

## High-intensity focused ultrasound combined with hysteroscopic and chemotherapy to treat metastatic choriocarcinoma after vaginal delivery

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### ABSTRACT

We present a case of choriocarcinoma treated by high-intensity focused ultrasound (HIFU) combined with hysteroscopic and chemotherapy. Initially, retained placenta accreta or gestational trophoblastic disease was suspected, After HIFU treatment, obvious bleeding during hysteroscopic surgery, and the  $\beta$ -HCG level decreased. Degeneration and necrotic cells can be seen in the HIFU area. And we give the patient 5 cycles of intravenous EMA/CO chemotherapy. The patient was stable after chemotherapy. The last follow-up time is December 14, 2018, the patient did not complain of discomfort, and the serum  $\beta$ -hCG results were normal.

**KEYWORDS:** High-intensity focused ultrasound, Chemotherapy, Metastatic Choriocarcinoma

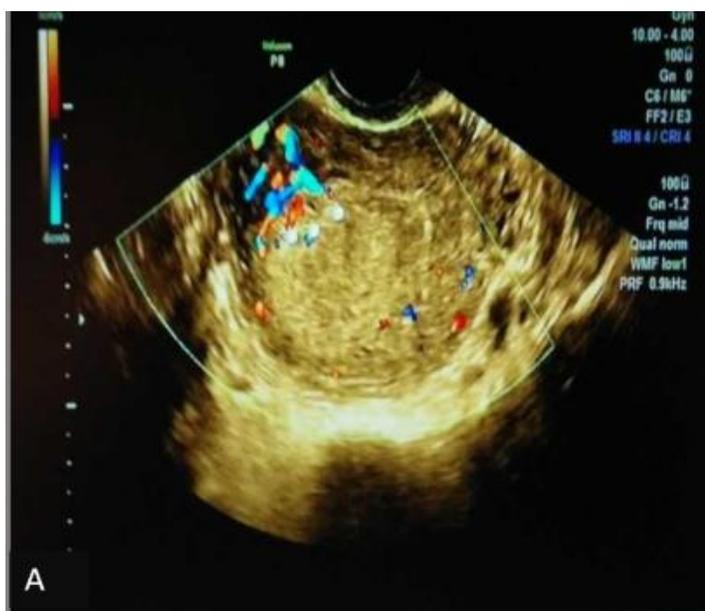
### INTRODUCTION

Gestational trophoblastic disease includes formation of a benign hydatidiform mole (partial and complete), invasive and metastatic hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. The latter 4 types are also classified as gestational trophoblastic neoplasia. Choriocarcinomas are extremely rare, and it is difficult to differentiate between choriocarcinomas secondary to hydatidiform moles and invasive hydatidiform moles. Therefore, it is difficult to assess their incidence accurately. According to some reports, the incidence of postpartum choriocarcinoma after term pregnancy is very lower, at around 1 in 160,000 pregnancies [1]. Due to the difficulty of diagnosis, treatment is often delayed, resulting in poor outcomes. However, if choriocarcinomas are diagnosed and treated timely, their remission rate reaches 87.5% [2]. In this case, we present a case of choriocarcinoma treated by high-intensity focused ultrasound (HIFU) combined with hysteroscopic and chemotherapy.

### Case report

This case presentation has been consent by the patient and approved by the ethics committee. On October 18, 2016, a 36-year-old Chinese was admitted into our hospital, complaining of Sustained vaginal bleeding for 3 months after delivery, and serum beta-human chorionic gonadotropin ( $\beta$ -HCG) was found to be elevated by 2 weeks. She delivered a full term baby 3 months ago, and the postpartum lochia has not been stopped. Ultrasound examination revealed an irregular hyperechoic area of about 26 × 19 × 21 mm in uterine cavity in August 18, 2016, so she took some drugs to promote the excretion of lochia, and the bleeding had been reduced, however vaginal bleeding occurred again after 7 days. And then two times of ultrasound examination showed that the intrauterine hyperechoic area was uneven, and the volume increased

before contrast. On October 18, 2016, Serum  $\beta$ -HCG level was 13 552.32 U/L. The general condition of the patient was clinically normal. On physical examination, the abdomen was soft, a fist-sized uterus was palpated and vaginal bleeding was noticed on pelvic examination. Both adnexae were intact. There was 45 ×34×43mm a hyperechogenic shadow in the endometrial cavity on transabdominal and transvaginal ultrasonography (Figure 1A).

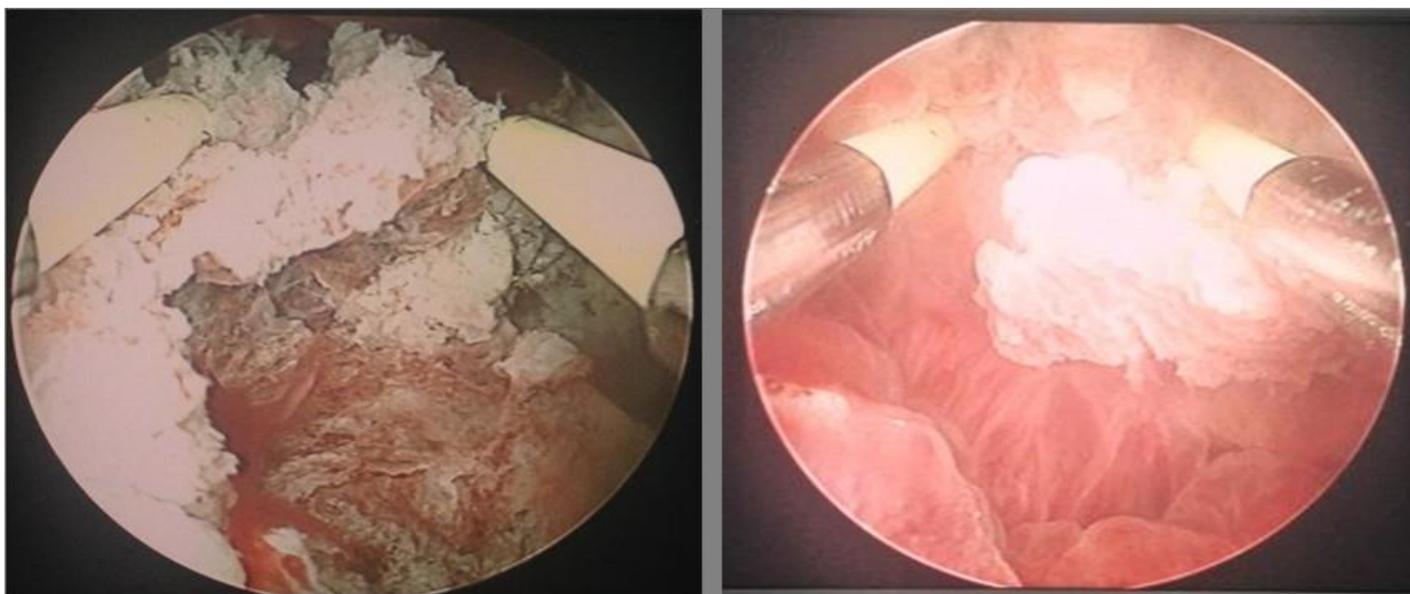


**Figure 1 A:** Pelvic B-ultrasound (preoperative)



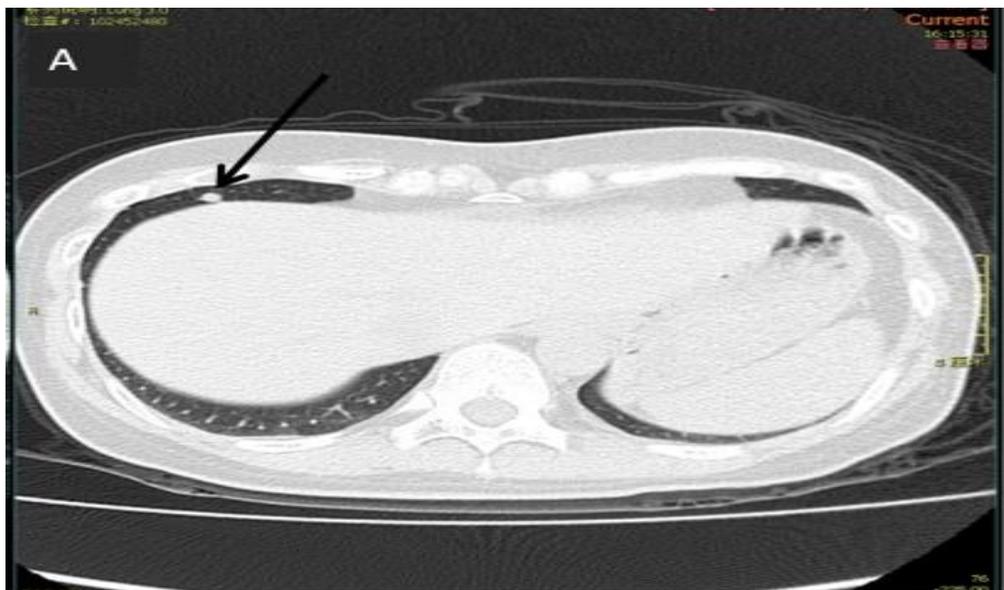
**Figure 2A:** Total abdominal MR (preoperative)

A full-abdominal MRI examination suggests a right uterine wall-cavity occupying position (Figure 2A). Intermuscular hematoma may be considered, considering the right front and left posterior placenta of the uterus. There was no obvious abnormality in chest X-ray examination. After admission, repeated examination of serum  $\beta$ -hCG values has been on the rise, with a maximum of 37819.18 IU/L. Based on the history, clinical manifestations and, serum  $\beta$ -hCG values, and sonographic findings, retained placenta accreta or gestational trophoblastic disease was suspected. So we give the patient high-intensity focused ultrasound (HIFU) treatment, the specific methods and steps of HIFU are detailed in the following methods. After HIFU treatment, a hysteroscopic resection which was guided by ultrasound was performed to remove Intrauterine occupying tissue On October 27, 2016. The uterine cavity morphology was abnormal during operation, and the gray-white lesions and uterus were unclear in the posterior wall of the uterus (Figure 3).



**Figure 3:** Hysteroscopic uterine lesion resection

Postoperative pathology suggests placenta implantation. No abnormal vaginal bleeding or discharge was seen after the procedure, The patient was stable postoperatively, and serum  $\beta$ -hCG value decreased, the volume of hyperechogenic shadow in the uterine cavity was significantly reduced, about  $19 \times 13 \times 17$  mm. the patient discharged on November 2, 2016. Patients with late follow-up found that serum  $\beta$ -hCG increased again after falling to 1251 IU/L, accompanied by cough, no hemoptysis, On November 22, 2016, the patient was excluded from the pregnancy and admitted to the hospital again. CT shows the subpleural nodules outside the middle lobe of the right lung, the boundary is clear, combined with the basin Intraluminal space-occupying lesions may be considered as metastases (Figure 5A).



**Figure 5A:** Chest CT (before chemotherapy)

Uterine volume and volume of uterine cavity occupying lesions are larger than before; gestational trophoblastic disease was suspected (Figure 1C).

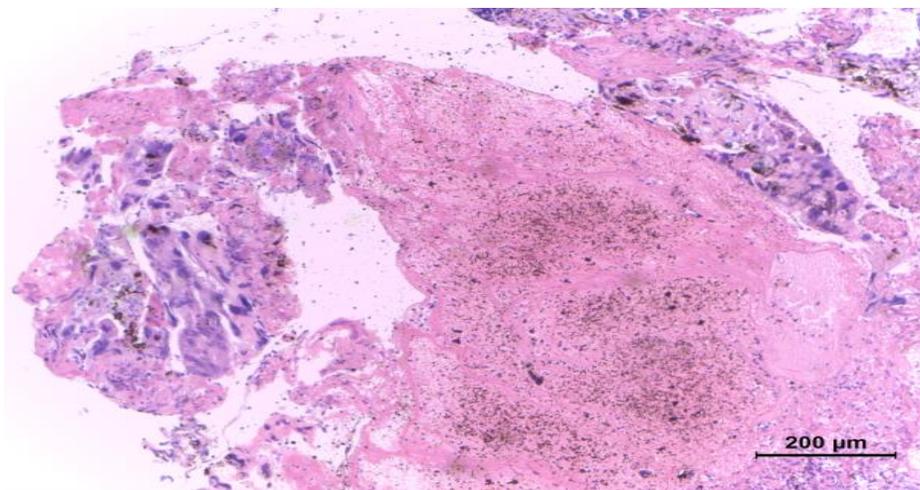


**Figure 1C:** Pelvic B-ultrasound (before chemotherapy)



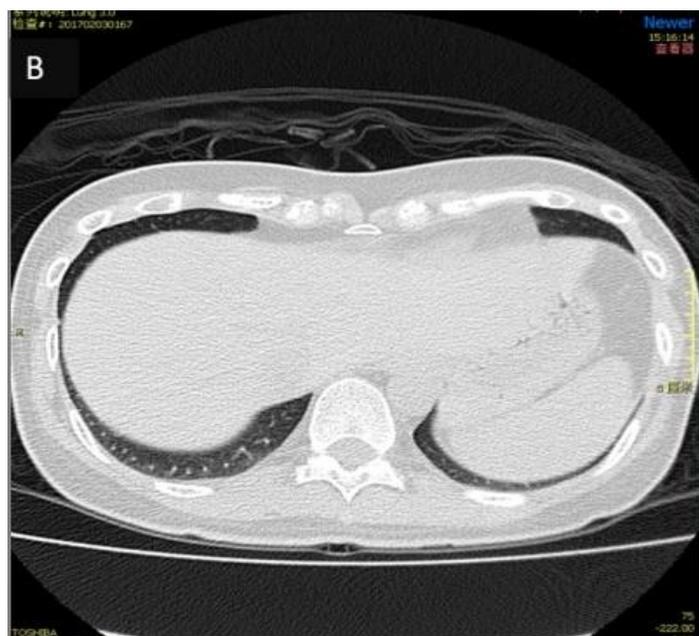
**Figure 2B:** Total abdominal MR (before chemotherapy)

Full abdominal MR showing right side uterine wall-cavity occupying position, considering choriocarcinoma with hematoma (Figure 2B) Skull MRI showed no obvious abnormalities. So we review of pathological sections: under the microscope, there was more fibrinous necrosis, visible nourishing leaf cells infiltrate into the superficial myometrium, nourishing cells mild heterosexuality, no villus tissue, does not rule out the nourishment of the placenta cell tumor. Beside the atypical trophoblast, the traces can be clearly seen the after HIFU, a few degeneration and necrotic cells can be seen in the HIFU area (Figure 4).



**Figure 4:** Pathological HE staining of hysteroscopic uterine lesions (HE×20)

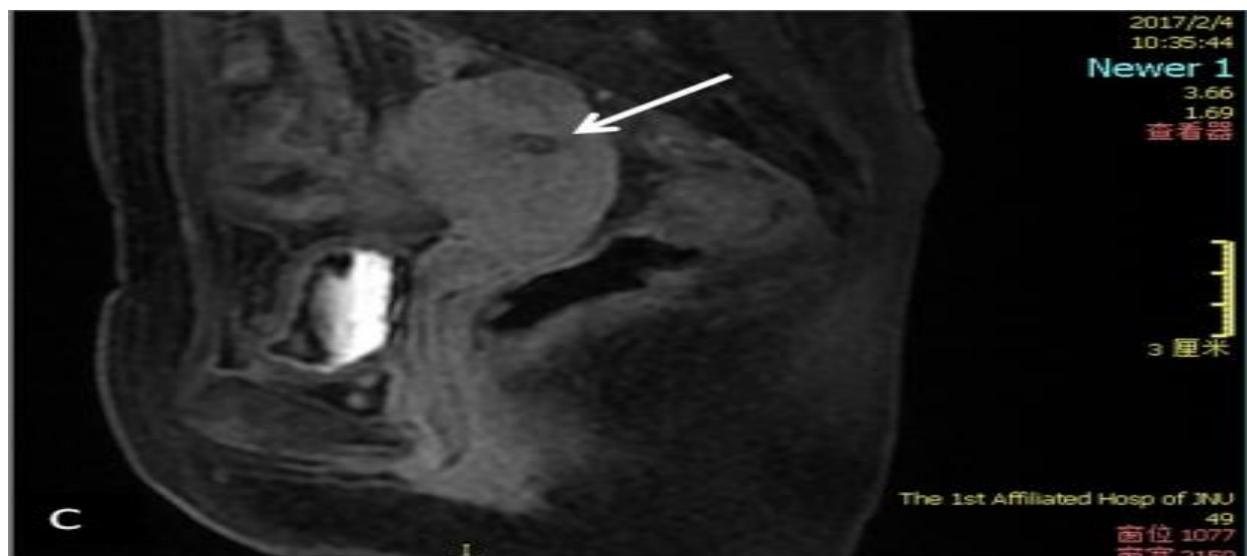
Comprehensive analysis of the patient's condition, the patient is considered to be diagnosed as postpartum choriocarcinoma. On November 23, 2016, the patient started chemotherapy twice a week. The chemotherapy consisted of intravenous EMA/CO (etoposide 100 mg/m<sup>2</sup>, methotrexate 100 mg/m<sup>2</sup> with folic acid 200 mg/m<sup>2</sup> and actinomycin D 0.5 mg, alternating with cyclophosphamide 600 mg/m<sup>2</sup> and vincristine 1 mg/m<sup>2</sup>), The chemotherapeutic effect was remarkable, at the end of the second chemotherapy, the serum β-hCG value decreased to normal, and the symptoms of cough gradually eased during chemotherapy. After 5 cycles of intravenous EMA/CO, on February 3, 2017, Review of chest CT shows that the pulmonary nodules disappear (Figure 5B),



**Figure 5B:** Chest CT (after chemotherapy)



**Figure 1D:** Pelvic B-ultrasound (after chemotherapy)



**Figure 2C:** Total abdominal MR (after chemotherapy)

And pelvic ultrasound showed uterus has a normal size and have no lesions in the uterine cavity (Figure 1D). Review of pelvic MR showed significant reduction of intrauterine lesions (Figure 2C). On February 5, 2017, she discharged. After discharged from hospital, the regular monitoring of serum  $\beta$ -hCG levels was normal. Menstruation recovered after 2 months of discharge, and on June 11, 2017, pelvic MR showed that the intrauterine lesion disappeared. The last follow-up time is December 14, 2018, the patient did not complain of discomfort, and the serum  $\beta$ -hCG results were normal.

## Discussion

Choriocarcinoma is a highly aggressive variant of gestational trophoblastic diseases [3]. It has been reported that 22.5% of choriocarcinoma cases arise in normal pregnancy, often accompanied by irregular vaginal bleeding after birth and abnormal  $\beta$ -hCG measurement [4]. Pregnant women have irregular vaginal bleeding after full-term delivery, and often consider common causes such as placental residue or uterine incompleteness according to clinical routines, so that choriocarcinoma secondary to postpartum postpartum is difficult to diagnose early.

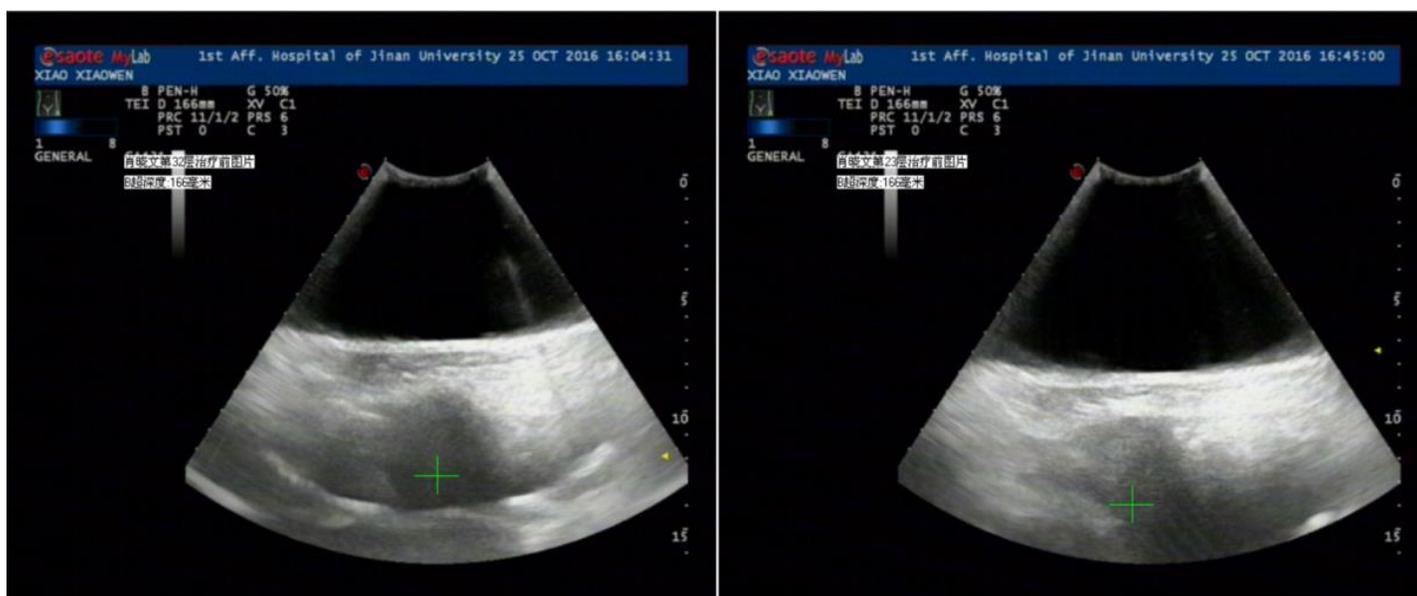
HIFU is a noninvasive treatment technique that is directed without harm across skin and damaged target tumor tissue. HIFU applies selective tissue necrosis through cavitation and heating by ultrasound. HIFU can be utilized in the treatment of both benign and malignant tumors [5]. This method has been reported to have an effect on soft tissue sarcoma [6], prostate Cancer [7], degenerative disc disease [8], hepatocellular carcinoma [9], cutaneous allodynia [10], retained placenta accrete [11], and other organs. In this case, we treat this patient with HIFU. HIFU was performed using an ultrasound-guided HIFU tumor therapeutic system. The ultrasound machine had been used for real-time monitoring of the HIFU procedure. After HIFU treatment, no additional vaginal bleeding or complications were observed. A hysteroscopic resection which was guided by ultrasound was performed to remove intrauterine occupying tissue. Coagulative necrosis of the lesion so no obvious bleeding during hysteroscopic surgery and the  $\beta$ -HCG level decreased. The patient was stable postoperatively, and the ultrasound suggested a significant reduction of the hyperechogenic shadow. We hypothesized that HIFU is an effective method for the treatment of choriocarcinoma. HIFU can narrow the lesions, reduce the possibility of bleeding. This makes hysteroscopic surgery possible. Through surgery, pathological results can be obtained. Even though the diagnosis of choriocarcinoma did not rely on the pathological diagnosis [12], but in this case, the patient's  $\beta$ -hCG is at a lower level, at this time, if there is a pathological diagnosis, it will play a key role in identifying the placental residue or implanting and choriocarcinoma. And if the lesion volume is reduced, it also has a certain effect on reducing metastasis. The patient' was re-admitted because of lung metastasis, and we still given five courses of chemotherapy according to the guidelines.

But from the patient's case, we should learn from experience:  $\beta$ -hCG tends to decrease when placenta is implanted, if progressive increase with residual tissue enlargement, firstly we should consider gestational trophoblastic disease. HIFU combined with hysteroscopic resection to obtain histological diagnosis is feasible, and there is no bleeding during the operation. Pulmonary enhanced CT is very important for judging the presence or absence of lung metastasis. It is also one of the reasons for misdiagnosis because the chest radiograph was negative for the first time. Postpartum postpartum choriocarcinoma is prone to metastasis, so the mortality rate is high, and the treatment effect is related to the presence or absence of extensive metastasis. Therefore, such patients should be promptly examined by MRI and full-abdominal MRI

after diagnosis to understand the metastatic lesions and increase cure rate. In addition, when the clinical and pathological or imaging and other auxiliary examinations do not match, it is necessary to carefully find out the cause, reflect on whether the diagnosis is correct, and closely follow up the patient.

## Methods

HIFU was performed using the “PRO2008” high intensity focused ultrasound system (SHENZHEN PROMETHE MEDICAL SCI-TECH CO., LTD., Shenzhen, China). Before starting the HIFU treatment, the patients were required to bladder filling. During the treatment, the patient is placed in the supine position, and the treatment area of the abdominal wall is uniformly applied with a coupling agent to ensure no bubble generation. Ultrasonic external probe positioning, laser light positioning, and accurate positioning of the built-in ultrasonic probe, the degassing water capsule membrane of the C-arm in the treatment system is in close contact with the skin of the treatment area coated with the coupling agent, and the treatment is started. The patient is treated in a awake state and communicates with the doctor at any time. Treatment parameters: emission frequency ( $1.2 \pm 0.18$ ) MHz, acoustic emission power  $5000\text{W}/\text{cm}^2$ ; focal length 12.6cm adjustable; adjustable focal length size adjustable. The transmission time is adjustable from 0.01 to 0.50s, and the interval is adjustable from 0.01 to 0.50s. The number of launches is adjustable from 0 to 50 times, the number of transducers is one, and the power is 60% to 100%. The scope of treatment covers the area of the irregular hyperechoic area tissue rich in blood vessels rather than the myometrium, keeping a certain distance from the uterine serosa (average thickness of the muscle layer)(Figure 6).



**Figure 6** The working interface of HIFU PRO2008

During the whole course of HIFU treatment, real-time ultrasonography was used to determine the location of the target area and to monitor the response to HIFU. The sagittal view of the ultrasound scanning mode was selected, and the treatment plan was made by dividing the irregular hyperechoic area tissue into different slices with a thickness of 3 mm each. The ablation procedure began from the innermost slice. During surgery, we compared the ultrasound image with the target image and their grey-scale values with each other and identified any coagulation necrosis by observing the lesions. HIFU ablation was terminated when any sign of irregular hyperechoic area tissue blood flow disappeared or a grey-scale change in the target tissue was observed on the colour Doppler ultrasound.

## Conclusion

We present a case of choriocarcinoma treated by high-intensity focused ultrasound (HIFU) combined with hysteroscopic and chemotherapy. HIFU can narrow the lesions, reduce the possibility of bleeding, and reduce the value of  $\beta$ -hCG. This makes hysteroscopic surgery possible. All in all, we hypothesized that HIFU is an effective method for the treatment of choriocarcinoma.

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