DOI: https://doi.org/10.21203/rs.3.rs-42542/v1

Abstract

Background: To summarize ultrasonographic features of rare primary and common cervical cancer and the association of these cancers with HPV infection so as to diagnose rare primary cervical cancer.

METHODS: Sixty-five cases with cervical cancer suspected by ultrasonography and three cases with clinical symptoms treated at our department underwent cervical biopsy. Sixty-four diagnosed cases were retrospectively analyzed and divided into common-type (CTCC) and rare-type (RTCC) cervical cancers.

RESULTS: Sixty-one cases were diagnosed, four misdiagnosed, three missed the diagnosis by ultrasonography, the sensitivity of which was 95.31% (61/64). The common-type cervical cancer had 43 cases of squamous cell carcinoma. The rare-type cervical cancer had 15 cases of adenocarcinoma, four of small-cell carcinoma, and two of adenosquamous carcinoma. The demographic characteristics of the two groups were not significantly different ($P > 0.2$). The tumor size in RTCC was smaller than those in CTCC ($P < 0.05$). Hypoechoic lesions in CTCC and isoechoic lesions in RTCC composed 74.42% (32/43) and 61.90% (13/21), respectively ($P < 0.001$). Exophytic in CTCC and endophytic in RTCC composed 67.44% (29/43) and 66.67% (14/21), respectively ($P = 0.01$). HPV infection composed 83.72% (36/43) in CTCC and 47.62% (10/21) in RTCC, respectively ($P = 0.003$). Color Doppler blood signals were found in all cases, as compared with normal cervical tissue. The consistency between ultrasonography and pathology staging diagnosis of RTCC was good (Weighted kappa (95%CI) = 0.87).

CONCLUSION: Most of patients in RTCC have isoechoic lesions. There is a good consistency between ultrasonography and pathology staging diagnosis of RTCC.

Précis

Ultrasonography can be used as an alternative non-invasive method to diagnose rare-type cervical cancers. The sensitivity of ultrasonographic diagnosis for cervical cancer was 95.31%. In rare-type cervical cancer , the tumor size was smaller compared with common-type cervical cancer, isoechoic lesions accounted for 61.90%, endophytic accounted for 66.67%, HPV infection accounted for 47.62%. The consistency between ultrasonography and pathology staging diagnosis of RTCC was good (Weighted kappa (95%CI) = 0.87).

Background

Cervical squamous cell carcinoma (CSCC) is the most common primary tumor in the cervical region; other rare primary tumors include clear-cell carcinoma of the cervix (CCCC) and small-cell carcinoma of the cervix (SCCC), [1–3] primary lymphoma of the cervix,[4] cervical choriocarcinoma,[5] sarcoma of the uterine cervix, [6] rhabdomyoma of the cervix,[7] malignant melanoma of the cervix,[8] Wilm's tumor of the cervix, [9] and malignant peripheral neurilemmoma of cervical fibroblasts.[10] Regardless of the type of cervical neoplasm, contact hemorrhage or fluor sanguinolentus are the main early clinical manifestations; late

clinical manifestations include irregular vaginal bleeding of varying amounts with corresponding symptoms of distant metastasis.

In recent decades, pap smear is used for primary prevention to detect preinvasive lesion, and some patients with cervical cancer receive early diagnosis and treatment; thus, the mortality rate has been reduced significantly. However, this method is not appropriate for women with rare cervical cancers, such as SCCC, which do not invade the surface epithelium of the cervix but diffusely infiltrate cervical stroma,[11] therefore, cytological examination is often negative in these patients. Recently, HPV test gradually replaced pap smear to screen for cervical cancer in some countries and district,[12, 13] and HPV vaccines were even injected to prevent cervical cancer,[14] but they had also some side effects, such as local reactions and ethnicity that vaccines would allow youth to become sexually adventurous. In addition, an increase of HPV-induced cancers and specific concerns regarding post-vaccination infertility or pregnancy or infant outcomes were also raised.[15]

Ultrasonography (US) is economical, convenient, non-invasive, and has been reported to have a diagnostic accuracy similar to that of magnetic resonance imaging (MRI) on local extension of the disease although it is not included in the protocols for cervical cancer, [16,17] so it is suitable for women with rare cervical cancers; specifically, color Doppler US (CDUS) can enhance the display rate of malignant tumors by Doppler flow imaging, and achieve clear images of lesions for accurate staging and targeted cervical biopsy. Thus, the diagnostic sensitivity and positive predictive value can be improved, thereby providing a basis for selecting appropriate treatment methods. In this paper, we summarized the different ultrasonographic features of rare primary and common cervical cancer to improve the diagnosis of rare primary cervical cancer, and examined the diagnostic and staging accuracy for US.

Methods

This study was approved by our Institutional Ethics Review Board (54.4 25). All patients provided informed consent for US assessment, and in turn underwent clinical examination, HPV inspection, and cervical biopsy after ultrasound.

We conducted a retrospective study of patients with cervical cancer who were diagnosed because of contact hemorrhage or fluor sanguinolentus at our hospital between June 1, 2014, and October 31, 2019. Records were searched for cases of cervical cancer respectively using “abnormal echo of cervix” and “suspicious cervical cancer” in the Image Workstation and “cervecal cancer” in the Pathology Specimen Bank as search strings. Sixty-five cases with cervical cancer suspected by US underwent cervical biopsy, out of who four were excluded due to a misdiagnosis by US. In addition, three cases with clinical symptom were misdiagnosed by US, and confirmed by cervical biopsy, and their ultrasonography images were extracted from the Image Workstation for review. Finally, 64 cases of cervical cancer were diagnosed by cervical biopsy and pathology (regarded as the gold standard to determine the accuracy of imaged-based diagnoses). These 64 cases were divided into common-type cervical cancers (CTCC, 43 cases) and rare-type cervical cancers (RTCC, 21 cases).

A high-resolution US system (Voluson E8 Expert; GE Healthcare, USA) equipped with a 3–5 MHz convex array transducer and a 7–12 MHz vaginal transducer was used to detect cervical cancer by examiners with over eight years experience. All data and images were counted according to the last ultrasound five days before treatment. The ultrasound technique was as follow: first, on two dimensions the uterus, endometrium, cervix, vagina, bilateral parametrium and appendages were observed; echoes (hypoechoic, isoechoic, hyperechoic, and mixed compared with the surrounding tissue) of cervical lesions were carefully observed, and three standardized diameters of primary cervical cancer (craniocaudal and anteroposterior in a longitudinal projection from the outmost margin of the lesion to the most cranial extension of the lesion and perpendicular to it, respectively, and laterolateral in the transverse projection from the outmost lateral aspects of the lesion) were measured when cervical cancer was suspected, the tumor volume was calculated using the ellipsoid formula *A X B X C*

$$\frac{\pi}{6}, 18$$

where *A*, *B*, and *C* were the diameters of the tumor (craniocaudal, anteroposterior, and laterolateral measurements, respectively). Then, blood flow signals distribution in and around the cervical lesions was observed under color Doppler flow imaging. Next, abnormal echoes of lesions and Doppler flow signals (compared to that of adjacent normal tissue) were used to judge whether adjacent tissues (including the corpus, parametrial tissue, bilateral appendages, bladder, and rectum) had infiltration and the depth of the infiltration (for multiple simultaneous local infiltrations, one case of local tissue infiltration was calculated and the staging was precisely defined according to the location and depth of infiltration). Then, first-grade-group lymph nodes were observed. Next, growth pattern was judged and divided into exophytic (papillary growth) and endophytic (the lesion infiltrating into deep cervical tisuue). Finally, all patients was staged accoding to TNM criteria. The vascularization was classified subjectively using a “color score”: punctate blood flow signals (color score = 1), short rod blood flow signals (color score = 2), strip blood flow signals (color score = 3), and reticular blood flow signals (color score = 4). Meanwhile, 40 patients with self-conditional permission underwent magnetic resonance imaging (MRI) (Signa; GE Medical Systems, Milwaukee, WI, USA) to assist with staging. The patients suspected to have cervical cancer underwent targeted cervical biopsy.

Statistical analysis was performed using SAS software version 9.4 (SAS Inc.; Carey, NC). Data were presented as mean ± SD. Data between RTCC and CTCC were analyzed using either a Student’s *t* test, two-tailed Fisher’s exact probability test, or chi-square tests or Mann-Whitney U test. Weighted Kappa evaluated the consistency between ultrasonography and pathology staging diagnosis. A two-sided *P*-value < 0.05 was considered to be statistically significant.

Results

The average ages of the patients in the CTCC and RTCC groups were 51.05 ± 9.41 years (range: 31–69) and 48.05 ± 9.67 years (range: 23–64), respectively. Sixty-three cases in the CTCC and RTCC group were

married and sexually active; one case in the RTCC group was unmarried and celibate.

Regarding the pathological results, 64 cases were diagnosed as cervical cancer. CTCC included 43 cases of CSCC (one case of squamous cell carcinoma in situ). RTCC included 15 cases of adenocarcinoma (one case of CCCC), and two cases of adenosquamous carcinoma and four cases of SCCC. Chronic cervicitis and submucosal myoma occurred in two cases each. The patient with CCCC had positive immunohistochemical staining for Napsin A, HNF-1B, CK7, PAX, and P53. The patients with SCCC had positive immunohistochemical staining for Syn, chromogranin A (CgA), neuron-specific enolase (NSE), Ki-67, carcinoembryonic antigen (CEA), and P16 (Figs. 1 and 2).

Regarding the ultrasonographic results, 65 cases of suspected cervical cancer were detected by preoperative US; of these, two cases of chronic cervicitis and two cases of submucosal myoma were misdiagnosed as cervical cancer. Three cases with clinical symptom were missed diagnosis by US, but confirmed by cervical biopsy. The sensitivity and positive predictive value of ultrasound diagnosis was 95.31% (61/64) and 93.85% (61/65), respectively. According to TNM criteria, ultrasonography diagnosed 27 cases of stage T1b1, seven cases of stage T1b2, five cases of T2a1, 13 cases of stage T2a2, three cases of stage T2b, one case of stage T3a, eight cases of stage T4. General information, ultrasonographic and histological characteristics, HPV infection of 43 cases in CTCC and 21 cases in RTCC are shown in Table 1, Figs. 1 and 2. CDUS showed sparse or dense punctate blood flow signals (color score = 1) in seven cases, short rod blood flow signals (color score = 2) in nine cases, strip blood flow signals (color score = 3) in 16 cases, and reticular blood flow signals (color score = 4) in 32 cases.

Table 1
General information and ultrasonographic and histological characteristics of 64 patients with cervical cancer.

	CTCC (n = 43)	RTCC (n = 21)	t/Z/χ2	*P*-value
Demographics	51.05 ± 9.41	48.05 ± 9.67	1.19	0.240
Age (mean ± SD)	0 (0.00)	1 (4.76)	-	0.328#
Sexual history, n%	43 (100)	20 (95.24)	-	0.328#
no	0 (0.00)	1 (4.76)		
yes	43 (100)	20 (95.24)		
Marital history, n%				
un-married				
married				
Ultrasonography				
Tumor size (mean ± SD)				
Craniocaudal (mm)	39.58 ± 12.94	31.62 ± 14.06	2.25	0.028
Anteroposterior (mm)	29.35 ± 10.90	23.05 ± 10.96	2.17	0.034
Laterolateral (mm)	29.70 ± 9.61	24.00 ± 11.03	2.12	0.038
Volume (cm^3), median (IQR)	17.89 (9.96, 34.14)	10.61(1.77, 19.56)	-2.17	0.030*
Echogenicity, n%			-	< 0.001#
Hypoechoic	32 (74.42)	5 (23.81)		
Hyperechoic	2 (4.65)	0 (0.00)		
Isoechoic	3 (6.98)	13 (61.90)		
Mixed echoic	6 (13.95)	3 (14.29)		
Hysterocele, n (%)			-	0.673#

Abbreviations: CTCC, common type cervical cancer; RTCC, rate type cervical cancer. Data presented as mean ± SD or n%. ⁎Echogenicity compared with surrounding cervical tissue. ※Color score is a subjective estimation of the vascularity within the tumor. - without value; *Mann-Whitney U test (rank sum test of non-normal distribution data); #Two-tailed Fisher's exact test (expected frequency < 1, accurate probability method); Other unmarked variables adopt Student's t test or chi-square tests.

	CTCC (n = 43)	RTCC (n = 21)	t/Z/χ2	*P*-value
no	35 (81.39)	16 (76.19)	-	0.514#
yes	7 (16.28)	5 (23.81)		
Pregnancy	1 (2.33)	0 (0.00)		
Color score※	2 (4.65)	5 (23.81)		
1	6 (13.95)	3 (14.29)		
2	12 (27.90)	4 (19.05)		
3	23 (53.50)	9 (42.85)		
4				
Grade, n (%)	7 (16.28)	6 (28.57)	-	0.507#
Poorly differentiated	26 (60.47)	11 (52.38)	6.67	0.010
Moderately differentiated	10 (23.26)	4 (19.05)	9.1	0.003
Well differentiated	14 (32.56)	14 (66.67)		
Growth pattern, n (%)	29 (67.44)	7 (33.33)		
Endophytic	7 (16.28)	11 (52.38)		
Exophytic	36 (83.72)	10 (47.62)		
HPV infection, n (%)				
no				
yes				

Abbreviations: CTCC, common type cervical cancer; RTCC, rate type cervical cancer. Data presented as mean ± SD or n%. ⁎Echogenicity compared with surrounding cervical tissue. ※Color score is a subjective estimation of the vascularity within the tumor. - without value; *Mann-Whitney U test (rank sum test of non-normal distribution data); #Two-tailed Fisher's exact test (expected frequency < 1, accurate probability method); Other unmarked variables adopt Student's t test or chi-square tests.

The results of pathology showed that lesions were limited to the cervix in 31 cases and had infiltrated adjacent local tissues in 33 cases; local lymph node metastases occurred in seven cases (16.28%, 7/43) of CTCC and three cases (14.29%, 3/21) of RTCC; intravascular cancer thrombus were found in five cases of CTCC (CSCC) and two cases of RTCC (SCCC). Analysis of weighted kappa showed that the consistency between ultrasonography and pathology staging diagnosis of CTCC was good (Weighted Kappa (95% confidence interval [CI]) = 0.80); The consistency between ultrasonography and pathology staging diagnosis of RTCC was very good (Weighted Kappa (95%CI) = 0.87, Table 2).

Table 2
The staging consistency of ultrasonography and pathology in RTCC.

US	pathology									
	Tis	T1b1	T1b2	T2a1	T2a2	T2b	T3a	T3b	T4	total
Tis	0	0	0	0	0	0	0	0	0	0
T1b1	0	11	0	0	0	0	0	0	0	11
T1b2	0	0	3	0	0	0	0	0	0	3
T2a1	0	0	0	2	0	0	0	0	0	2
T2a2	0	0	0	0	2	0	0	0	0	2
T2b	0	0	0	0	0	1	0	0	0	1
T3a	0	0	0	0	0	0	0	0	0	0
T3b	0	0	0	0	0	0	0	0	0	0
T4	0	0	0	1	0	0	0	0	1	2
total	0	11	3	3	2	1	0	0	1	21

Note: Weighted Kappa (95%CI) = 0.87(range: 0.65-1.00). For the convenience of statistics, T2a2N1 was marked T2a2; T2bN2 was marked T2b; T3aN1 was marked T3a; T3bN1 was marked T3b.

Abbreviations: RTCC, rate type cervical cancer; CI: confidence interval

Discussion

In this study, 63 married patients underwent transvaginal ultrasonography (TV US), one unmarried patient underwent transabdominal ultrasonography (TA US). Two-dimensional US showed an enlarged cervix, hypoechoic in most of CTCC and isoechoic in most of RTCC compared to adjacent normal cervical tissue, and CDUS showed abundant color flow signals in the lesions. Finally, 64 cases of cervical cancer were diagnosed through biopsy; the sensitivity and positive predictive value of ultrasound diagnosis was 95.31% (61/64) and 93.85% (61/65), respectively. The demographic characteristics (including age, sexual history, marital history) and tumor grade were not significantly different between RTCC and CTCC.

A recent study[19] has shown that cervical cancer lesions are mostly hypoechoic; while isoechoic, hyperechoic and mixed echoic lesions are rare. In this study, total hypoechoic lesions accounted for 57.81% of the cases, lower than that reported in previous studies. However, in CTCC, hypoechoic lesions accounted for 74.51%, of the cases, which is consistent with previous studies; whereas in RTCC, the

lesions were hypoechoic only in five cases (23.81%), with 13 cases (61.90%) showing isoechoic lesions, which is consistent with the study of Epstein.[20] Furthermore, the echo of lesions was significantly different between the two groups; three of 13 cases with isoechoic lesions in RTCC were missed diagnosis by US, but CDUS showed slightly abundant color flow signals in these lesions, which showed that CDUS is helpful to diagnose RTCC. In addition, there were significant differences in the mean craniocaudal diameter, anteroposterior diameter, transverse diameter, and volume of cervical cancer between the two groups. Therefore, tumor size and the echo of lesions can be used to discover RTCC.

Uterine effusion is often caused by the accumulation of fluid secreted in the uterine cavity and the obstruction of the cervical canal by the lesion. In this study, five cases (23.81%) of RTCC had intrauterine effusion, while seven cases (16.28%) with uterine effusion were found in CTCC; however, there was no significant difference between the two groups. Therefore, uterine effusion cannot be used to differentiate RTCC from CTCC. In contrast, exophytic in CTCC and endophytic in RTCC accounted for 67.44% and 66.67%, respectively, the difference was significant between the two groups, which showed that RTCC often diffusely infiltrates the cervical stroma.[11]

Malignant tumors have the ability to metastasize distantly and infiltrate locally. Similarly, cervical cancer can infiltrate adjacent tissues or metastasize distantly after developing over time, and a large amount of neovascularization occurs in the involved tissues to promote tumor growth or ischemic necrosis of the tumor tissues. In this study, Color Doppler flow signals were found in all cases, as compared with normal cervical tissue in which virtually no detectable vascularization was found. Using these blood flow characteristics, we were able to use US to diagnose 27 cases of stage T1b1, seven of stage T1b2, five of stage T2a1, 13 of stage T2a2, three of stage T2b, one of stage T3a, and eight of stage T4. The consistency between preoperative US and TNM staging was 80% in CTCC and 87% in RTCC, which was higher than that shown in Byun et al. (62.5%), but the same as that demonstrated by Ghi et al. (85.71%).[21,22] The deviation between these may be caused by local infection as a result of prolonged vaginal bleeding in patients with cervical cancer.

Cervical biopsy is the gold standard for the diagnosis of cervical cancer; however, ultrasonography is helpful for targeted cervical biopsy, especially for early diagnosis of RTCC. Although MRI has a high soft-tissue resolution and can be used for preoperative staging, it is contraindicated in certain circumstances: if metal parts are present in the body; in the presence of a pacemaker; or cochlear implants.[16,18] With improvements in the resolution achieved by ultrasonic instruments and the accumulated experience of doctors, US can be used to observe whether the cervical line is interrupted or the cervical intima is thickened. Moreover, US is an economical and non-invasive technique that patients willingly accept, which has resulted in US becoming the preferred method for early diagnosis of cervical cancer. Specifically, TV US is a superior method for showing the detected site and the degree of infiltration in the adjacent tissues. Furthermore, TV US is superior to MRI in determining the scope of surgery, whether radiotherapy and chemotherapy are needed before surgery, as well as the size of the radiation field.[17] However, ultrasonography has its limitations as it can only discover invasive cervical cancer. Pap smear

is normally used for primary prevention to detect preinvasive lesions, however since recently it has been replaced by HPV test in many diagnostic procedures.[14] Despite all these, the primary prevention of cancer, including HPV vaccines, were not 100% effective. In this study, 36 cases (83.72%) in CTCC had HPV infection, while 10 cases (47.62%) in RTCC had HPV infection, which showed that HPV vaccines were effective only for some RTCC cases.

CCCC is a rare type of adenocarcinoma; however, its incidence is increasing among young women, accounting for 4–9% of cervical adenocarcinoma.[23] Spörri et al. believe that CCCC is related to genitourinary malformation and endometriosis of the cervix.[24,25] Herbst[26] discovered that the peak age of CCCC is about 20 years. However, Thomas et al. found that the median age of onset for CCCC is 53 years.[27] In this study, a 23-year-old unmarried celibate woman presented with irregular but severe vaginal bleeding 3 years ago, leading to anemia. She was misdiagnosed with anovulatory dysfunctional uterine bleeding and treated wrongly for this condition in a local hospital. After being transferred to our hospital, TA US showed an enlarged and hypoechoic cervix; she was suspected to have cervical cancer and underwent cervical biopsy. Finally, according to microscopic morphological characteristics and positive immunohistochemical staining for Napsin A, HNF-1B, CK7, PAX, and P53, she was diagnosed with CCCC. She received preoperative paclitaxel combined with cisplatin chemotherapy, followed by radical laparoscopic hysterectomy + bilateral salpingoovariectomy + pelvic lymphadenectomy + paraaortic lymph node biopsy. Postoperative pathological report showed no cancer infiltration in other adjacent tissues and no metastasis in lymph nodes except left parauterine infiltration. No recurrence was found after 37 months. Therefore, pelvic US should be performed carefully when abnormal vaginal bleeding cannot be explained and treated in adolescent patients.

SCCC is a rare and highly malignant neuroendocrine neoplasm with rapid growth, a high recurrence rate, and poor prognosis, accounting for 1–3% of cervical cancer cases that occur either in celibate or sexually active women.[28–30] In this study, four cases had SCCC, one of them with enlarged cervix and hypoechoic lesion was suspected by US; the other three with normal size cervix and isoechoic lesions were missed diagnosis by US, but had clinical symptoms, and they all underwent cervical biopsy. Finally, according to microscopic morphological characteristics and positive immunohistochemical staining for Syn, chromogranin A (CgA), neuron-specific enolase (NSE), Ki-67, carcinoembryonic antigen (CEA), and P16, these patients were diagnosed with SCCC and received preoperative paclitaxel combined with cisplatin chemotherapy, followed by radical laparoscopic hysterectomy + bilateral adnexectomy + pelvic lymphadenectomy. Postoperative pathological report of one case showed that the lesion infiltrated the whole wall of the cervix, and cancer could be seen on the serosal surface; metastases were also seen in the internal iliac and obturator lymph nodes, and intravascular cancer thrombus was found. In 6 months, multiple metastases to the liver and other organs occurred. The patient died 8 months after the surgery. Therefore, patients with RTCC had a worse prognosis than those with CTCC. Postoperative pathological report of one case demonstrated that the lesion infiltrated the deep fibromuscular layer of the cervical wall, and tumor thrombus could be seen in the vein. Postoperative pathological report of the other case

showed no cancer infiltration in other adjacent tissues and no metastasis in lymph nodes except parauterine infiltration. At present, these patients undergo follow-up over 5 months after surgery.

Our study had some limitations. All patients were treated at our hospital; therefore, selection bias and errors in the analysis may have distorted our results. Thus, it is necessary to accumulate more cases from multiple centers and perform a multi-factor comprehensive analysis.

Conclusion

In conclusion, in RTCC, most of the lesions were isoechoic, tumor size was smaller, the growth pattern was endophytic, most of these patients often had negative pap smear and low HPV infection, so pap smear and HPV vaccines play smaller role in the primary prevention of RTCC, most of these patients were easily missed diagnosis and had bad prognosis. Therefore, we know these ultrasonographic features and use them to diagnose RTCC as early as possible so as to treat early and improve prognosis.

List Of Abbreviations

US: Ultrasonography; MRI: Magnetic resonance imaging; CT: Computed tomography; CDUS: Color Doppler ultrasonography; TV US: Transvaginal ultrasonography; TA US: Transabdominal ultrasonography; CTCC: Common-type cervical cancer; RTCC: Rare-type cervical cancer; CSCC: Cervical squamous cell carcinoma; CCCC: Clear-cell carcinoma of the cervix; SCCC: Small-cell carcinoma of the cervix; HE: Haematoxylin and eosin; CgA: Chromogranin A; NSE: Neuron-specific enolase; CEA: Carcinoembryonic antigen; HNF: Hepatocyte nuclear factor; Syn, synaptophysin

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Review Board of Guangzhou Women and Children's Medical Center (54.4 25; January 6, 2014). All patients provided and wrote informed consent for US assessment, and in turn underwent clinical examination, HPV inspection, and cervical biopsy after ultrasound and before treatment.

Consent for publication: All authors consented for publication

Availability of data and material: Data and material can be seen in addition 1.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by funding from Guangzhou Institute of Pediatrics/Guangzhou Women and Children's Medical Center (NO: GCP-2019-005).

The funder was the first author and corresponding author in this study.

Authors' contributions: Jl L, Xp G and Xf L were involved in ultrasonographic diagnosis of all cases with cervical cancer, and analyzed and interpreted the data regarding cervical cancer. Hy W performed clinical diagnosis and treatment on the patients with cervical cancer, and analyzed and interpreted the data. Cm G was involved in pathological diagnosis of all cases with cervical cancer, and analyzed and interpreted the data regarding cervical cancer. Hq Zh was responsible for analyzing the data. All authors contributed to the preparation of the manuscript and approve of the final version of the paper to be submitted. Each author can respond to any questions in regard to this study in their area of expertise.

Acknowledgements

We would like to thank our image section director, Liao Can, for supporting all aspects of the study (ethics, consent, data handling and storage, and all other aspects of Good Research Practice). Thank Guangzhou Institute of Pediatrics/Guangzhou Women and Children's Medical Center for providing the fund, a total of 140 000 yuan, 80 000 yuan was used in the design of the study and collection, analysis, and interpretation of data, and 60 000 yuan was used in writing the manuscript. The authors declare that they have no competing interests.

References

1. Lei J, Andrae B, Ploner A, et al. Cervical screening and risk of adenosquamous and rare histological types of invasive cervical carcinoma: population based nested case-control study. BMJ 2019; 365:i1207. https://doi.org/10.1136/bmj.l1207.
2. Zhang D, Ma X. Prognostic factors and outcomes of early-stage small cell neuroendocrine carcinoma of the cervix: 37 cases from a single center. PeerJ 2019;7:e6868. https://doi.org/10.7717/peerj.6868.
3. Lin AJ, Hassanzadeh C, Markovina S, Schwarz J, Grigsby P. Brachytherapy and survival in small cell cancer of the cervix and uterus. Brachytherapy 2019;18:163-170. https://doi.org/10.1016/j.brachy.2018.11.006.
4. Groszmann Y, Benacerraf BR. Sonographic features of primary lymphoma of the uterine cervix. J. Ultrasound. Med 2013;32:717-718. https://doi.org/10.7863/jum.2013.32.4.717.
5. Park M, Han SS, Lee EJ, et al. Primary cervical choriocarcinoma during viable intrauterine pregnancy, J. Obstet. Gynaecol. Res 2015; 41:1291-1294. https://doi.org/10.1111/jog.12715.
6. Kimyon Comert G, Turkmen O, Karalok A, Basaran D, Bulbul D, Turan T. Therapy modalities, prognostic factors, and outcome of the primary cervical carcinosarcoma: Meta-analysis of extremely rare tumor of cervix. Int. J. Gynecol. Cancer 2017;27:1957-1969. https://doi.org/10.1097/IGC.0000000000001086.
7. Mainguene C, Hugol D, Caulet S, et al. Botryoid rhabdomyosarcoma of the cervix. Clinico-pathologic study of a case, Ann. Pathol 1993;13:40-44.
8. Sun H, Chen Y, Chen Y, et al. Primary malignant melanoma of the cervix: 14 cases and literature overview. Melanoma Res 2018;28:578-585. https:doi.org/10.1097/CMR.0000000000000469.

9. Hashimoto H, Horibe YU, Ezaki J, et al. Laparoscopically removed streak gonad revealed gonadoblastoma in Frasier syndrome. Anticancer Res 2017;37:3975-3979. https://doi.org/10.21873/anticanres.11782.
10. Sangiorgio V, Zanagnolo V, Aletti G, et al. Fibroblastic malignant peripheral nerve sheath tumour of the uterine cervix: Report of a case and literature review with emphasis on possible differential diagnosis. Int. J. Gynecol. Pathol 2018;37:497-503. https://doi.org/10.1097/PGP.0000000000000453.
11. Intaraphet S, Kasatpibal N, Siriaunkgul S, Chandacham A, Sukpan K, Patumanond J. Prognostic factors for small cell neuroendocrine carcinoma of the uterine cervix: An institutional experience. Int. J. Gynecol. Cancer 2014;24:272-279. https://doi.org/10.1097/IGC.0000000000000059.
12. Zhao XL, Xu XQ, Duan XZ, Basu P, et al. Comparative performance evaluation of different HPV tests and triaging strategies using self-samples and feasibility assessment of thermal ablation in 'colposcopy and treat' approach: a population-based study in rural China. J. Cancer 2020;Jan 22. https://doi.org/10.1002/ijc.32881.
13. Ponti A, Basu P, Ritchie D, Segnan N, et al. Key issues that need to be considered while screening. Int. J. Cancer 2020;Jan 22. https://doi.org/10.1002/ijc.32885.
14. Arbyn M, Weiderpass E, Bruni L, Bray F, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020;8(2):191-203. https://doi.org/10.1016/S2214-109X(19)30482-6.
15. Näsman A,Du J,Dalianis T, A global epidemic increase of an HPV-induced tonsiland tongue base cancer - potential benefit from a pan-gender use of HPV vaccine. J Intern Med 2020;287(2):134-152. DOI: 10.1111/joim.13010
16. Fischerova D, Cibula D. Ultrasound in gynecological cancer: is it time for re-evaluation of its uses? Curr. Oncol. Rep 2015;17(6):28. https://doi.org/10.1007/s11912-015-0449-x.
17. Testa AC, Ludovisi M, Manfredi R, et al. Transvaginal ultrasonography and magnetic resonance imaging for assessment of presence, size and extent of invasive cervical cancer. Ultrasound Obstet. Gynecol 2009;34:335-344. https://doi.org/10.1002/uog.7325.
18. Pinkavova I, Fischerova D, Zikan M, et al. Transrectal ultrasound and magnetic resonance imaging in the evaluation of tumor size following neoadjuvant chemotherapy for locally advanced cervical cancer.Ultrasound Obstet. Gynecol 2013;42:705-712. https://doi.org/10.1002/uog.12455.
19. Xu Y, Ru T, Zhu L, et al. Ultrasonic histogram assessment of early response to concurrent chemo-radiotherapy in patients with locally advanced cervical cancer: A feasibility study. Clin. Imaging 2018;49:144-149. https://doi.org/10.1016/j.clinimag.2018.01.002.
20. Epstein E, Di Legge A, Måsbäck A, Testa, AC, et al. Sonographic characteristics of squamous cell cancer and adenocarcinoma of the uterine cervix. Ultrasound Obstet Gynecol 2010;36(4):512-516. https://doi.org/10.1002/uog.7638

21. Byun JM, Kim YM, Jeong DH, Kim KT, Sung MS, Lee KB, Three-dimensional transvaginal ultrasonography for locally advanced cervical cancer. Int. J. Gynecol. Cancer 2013;23:1459-1464. https://doi.org/10.1097/IGC.0b013e3182a16997.
22. Ghi T, Giunchi S, Kuleva M, et al. Three-dimensional transvaginal sonography in locally staging of cervical carcinoma: Description of a novel technique and preliminary results. Ultrasound Obstet. Gynecol 2007;30:778-782. https://doi.org/10.1002/uog.5147.
23. Reich O, Tamussino K, Lahousen M, Pickel H, Haas J, Winter R. Clear cell carcinoma of the uterine cervix: pathology and prognosis in surgically treated stage IB-IIB disease in women not exposed in utero to diethylstilbestrol. Gynecol. Oncol 2000;76:331-335. https://doi.org/10.1006/gyno.1999.5700.
24. Spörri S, Altermatt HJ, Dreher E, Hänggi W. Clear cell adenocarcinoma of the cervix associated with a rare genitourinary malformation. Obstet. Gynecol 2000;96:834-836.
25. Hashiguchi M, Kai K, Nishiyama S, Nakao Y, Yokoyama M, Aishima S. Clear cell carcinoma of the uterine cervix presented as submucosal tumor arising in a background of cervical endometriosis. Int. J. Gynecol. Pathol 2018;37:88-92. https://doi.org/10.1097/PGP.0000000000000386.
26. Herbst AL. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). Gynecol. Oncol 2000;76:147-156. https://doi.org/10.1006/gyno.1999.5471.
27. Thomas MB, Wright JD, Leiser AL, et al. Clear cell carcinoma of the cervix: A multi-institutional review in the post-DES era, Gynecol. Oncol 2008;109:335-339. https://doi.org/10.1016/j.ygyno.2008.02.007.
28. Singh S, Redline R, Resnick KE. Fertility-sparing management of a stage IB1 small cell neuroendocrine cervical carcinoma with radical abdominal trachelectomy and adjuvant chemotherapy. Gynecol. Oncol. Rep 2015;13:5-7. https://doi.org/10.1016/j.gore.2015.04.004.
29. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: Treatment and survival outcomes of 188 patients. Am. J. Obstet. Gynecol 2010;203(4):347.e1-6. https://doi.org/10.1016/j.ajog.2010.04.019.
30. Liao LM, Zhang X, Ren YF, et al. Chromogranin A (CgA) as poor prognostic factor in patients with small cell carcinoma of the cervix: Results of a retrospective study of 293 patients. PLoS ONE 2012; 7:e33674. https://doi.org/10.1371/journal.pone.0033674.

Figures

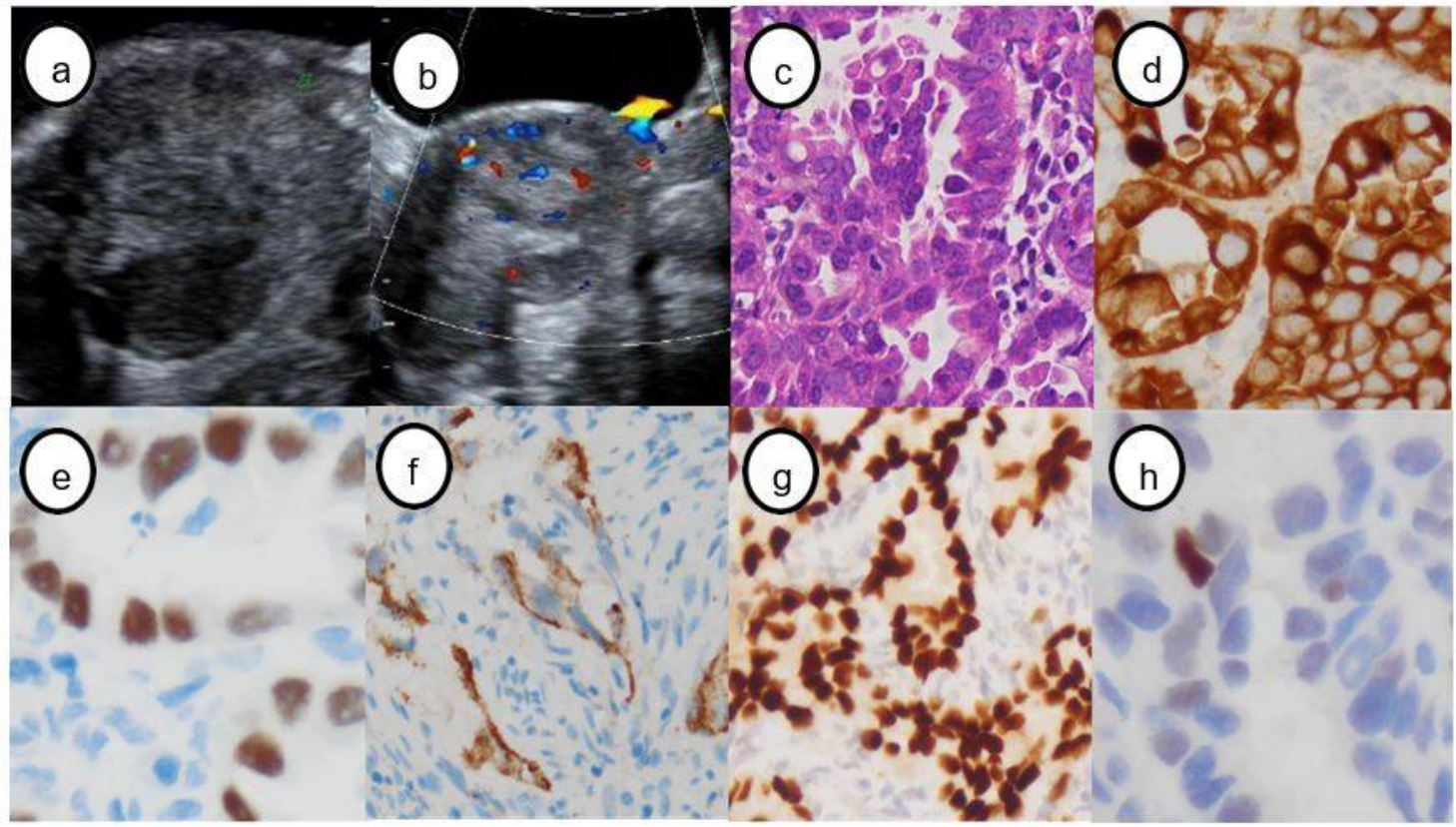

Figure 1

Ultrasonographic features and immunohistochemical staining of primary CCCC in an unmarried celibate woman. (a) Two-dimensional ultrasonography showing a hypoechoic cervical lesion. (b) Colour Doppler ultrasonography showing significant short rod blood flow signals in the lesion. (c) Pathological features of CCCC (HE, ×20). (d) CK7 was positive in CCCC (×20). (e) HNF was positive in CCCC (×20). (f) Napsin A was positive in CCCC (×20). (g) PAX was positive in CCCC (×10). (h) P53 was positive in CCCC (×20). Abbreviations: CCCC, clear-cell carcinoma of the cervix; HE, haematoxylin and eosin; HNF, hepatocyte nuclear factor

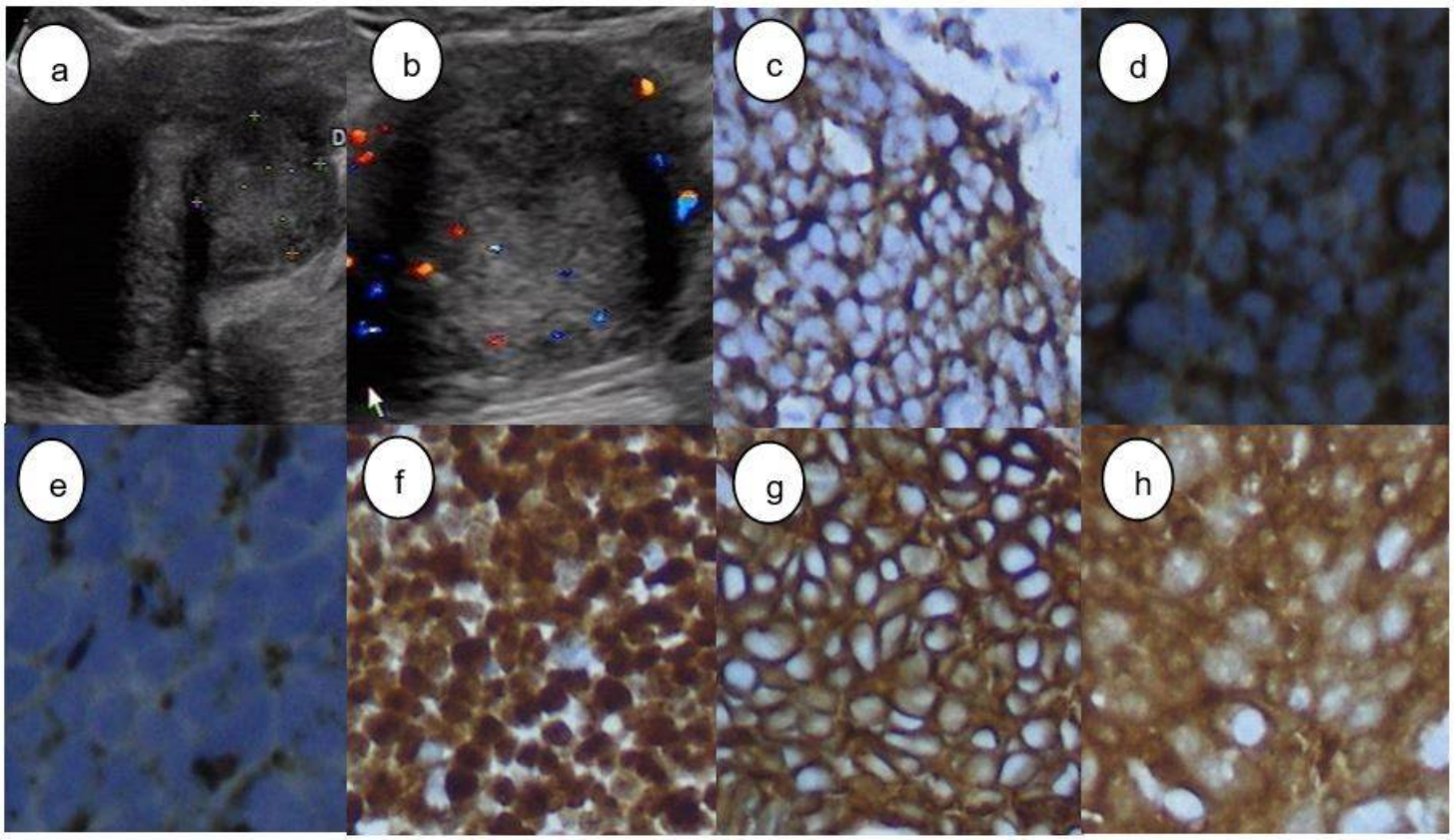

Figure 2

Ultrasonographic features and immunohistochemical staining of primary SCCC in a sexually active married woman. (a) Two-dimensional ultrasonography showing an isoechoic cervical lesion. (b) Colour Doppler ultrasonography showing significant strip blood flow signals in the lesion. (c) Syn was positive in SCCC (×20). (d) NSE was positive in SCCC (×40). (e) CGA was positive in SCCC (×40). (f) Ki-67 was positive in SCCC (×20). (g) CEA was positive in SCCC (×20). (h) P16 was positive in SCCC (×20). Abbreviations: SCCC, small-cell carcinoma of the cervix; NSE, neuron-specific enolase; CGA, chromogranin A; CEA, carcinoembryonic antigen; Syn, synaptophysin

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- cervicalcancersdata.xlsx