BIO Integration

Preliminary Investigation into Ultrasound and MRI Presentation of Large-Cell Neuroendocrine Carcinomas of the Uterine Cervix

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Abstract

Objective: The aim of this study was to analyze the ultrasound and MRI features of eight patients with cervical large-cell neuroendocrine carcinoma to improve awareness of this disease among sonographers, radiologists, and clinicians.
Methods: Clinical data for eight patients with cervical large-cell neuroendocrine carcinoma confirmed by pathology at Sun Yat-sen Memorial Hospital of Sun Yat-sen University between February 2018 and April 2021 were retrospectively analyzed according to clinical, conventional ultrasound, contrast-enhanced ultrasound, and MRI characteristics.
Results: Conventional ultrasound examination of the cervical large-cell neuroendocrine carcinoma lesions in the eight patients revealed two features: (1) irregular hypoechoic areas in the muscular layer, with slightly hyperechoic inlay streaks, and poorly delineated lesions, and (2) slightly abundant blood flow distribution in the lesions. The contrast-enhanced ultrasound showed a "fast-in and fast-out" mode; after subsidence, a "fence-like" change was observed, and the enhancement range was significantly greater than the range of two-dimensional ultrasound. In MRI, T1WI showed a low signal or isosignal; T2WI showed a high signal; DWI showed a high signal and low ADC value; and most of the enhanced MRI showed inhomogeneous hyperenhancement.
Conclusion: Conventional ultrasound, contrast-enhanced ultrasound and MRI are complementary methods that provide additional imaging information for the diagnosis of cervical large-cell neuroendocrine carcinoma.

Keywords

Cervical large celllarge-cell neuroendocrine carcinoma, contrast-enhanced ultrasonography, MRI, ultrasonography.

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Introduction

Cervical neuroendocrine carcinoma is a rare epithelial tumor type accounting for approximately 1.4% of all cervical malignancies [1]. Histologically, cervical neuroendocrine carcinoma has been divided primarily into carcinoids, atypical carcinoids, small-cell neuroendocrine carcinoma, and large-cell neuroendocrine carcinoma (LCNEC) [2]. Among these, LCNEC is the second most common, accounting for approximately 12% of cases. LCNEC has a higher degree of malignancy and a poorer prognosis than the most common cervical cancer, squamous cell carcinoma and adenocarcinoma [3]. Because of the low incidence of LCNEC, few cases have been reported. Moreover, although ultrasonography findings have been described [4], no summary of ultrasound two-dimensional features or ultrasound-enhanced imaging has been reported. The purpose of this study was to retrospectively analyze the clinical features, ultrasound images, and MRI features of eight cases of LCNEC in our hospital, to provide useful reference information for clinical diagnosis and treatment.

Methods

Between February 2018 and September 2022, we identified eight cases of cervical LCNEC diagnosed pathologically in our hospital. In this study, the clinical features—including patient age, clinical symptoms, clinical stage, lymph node metastasis, immunohistochemistry, ultrasound, and MRI imaging features—were retrospectively examined. The International Federation of Gynecology and Obstetrics staging from 2018 was used for tumor staging [5]. Pathological diagnosis was performed with the WHO classification of female genital tumors, fifth edition [6].

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The ethics committees of Sun Yat Sen Memorial Hospital and Sun Yat-sen University approved this retrospective study.

In this study, all eight patients underwent routine ultra sound examinations, and two received Contrast-enhanced ultrasound (CEUS). A GE LOGIQ E8 ultrasound with a RIC5-9-D volume probe (5–9 MHz) was used. The probe was placed in the vaginal fornix in a truncated bladder position, and a multi-sectional scan was performed close to the cervix to record routine ultrasound parameters. The best ultrasonographic view is to select the largest section of the lesion, while preserving the surrounding normal myometrium as a reference. The contrast medium was Sono Vue (Bracco, Italy). 5 ml of saline was used to dissolve the dry contrast powder, shaken and mixed, and 2.4 ml was withdrawn and injected through the elbow vein, initiating the contrast-enhanced ultrasound imaging mode and continuous observing for 5 min. The ultrasound images were dynamically stored for analysis of areas of interest.

Results

Patient information

The ages of the eight patients with cervical LCNEC ranged from 32 to 69 years, and the average age was 49.5±14.5 years. The pathology was simple in five patients and mixed (with adenocarcinoma, squamous cell carcinoma, or small-cell neuroendocrine carcinoma) in three patients. The main symptoms were contact bleeding (three cases), postmenopausal vaginal bleeding and discharge (two cases), and irregular vaginal bleeding (three cases).

Clinical stages and lymph node metastasis

Among the eight patients with cervical LCNEC, three were in stage IB2 (37.5%), one was in stage IIA2 (12.5%), three were in stage IIIC1 (37.5%), and one was in stage IV (12.5%). Four patients with cervical LCNEC (three with stage IIIC1 disease and one with stage IV disease) had pelvic lymph node metastasis, all located in the inguinal region, and the lymph node metastasis rate was as high as 50%. Among them, one patient with stage IV LCNEC also had para-aortic lymph node metastasis. MRI suggested suspicion for pelvic lymph node metastases in two cases, in agreement with the pathology results; two cases did not have suspicion of pelvic lymph nodes; and one case had suspicion of pelvic lymph nodes and was not consistent with the pathology findings. Only one case of suspicious pelvic lymph nodes was identified by conventional ultrasound and was consistent with the pathology findings.

Immunohistochemistry

All eight patients were positive for p16 and chromogranin A (CGA), 75% (6/8) were positive for neuron-specific enolase (NSE), 75% (6/8) were positive for synaptophysin (SYN), and 37.5% (3/8) were positive for CD56 (**Table 1**).

Ultrasound and MRI features

We used ultrasound and MRI to describe and compare the lesions in detail (**Tables 2** and **3**). In the eight patients with LCNEC, the conventional ultrasound lesions showed irregular hypoechoic areas within the muscular layer, a mosaic of slightly hyperechoic strips, and poorly defined lesions; the lesions were slightly rich in blood flow distribution. CEUS showed a “fast-in-fast-out” pattern and “fence-like” changes after fading; T1 WI showed a low signal or isosignal; T2WI showed a high signal; DWI showed a high signal; and the ADC value was low. Most enhanced MRI showed heterogeneous hyperenhancement.

Table 1 Clinical Data for Eight Patients with Cervical LCNEC

No.	Age	2018 FIGO Cervical Cancer Staging	Symptoms	Lymph Node Metastasis	Main Positive Immunohistochemical Markers	Surgical Lesion Size (mm)
1	33	IB2	Contact bleeding	–	P16, CGA, SYN, NSE, CD56	30×30×27
2	32	IB2	Irregular vaginal bleeding	–	P16, CGA, SYN, NSE	25×20×11
3	42	IB2	Contact bleeding	–	P16, CGA, SYN, NSE	20×17×12
4	69	IIA2	Irregular vaginal bleeding	–	P16, CGA	55×50×33
5	45	IIIC1	Contact bleeding	+	P16, CGA, SYN, NSE, CD56	38×28×8
6	67	IIIC1	Postmenopausal vaginal discharge with a small amount of bleeding	+	P16, CGA, SYN, NSE, CD56	40×33×17
7	61	IIIC1	Vaginal bleeding after menopause	+	P16, CGA, NSE	100×70×27
8	47	IV	Irregular vaginal bleeding	+/*	P16, CGA, SYN	–

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; P16: immunohistochemical factor P16; CGA: chromogranin A; SYN: synaptophysin; NSE: neuron-specific enolase; CD56: immunohistochemical factor CD56.
Note: pelvic lymph node metastasis: “–“ indicates no lymph node metastasis; “+” indicates lymph node metastasis; and “*” indicates para-aortic lymph node metastasis.

Table 2 Features of Conventional Ultrasound Imaging in Eight Patients with LCNEC

No.	Shape	Internal Echo	Echo Distribution	Lesion Border	Relationship with Cervical Serosa	Relationship with Cervical Mucosa	Intralesional Adler Flow Classification	Ultrasound Lesion Size (mm)
1	+	–	+	+	–	NS	I	28×24×15
2	+	–	+	+	–	NS	I	36×36×29
3	+	–	+	+	–	NS	I	24×15×13
4	+	–	+	+	–	NS	I	90×57×49
5	+	–	+	+	–	NS	I	28×21×9
6	+	–	+	+	–	NS	II	44×37×27
7	+	–	+	+	–	NS	I	38×33×32
8	+	–	+	+	–	NS	II	47×35×18

Note: Shape: "–" indicates regular shape; "+" indicates irregular shape.
Internal echo: "–" indicates low internal echo; "+" indicates high internal echo.
Echo distribution: "–" indicates uniform internal echo; "+" indicates unevenly distributed internal echo of the lesion, some with cord-like hyperechoic structures.
Lesion boundary: "–" indicates clear boundary; "+" indicates unclear boundary.
Relationship with cervical serosa: "–" indicates clear; "+" indicates unclear.
Relationship with cervical mucosa: "NS" indicates uncertain.
Alder blood flow classification: grade 0, no blood flow/insignificant blood flow; grade I, small amount of blood flow/inadequate and sparse blood flow; grade II, moderate blood flow (one main blood vessel or several small blood vessels can be seen inside); grade III, rich blood flow (more than four blood vessels seen inside).
Contrast-enhanced ultrasound of two cases showed lesions enhanced in a "fast-in, fast-out" fashion, with "fenestrated" changes after fading. The degree of enhancement was close to that of the myometrium of the cervix. The extent of enhancement was greater than that in the two-dimensional ultrasound image, and the boundary with the myometrial tissue was unclear, as was the boundary with the cervical mucosa in some cases.

Table 3 MRI Imaging Features of Eight Patients with LCNEC

No.	T1 WI	T2 WI	ADC (mm^2/s)	DWI	Enhanced MRI	Lesion Border	Relationship with Cervical Serosa	Relationship with Cervical Mucosa	MRI Lesion Size (mm)
1	Low	High	0.783	High	Uneven reinforcement	+	–	+	33×31×30
2	Low	High	0.653	High	Uneven reinforcement	+	–	+	30×27×17
3	Equal	High	0.857	High	Uneven reinforcement	+	–	+	55×36×31
4	Low	High	0.352	High	Uneven reinforcement	+	–	+	67×60×35
5	Low	High	0.448	High	Even reinforcement	+	–	–	37×28×8
6	Low	High	0.352	High	Uneven reinforcement	+	–	+	49×42×37
7	Low	High	0.552	High	Uneven reinforcement	+	–	+	89×67×30
8	Equal	High	0.932	High	Uneven reinforcement	+	–	+	59×54×40

Abbreviations: MRI: magnetic resonance imaging; T1WI: T1-weighted imaging; T2WI: T2-weighted imaging; ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; MRI enhanced: contrast-enhanced MRI.
Lesion boundary: "–" indicates clear boundary; "+" indicates unclear boundary.
Relationship with cervical serosa: "–" indicates clear; "+" indicates unclear.
Relationship with cervical mucosa: "NS" indicates unclear.

Discussion

Cervical neuroendocrine carcinoma is an extremely rare pathological type of cervical malignancy, of which cervical LCNEC, a high-grade neuroendocrine carcinoma, is the second most common subtype [1, 3, 7]. The prognosis of cervical LCNEC is significantly poorer than that of cervical squamous cell carcinoma and adenocarcinoma, and the median overall survival time for LCNEC is less than 20 months [8]. The reason for this poor prognosis is the early occurrence of vascular and lymphatic metastases and rapid progression.

In this study, eight patients with LCNEC were analyzed, all of whom presented with irregular vaginal bleeding/fluid or contact bleeding, in agreement with reported findings that LCNEC extensively infiltrates the mucosal epithelium [9]. A medical study has indicated that CGA is a specific marker for LCNEC, whereas most cervical high-grade neuroendocrine carcinomas are diffusely positive for p16 [3]. Our findings were consistent with these reports, showing 100% positivity for both CGA and p16.

In the past, MRI was the most commonly used examination method for cervical LCNEC. For tumors confined to the cervix and larger than 10 mm, pelvic MRI is the preferred imaging method for evaluating tumor size and local invasion [10]. In the eight patients with LCNEC in this study, the lesion sizes all exceeded 10 mm. Compared with the extent of lesions in postoperative pathology specimens, conventional ultrasound measured a significantly smaller range, and the size of some lesions on MRI was similar to the extent of lesions in postoperative pathology specimens. In two cases, we attempted contrast-enhanced ultrasound, which indicated a significantly

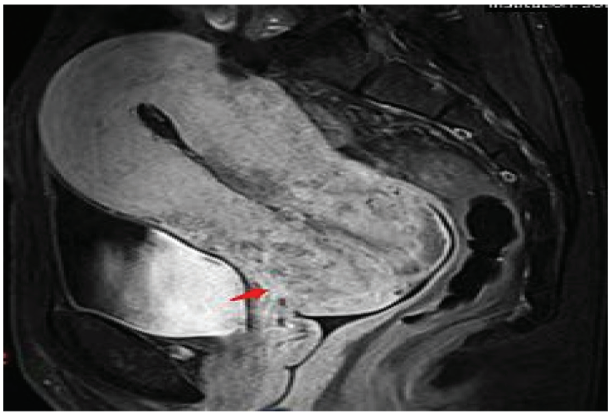

Figure 1 MRI showing cervical LCNEC. Female patient, 47 years of age, with T1WI compression lipid enhancement scan showing an enlarged cervix, markedly heterogeneous enhancement of intracervical lesions with unclear borders, and interrupted endocervical continuity after enhancement.

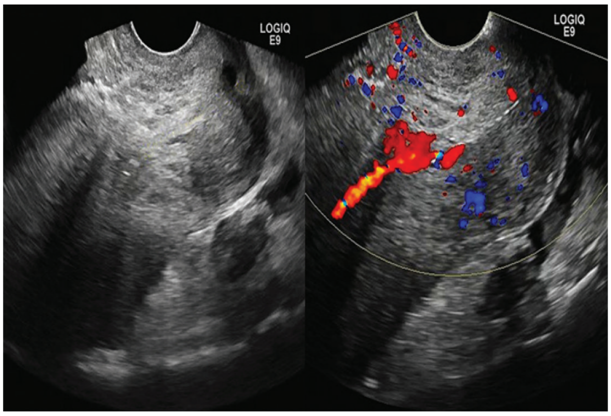

Figure 2 Two-dimensional ultrasound and CDFI of cervical LCNEC. Female patient, 47 years of age, with an enlarged cervix, approximately 26×34×45 mm in size, that is multilamellar and slightly hypoechoic, with an unclear boundary and CDFI. A few short strips of blood flow signal (Adler grade 2) are seen inside.

larger lesion range than that with conventional ultrasound, which to some extent compensates for the disadvantages of conventional ultrasound. Our findings suggested that conventional ultrasound should be combined with contrast-enhanced ultrasound to provide more useful information. In the eight patients with LCNEC in this study, MRI indicated several clear characteristics: T1WI showed a low signal or isointensity; T2WI showed a high signal; DWI showed a high signal; the ADC value was low; and most of the enhanced MRI scans showed a heterogeneous high signal, in agreement with the malignant characteristics of cervical cancer (**Figure 1**). MRI indicated that the LCNEC lesions were closely associated with the mucosal layer, whereas conventional ultrasound showed uncertain boundaries with the mucosal layer. Therefore, MRI performed significantly better than conventional ultrasound in revealing the relationship between lesions and the cervical mucosa. Compared with conventional ultrasound, contrast-enhanced ultrasound clearly revealed the relationship between the lesions and the cervical mucosa.

Conventional ultrasound of cervical LCNEC lesions, compared with cervical squamous cell carcinoma and adenocarcinoma, showed different manifestations, primarily an enlarged cervix, irregular hypoechoic areas in the muscle layer, slightly hyperechoic inlaid cords, and unclear boundaries. Slightly rich blood flow signals were observed in the lesions (**Figure 2**). On conventional ultrasound, the lesion is unclear from the myometrium; however, the boundary with the cervical mucosa is uncertain. We attempted to perform CEUS on two cases of LCNEC and found that the enhancement of LCNEC showed a “fast-in and fast-out” mode and a “fence-like” change after subsidence, and the degree of enhancement was close to that of cervical myometrium tissue. The display range was larger than the two-dimensional image, the boundary between the hypoechoic area and the muscularis tissue was unclear, and some findings were unclear with respect to the cervical mucosa (**Figure 3A, B**). Comparison of the imaging characteristics of MRI, LCNEC-enhanced

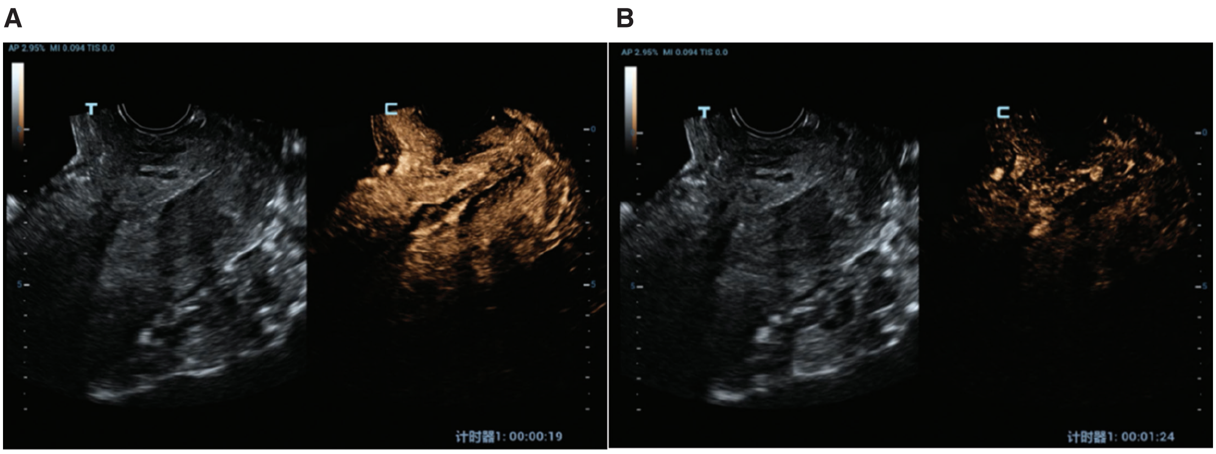

Figure 3 (A) CEUS 19S. (B) CEUS 84S. Female patient, 47 years of age, with diffuse, heterogeneous enhancement of the cervical echogenic zone starting at 10–12 s and peaking at 17 s. The degree of enhancement is close to the myocervical tissue, and in the late phase of imaging, the lesion is seen as a linear-like enhancement surrounding a low enhancement zone of varying size, with “fence-like” changes and a “fast-in, fast-out” pattern of enhancement.

MRI indicated heterogeneous enhancement, limited diffusion on DWI, and a low ADC value. Ultrasound and MRI imaging findings shared a common pathological basis; that is, the observed characteristics could be explained by histopathology. LCNEC is characterized by tumor cells arranged in beam-like, nested sheets or a gland-like pattern, with large-cells and intercellular boundaries, and indistinct, map-like necrosis is easily seen [9]. The two-dimensional ultrasound images of cervical LCNEC significantly differed from the homogeneous hypoechoic and clear nodularity typically observed in cervical squamous cell carcinoma and adenocarcinoma. Color Doppler imaging indicated that the internal blood flow of cervical squamous cell carcinoma and adenocarcinoma was more abundant than that of LCNEC. This finding is consistent with those from prior reports [11] and might have been associated with the pathological characteristics of LCNEC.

In this study, conventional ultrasound and MRI demonstrated that LCNEC lesions had a clear boundary with the cervical serosa, thereby reflecting the pathological characteristics of LCNECs, which do not readily infiltrate into surrounding tissues, and are prone to vascular and lymphatic metastasis [7]. For lymph node metastasis, the positive rate of MRI in diagnosis of suspicious pelvic lymph nodes in patients with LCNEC was slightly higher than that of ultrasound (50% vs. 25%), but the false positive rate was 50%. Possible reasons for missed diagnoses of lymph node metastasis by ultrasound included that the metastatic lymph nodes might have been too small, the conventional ultrasound scan of the pelvis had no clear parametrial infiltration images, the groin was not scanned afterward, and a high-frequency probe was not used to scan the groin. Possible reasons for the missed diagnosis and misdiagnosis of lymph node metastasis by MRI might have been that the shape of the metastatic lymph node did not change; the metastatic lymph nodes were small, and thus the DWI of the lymph nodes did not significantly increase, and the ADC value did not significantly decrease; the scan slice thickness might have been too large; and inflammatory factors might have caused interference.

MRI examination can accurately assess cervical LCNEC lesion size and clearly show the relationship between LCNEC lesions and the cervical mucosa; it also can be used to preliminarily assess benign and malignant cervical LCNECs. However, MRI is relatively expensive and time-consuming. Although conventional ultrasound cannot accurately assess the size of cervical LCNEC tumors, it can be used to observe tumor internal structure and blood flow. Herein contrast-enhanced ultrasound appeared to effectively overcome the disadvantages of two-dimensional ultrasonography. This method also has a fast-in and fast-out enhancement mode, and exhibits specific manifestations, such as fence-like changes after subsidence. For the diagnosis of lymph node metastasis, both MRI and conventional ultrasound each have drawbacks. The scope of ultrasonography for cervical cancer patients should routinely include scanning of the groin with a high-frequency probe, which may improve the diagnosis rate of lymph node metastasis.

This study has several limitations: first, the sample size was relatively small and may not be representative of all patients with LCNEC; second, this was a retrospective study in patients attending our hospital. The results will be followed up with multicenter validation.

Conclusion

Conventional ultrasound, contrast-enhanced ultrasound, and MRI are complementary techniques that provide more information for the diagnosis of cervical LCNEC. MRI examination can aid in the preoperative diagnosis of cervical LCNEC, whereas conventional ultrasound combined with contrast-enhanced ultrasound provides new ideas for the diagnosis of cervical LCNEC and therefore may aid in the diagnosis and treatment of this disease.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Sun Yat-sen Memorial Hospital of Sun Yat-sen University (SYSKY-2022-040-01). No informed consent was required due to the retrospective nature of data acquisition.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

LT and SJW are the common first authors and the major contributors in writing the manuscript. ND edited the manuscript and approved the final version. YQ, YJ, SZ, SLZ, and BML were responsible for reviewing the literature and collecting the information of the patients. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

References

[1] McCann GA, Boutsicaris CE, Preston MM, Backes FJ, Eisenhauer EL, et al. Neuroendocrine carcinoma of the uterine cervix: the role of multimodality therapy in early-stage disease. Gynecol Oncol 2013;129:135-9. [PMID: 23357610 DOI: 10.1016/j.ygyno.2013.01.014]

[2] Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of Female Reproductive Organs. Lyon: International Agency for Research on Cancer; 2014.

[3] Zhang SQ, Qu QX, Lin ZQ. Expert guidance for diagnosis and treatment of neuroendocrine cervix carcinoma (2022). Chin J Pract Gynecol Obstet 2022;38:170-6. [DOI: 10.19538/j.fk2022020111]

[4] Habeeb A, Habeeb H. Large cell neuroendocrine carcinoma of the uterine cervix. BMJ Case Rep 2019;12:bcr-2018-225880. [PMID: 30642849 DOI: 10.1136/bcr-2018-225880]

[5] Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstet 2019;145:129-35. [PMID: 30656645 DOI: 10.1002/ijgo.12749]. Erratum in: Int J Gynaecol Obstet 2019;147:279-80.

[6] WHO Classification of Tumours. Female genital tumours: WHO classification of tumours series. 5th ed. Lyon, France: International Agency for Research on Cancer; 2020. https://publications.iarc.fr/592.

[7] Li S, Zhu H. Twelve cases of neuroendocrine carcinomas of the uterine cervix: cytology, histopathology and discussion of their histogenesis. Acta Cytol 2013;57:54-60. [PMID: 23221311 DOI: 10.1159/000342516]

[8] Burkeen G, Chauhan A, Agrawal R, Raiker R, Kolesar J, et al. Gynecologic large cell neuroendocrine carcinoma: a review. Rare Tumors 2020;12:2036361320968401. [PMID: 33194158 DOI: 10.1177/2036361320968401]

[9] Zhang HP, Huang GX, Chen QY, Zhong LL, Chen HH, et al. A case of primary large cell neuroendocrine carcinoma of the uterine cervix. Chin J Pathol 2022;51:71-3.

[10] Hricak H, Gatsonis C, Chi DS, Amendola MA, Brandt K, et al. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. J Clin Oncol 2005;23:9329-37. [PMID: 16361632 DOI: 10.1200/JCO.2005.02.0354]

[11] Epstein E, Di Legge A, Måsbäck A, Lindqvist PG, Kannisto P, et al. Sonographic characteristics of squamous cell cancer and adenocarcinoma of the uterine cervix. Ultrasound Obstet Gynecol 2010;36:512-6. [PMID: 20336641 DOI: 10.1002/uog.7638]