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REVIEW PAPER / GYNECOLOGY

mTOR inhibitor in the treatment of TFE-positive advanced maligmnant PEComa of the uterus: a case report and literature review

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ABSTRACT

Background: The pre- and intra-operative diagnoses of malignant uterine vascular perivascular epithelioid cell tumors (PEComas) can be challenging, for which the literature is limited. Some cases have been shown to have TSC gene mutations or rearrangements of the MiT factor family, resulting in variable responses to mTOR inhibitors. We report a case of a TFE-positive malignant PEComa of the uterus with pulmonary metastases that responded favorably to the mTOR inhibitor, everolimus.

Case presentation: A 52-year-old female underwent a total hysterectomy 5 years ago for suspected sub-serosal or broad ligament fibroids. The intraoperative pathologic diagnosis was leiomyosarcoma of the uterus and the postoperative diagnosis was malignant PEComa of the uterus. The patient declined genetic testing and further treatment. In December 2020 the patient presented with a pelvic mass and underwent open abdominal mass resection and pelvic adhesiolysis. The pathologic findings confirmed recurrent malignant PEComa of the uterus. The pulmonary lesions gradually progressed during the follow-up period, so treatment with everolimus was initiated. Close follow-up evaluation for nearly 3 years showed disease remission without recurrence or progression.

Conclusion: The patient described herein had a TFE-positive uterine malignant PEComa with lung metastasis and responded well to the mTOR inhibitor, everolimus.

Close follow-up in the last 3 years showed remission without recurrence or progression.

Keywords: gynecologic tumors; mTOR inhibitors; uterine PEComa; TFE; vascular perivascular epithelioid cell cumors

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INTRODUCTION

Perivascular epithelioid cell tumors (PEComas) are rare tumors characterized by the presence of the following two main cell types: epithelioid cells, which are polygonal with transparent-to-granular cytoplasm and often express melanocytic markers, such as HMB45, Melan-A, and MITF [1]; and spindle cells, which are present in approximately 37% of cases and exhibit smooth muscle differentiation, expressing corresponding markers. such as SMA, desmin, and calponin [2]. PEComas can occur in various locations throughout the body but are relatively rare in the uterus and the female reproductive tract [3]. The concurrent presence of thin- and thick-walled vessels is a distinguishing histopathologic feature of uterine PEComas. Tumor cells demonstrate clear or eosinophilic cytoplasm with nuclei appearing round or oval and often centrally or eccentrically located. These cells are characteristically arranged in an epithelioid nesting or sheeting pattern around blood vessels. The concurrent expression of two melanocytic markers (HMB-45 and Melan A) with muscular markers (most often SMA) in PEComas is detected by immunohistochemical staining. These defining features are essential for accurate diagnosis and classification of this

rare neoplasm.

Forty-one patients (age range, 9–79 years; mean age, 49 years) with PEComas have been reported in the literature [4]. Notably, the youngest reported patient with uterine PEComa was 9 years old [4]. PEComas lack specific clinical, physical, and imaging features. Therefore, an accurate preoperative PEComa evaluation relies heavily on histopathologic features, immunohistochemistry findings, and sometimes genetic testing. A PEComa is frequently misdiagnosed as a benign tumor, such as a uterine fibroid, or other malignancies, including sarcomas. The absence of specific diagnostic markers poses a significant challenge in the diagnosis and treatment of PEComas [5].

The most common sites of metastasis for PEComas are the lungs, followed by the liver, lymph nodes, and peritoneum [5, 6]. While the majority of PEComas follow a benign course, reports of malignant behavior, including recurrence and metastasis, are increasing. Herein we report a case of a malignant uterine PEComa expressing TFE3 and exhibiting dual cell patterns of epithelioid and spindle cells. The PEComa had high expression of HMB45, desmin, calponin, SMA, and TFE3, and partial expression of Ki67 and cyclin D1. Following the primary surgical resection and subsequent recurrence with pulmonary progression, the patient experienced long-term relief from metastatic disease after treatment with the mTOR inhibitor, everolimus. This case highlights the need to further investigate the clinical, pathologic, and immunohistochemical features, diagnosis, treatment options, and prognosis of PEComas to improve outcomes.

CASE PRESENTATION

This case report followed ethical guidelines. Written informed consent was obtained from the patient.

History of the Illness

The patient, a 52-year-old female, was noted to have a uterine mass during a routine physical examination in 2015 (Fig. 1A). Her medical history was unremarkable. The

menstrual history was regular, and she denied any history of abdominal pain or discomfort and hormone or medication use. She had been pregnant seven times and given birth to four children. The physical examination revealed no palpable superficial lymph nodes. A firm, movable, and painless periumbilical mass was palpable. The gynecologic examination was significant for an enlarged uterus and a left adnexal mass, the width of a finger, with good mobility, well-defined borders, and no tenderness. The tumor marker levels were within normal limits. Ultrasonography and a pelvic CT scan showed an irregular uterine contour and a mass in the upper aspect of the uterus and left adnexal region with indistinct borders. Endometrial curettage specimens revealed endometrial proliferative phase changes and chronic inflammatory changes in the cervical mucosa. Gastrointestinal endoscopy did not reveal any significant lesions, and the tumor marker test results were within normal limits. Then, she underwent a total hysterectomy.

Postoperative pathology in 2015 confirmed that the tumor was a PEComa. The tumor tissue and surrounding fascia and muscle tissue were completely resected. The tumor had a hard consistency, intact capsule, yellow-white color, and firm texture. Some areas of the PEComa exhibited a sandy consistency with focal cystic changes and minimal bleeding. The postoperative histopathologic examination confirmed that the tumor cells were arranged in an epithelial pattern surrounded by blood vessels in nests and sheets. Immunohistochemical staining results were positive for HMB45 (focal), MelanA (−), desmin (+), SMA (+), Ki67 (approximately 5%+), TFE (partial +), CD10 (−), S100 (−), cyclin D1 (focal +), CR (−), CD117 (−), and DOG1 (−). The histopathologic features were consistent with a PEComa originating from blood vessels. In 2020 she again developed a palpable pelvic mass (Fig. 1B and 1C) and underwent an abdominal tumor resection and pelvic adhesiolysis.

Imaging assessments in 2020

An MRI of the upper abdomen and pelvis in 2020 showed a right lower abdominal mass suggestive of malignancy with a high likelihood of metastasis (Fig. 2). There

was a signal abnormality involving the fifth sacral vertebrae, which could not be excluded as a metastatic lesion. A PET-CT (Fig. 3) confirmed absence of the uterus and bilateral adnexa, and no obvious malignant lesions were observed in the surgical area. A mass measuring approximately 5.1 × 3.4 cm was noted in the right lower abdomen. No abnormal radioactive concentration was observed on PET-CT, suggesting a high likelihood of metastasis. Multiple pulmonary nodules with low metabolic activity were seen, suggestive of metastatic tumors.

Immunohistochemistry in 2020

HMB45, desmin, calponin, and SMA were positive (SMA was weakly positive). TFE3 staining was focal positive. Tumor cells were negative for S100, MyoD1, myoglobin, myogenin, EMA, Vim, a-inhibin, CD10, CDX2, CK20, TTF-1, and CK7. The Ki67 index was approximately 10%. A few cells were positive for cytokeratin (CK). Based on the histopathologic and immunohistochemical findings, the tumor was consistent with a PEComa. The pelvic lymph nodes were free of metastasis. The tumor specimen had high-risk features (diameter > 5 cm, infiltrative growth, necrosis, mitotic count >1/50 HPFs, and elevated cell density) and she was therefore diagnosed with a malignant PEComa (Fig. 4).

The pathologic slides were sent to Sun Yat-sen University Cancer Center for further evaluation and the results were consistent with a PEComa. The Ki67 index was 10%. Additionally, few cells were positive for CK. Given these findings, there was a risk of tumor recurrence and metastasis. Therefore, adjuvant radiotherapy was recommended. However, the patient and her family declined this treatment option.

Postoperative follow-up

Three months after surgery (in 2020), a follow-up chest CT (Fig. 5A) showed multiple nodules in both lungs that were similar in number but slightly larger. The largest nodule was approximately 0.6 cm in diameter (previously 0.5 cm) with clear boundaries, suggesting the possibility of metastases. An MRI showed absence of the uterus and no tumor recurrence or metastases in the surgical area. The previously

palpable mass in the right lower abdomen had been completely resected, there were postoperative changes in the abdominal wall, and there was no change in the fifth sacral vertebra signal. Given the tumor recurrence and progression in the lungs, as well as TFE and Ki67 marker positivity, experimental treatment with everolimus (10 mg PO QD) was started. The patient developed oral inflammation and chest discomfort 2 months after treatment was initiated. The dose of everolimus was reduced to 5 mg QD and the symptoms resolved after treatment with mouthwash. Chest CT follow-up scans every 6–12 months showed that the number and size of nodules in the lungs were similar to previously observed (Fig. 5B).

Discussion and literature review

PEComa is a mesenchymal-derived tumor of uncertain origin encompassing a family that includes clear cell myomelanocytic tumors of the falciform/round ligament in the liver, angiomyolipomas of the liver and kidney, lymphangioleiomyomatosis, pulmonary clear cell "sugar" tumors, and non-specific PEComas [7]. Non-specific PEComas commonly occur in the pelvic cavity, peripheral soft tissues, and skin with the abdominal-pelvic region and uterus being the most frequent sites [8]. The primary lesion is often found in the female genitourinary tract with the uterus being the second most common affected site after the kidney. With respect to uterine involvement, most lesions occur in the uterine corpus, with fewer in the cervix, and rare occurrences in the ovary. Malignant manifestations or metastases are even more uncommon [9].

A PEComa is an interstitial-derived tumor of uncertain histogenesis. The limited published research involving PEComas, which is primarily based on small sample sizes and retrospective studies, has contributed to the unclear etiology and pathogenesis of this tumor [10]. At present it is believed that at least two main molecular sub-types of PEComa exist. The first sub-type is associated with mutations in the tuberous sclerosis complex (TSC) gene, which plays a crucial role in regulating the Rheb/mTOR pathway. TSC gene mutations lead to dysregulation of mammalian target of rapamycin complex 1 (mTORC1) activity, ultimately promoting tumor

development [7]. The second sub-type involves TFE3 translocation. Immunohistochemical staining results were positive for HMB45 (focal), MelanA (−), desmin (+), SMA (+), Ki67 (approximately 5%+), TFE (partial +), CD10 (−), S100 (−), cyclin D1 (focal +), CR (−), CD117 (−), and DOG1 (−) in our patient. The histopathologic features were consistent with PEComa tumors that originate from blood vessels. Based on the histopathologic and immunohistochemical findings, the tumor was consistent with PEComa features and TFE3 rearrangements. PEComas with TFE3 rearrangements exhibit an epithelioid phenotype and reduced or absent expression of muscle-specific markers, potentially rendering the PEComa resistant to treatment with mTOR inhibitors [11]. Both TFE tests were positive in our patient, but the patient and her family declined genetic testing. Currently, there is insufficient evidence to determine the exact etiology and pathogenesis of PEComas, necessitating further research and clinical data to gain a deeper understanding of this tumor entity.

A PEComa is a tumor of uncertain histogenesis, the main diagnostic basis for which is a pathologic examination. Most uterine PEComas present as single masses on gross examination and are often located in the muscular wall. The tumor is nodular with clear boundaries and does not commonly invade surrounding tissues. However, a minority of cases occur beneath the serosa or mucosa, and in rare instances the tumor may be multiple, with diameters ranging from 1.5–5.0 cm, although occasionally reaching up to 30 cm in diameter [12]. Microscopically, the tumor has a gray-brown or yellow appearance with clear or infiltrative borders. PEComas lack an envelope and have a soft texture, often accompanied by cystic changes, bleeding, or necrosis. The tumor cells exhibit vascular, epithelioid, or spindle tumor cells, adipose tissue, and other components. The cytoplasm is eosinophilic or clear, with small nuclei located eccentrically or at the center. The nuclei have a round or oval shape and indistinct nucleoli. The tumor cells have a low mitotic count (0–10/10 HPFs) and in rare cases atypical changes can occur that are characterized by deeply stained tumor cells with large nuclei and distinct nucleoli. The cells are often arranged in nests or sheets around thin- or thick-walled blood vessels, with some cells exhibiting tongue-

like infiltrative growth at the periphery [13]. PEComas are characterized immunohistochemically by the expression of at least two melanocytic markers (HMB-45, melan-A, and MiTF) and muscle markers (SMA, actin, and desmin). Uterine PEComas typically express HMB45 and MelanA, with HMB45 being the most sensitive marker. PEComas also express muscle markers, such as SMA, actin, and desmin, with SMA being the most commonly expressed smooth muscle marker [13]. Uterine PEComas do not typically express epithelial tumor markers, such as CK, CEA, or S-100. However, some studies have reported that PEComas often have TFE3 translocation mutations. Additionally, most PEComas demonstrate positive staining for TFE3 with a significantly higher positive rate than for HMB45 or SMA. Ki-67 has also been shown to have potential diagnostic value for distinguishing between benign and malignant uterine PEComas [14, 15]. When Ki-67 expression exceeds 5%, the risk of tumor metastasis significantly increases. In the current case, the gross appearance had a whorled structure and calcified spots within the tumor with clear boundaries and focal gray-yellow areas. Microscopically, the tumor cells exhibited round-to-polygonal shapes with eosinophilic cytoplasm and centrally located nuclei that were darkly stained and had a pleomorphic appearance. The tumor cells were diffusely arranged. The tumor expressed HMB45, desmin, calponin, SMA, TFE3, CK, and Ki67 (10%) on immunohistochemical staining, but was negative for muscle-specific markers, such as S-100, myogenin, and Myo-D1.

From an imaging perspective, the characteristics of uterine PEComas are non-specific and resemble benign smooth muscle lesions and other tumors with uncertain malignant potential [16]. Despite the use of ultrasound, CT, and MRI to assess these tumors, the imaging findings often overlap with other uterine pathologies. Indeed, the imaging features alone are insufficient to accurately diagnose PEComas [17–20]. In the current case, ultrasonography, MRI, and PET-CT were performed. Ultrasonography suggested a benign uterine tumor, while MRI and PET-CT suggested malignant metastases that could not be distinguished from other uterine tumors, so it is difficult to differentiate the tumor based on imaging features. Therefore, a

comprehensive evaluation that considers clinical presentation, histopathologic findings, and immunohistochemical staining is essential for accurate diagnosis and treatment planning.

A PEComa is a tumor with unclear benign or malignant potential [21]. To better classify the nature of PEComas, Folpe et al. [22] proposed clinicopathologic variables that predict tumor behavior, as follows: tumor diameter > 5 cm; aggressive or necrotic appearance (invasive growth, necrosis, and vascular invasion); cellular richness or high nuclear atypia; and nuclear division > 1/50 HPFs. Schoolmeester et al. [22] showed that PEComsa can be classified as benign, of uncertain malignant potential, or malignant based on these criteria. The 20 20WHO Classification of Tumors of the Female Reproductive System proposed that malignant PEComas should have ≥ 3 high-risk factors and PEComas of uncertain malignant potential (UMP) should have only 2 or fewer atypia factors [23]. Due to the unpredictable biological behavior, the diagnosis of "benign" PEComas should be made cautiously. In the current case, the tumor had a diameter > 5 cm, aggressive manifestations, invasive growth, necrosis, tumor cell richness, and nuclear division > 1/50 HPFs. Therefore, the diagnosis of malignant PEComas is clear.

PEComas originating from the uterus have a low incidence, the course of the disease is not typical, malignant cases are rare, the patients are mostly middle-aged and elderly women, local recurrences and distant metastases are common, the clinical manifestations are not specific, and the mass may be palpable in the abdomen due to different growth sites, rapid growth, or tumor ulcerations. Abnormal uterine bleeding, lower abdominal discomfort, and even abdominal pain and other symptoms following tumor rupture can occur, including intra-abdominal bleeding, excessive more brisk bleeding, and symptoms, such as dizziness, dizziness, and even hemorrhagic shock. Clinically, patients often seek evaluation because of the above-mentioned symptoms. If there is a pelvic cavity mass that enlarges in a short period with postmenopausal vaginal bleeding, a tumor should be considered. The current patient had no definite subjective symptoms on both occasions and the masses were incidental findings

during physical examination. The tumor also had a short-term enlargement.

No consensus has been reached in the treatment of primary uterine PEComas, including the initial presentation, recurrence, and metastasis according to domestic and international literature. Currently, surgical resection is the widely accepted standard of care [24–26], typically in the form of a total hysterectomy with or without salpingo-oophorectomy. For cases involving the cervix, radical hysterectomy along with salpingectomy is considered the optimal surgical approach. For patients who desire fertility and have benign or uncertain malignant potential PEComas, tumor resection alone may be a feasible option. Intraoperatively suspected cases of malignancy within the PEComa tumor may require lymphadenectomy, omentectomy, and appendectomy. Postoperative adjuvant chemotherapy and radiotherapy are recommended for patients with metastatic disease or residual lesions [17, 27, 28]. In the current case, a frozen pathologic examination suggested a diagnosis of uterine leiomyosarcoma during the initial treatment. Because no other lesions were noted in the pelvic and abdominal cavities, adnexectomy and lymphadenectomy were considered the most appropriate treatment. However, following the abdominal wall recurrence and subsequent tumor debulking surgery, a complete resection of the tumor was achieved, highlighting an individualized treatment approach.

Multiple studies have investigated the application of mTOR inhibitors in patients with PEComas. Sanfilippo et al. [29] concluded that mTOR inhibitors may be an effective treatment option for patients with high-risk factors for postoperative recurrence. Mutations in the TSC gene can negatively regulate mTOR, which is a protein complex closely related to cell growth and synthesis [29]. In another study [28], patients treated with mTOR inhibitors had an objective response rate (ORR) of 41% and a progression-free survival (PFS) of 9 months, with some patients even experiencing a PFS >1 year. The use of mTOR inhibitors in the treatment of PEComa patients with lung metastases has also been reported, with some patients experiencing stable disease [30 –32]. Pollizzi et al. [33] showed that after 1 month of treatment with an mTOR inhibitor, the tumor shrank by 99%. However, tumor recurrence was

observed after discontinuation of the mTOR inhibitor. Based on these clinical practices, mTOR inhibitors can be considered potential therapeutic agents for PEComas associated with TSC gene mutations. However, this conclusion still requires further clinical validation [34]. The chemotherapy effect of PEComas has not been established. For patients with inoperable or unsatisfactory reduction, dacarbazine, isocyclophosphamide, doxorubicin, and vincristine can be considered for single or combined chemotherapy. Liu et al. [35] reported that the combination of mTOR inhibitors and surgical treatment can prolong disease-free survival in patients with malignant PEComas, whether adjuvant radiotherapy or chemotherapy is administered. Among other treatment options, the ORR and PFS of anthracycline-based chemotherapy and gemcitabine are similar but not high. The ORR of single-agent anti-angiogenic therapy is only 8.3% with a PFS of 5.4 months [35]. The ORR of some advanced malignant PEComas positive for hormone receptors treated with anti-estrogen therapy and mTOR inhibitors but the effect of anti-hormone therapy alone is not satisfactory. The combined use of mTOR inhibitors suggests that the lesions are stable and have a trend toward further improvement [35, 36]. Some studies have explored the use of radiotherapy in a limited number of patients, the specific efficacy of which still lacks large-scale clinical studies and efficacy feedback. A patient with a PEComa had a positive prognosis after debulking surgery, neoadjuvant chemotherapy, and adjuvant chemotherapy [37]. However, due to the lack of treatment guidelines for gynecologic PEComas at present, complete surgical resection and regular postoperative follow-up evaluations remain the mainstay of treatment. Whether or not to carry out the relevant adjuvant treatments for malignant and potentially malignant uterine PEComas is highly controversial and there is no evidence that pre- and post-operative adjuvant therapy has a significant clinical benefit.

With respect to the current case, the lesion is rare, has a low incidence, and there is no standard treatment. Radiotherapy and chemotherapy are not effective. Considering the high risk of recurrence and TFE positivity, although no in-depth genetic testing was performed, there was progression of lung lesions. Therefore, we decided to treat the

patient with the mTOR inhibitor, everolimus. After avoiding side effects and continuing everolimus treatment, we achieved significant biological efficacy compared to other reported cases in the literature, such as Sanfilippo et al. [29], Wagner et al. [31], Italiano et al. [32], and Pollizzi et al. [33]. During regular follow-up visits, no recurrences were detected in the pelvic and abdominal cavities, and the lung lesions had stabilized completely, thus disease progression was controlled, and recurrences were prevented.

The current patient presented with no subjective symptoms on two occasions. Tumor enlargement was an incidental finding on physical examination. MRI and PET-CT scans suggested a metastatic malignancy, but the findings were inconclusive. The tumor was initially suspected to be a leiomyosarcoma based on frozen pathologic examination and the tumor was resected completely. No other pathologic changes were noted. The tumor cells exhibited a round and polygonal morphology with immunohistochemical staining positive for HMB45, desmin, calponin, SMA, TFE, CK, and KI67 (10%). The tumor diameter exceeded 5 cm and exhibited aggressive features, infiltrative growth, and tumor cell necrosis. The diagnosis of malignant PEComas was confirmed with numerous tumor cells and mitoses > 150 HPF and positive TFE staining. Despite progression of lung disease, we used the mTOR inhibitor, everolimus, and achieved good outcomes. Regular follow-up evaluations showed no pelvic or abdominal disease recurrences, and the pulmonary lesions appeared stable.

Article information and declarations

Acknowledgments

Conflict of interest

The authors declare no conflict of interests.

Data availability statement

The datasets used and/or analyzed during the current study are available from the

corresponding author on reasonable request.

Author contributions

YZ and HY are the guarantors of integrity of the entire study and also responsible for the following items: study concepts, study design, definition of intellectual content, literature research, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review.

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Ethics statement

This case report followed ethical guidelines. Written informed consent was obtained from the patient.

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Figure 1. Preoperative images of the patient. A. Pelvic CT in 2015; B. Preoperative color Doppler ultrasound in 2020; C. Preoperative chest CT in 2020

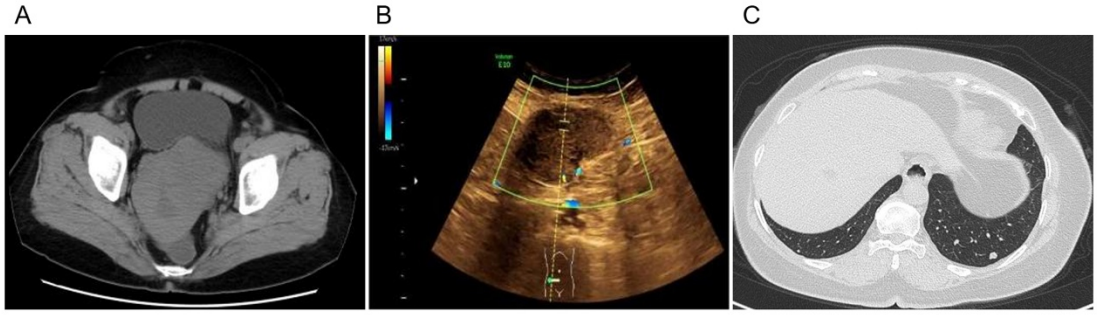

Figure 2. Repeat MRI in 2020

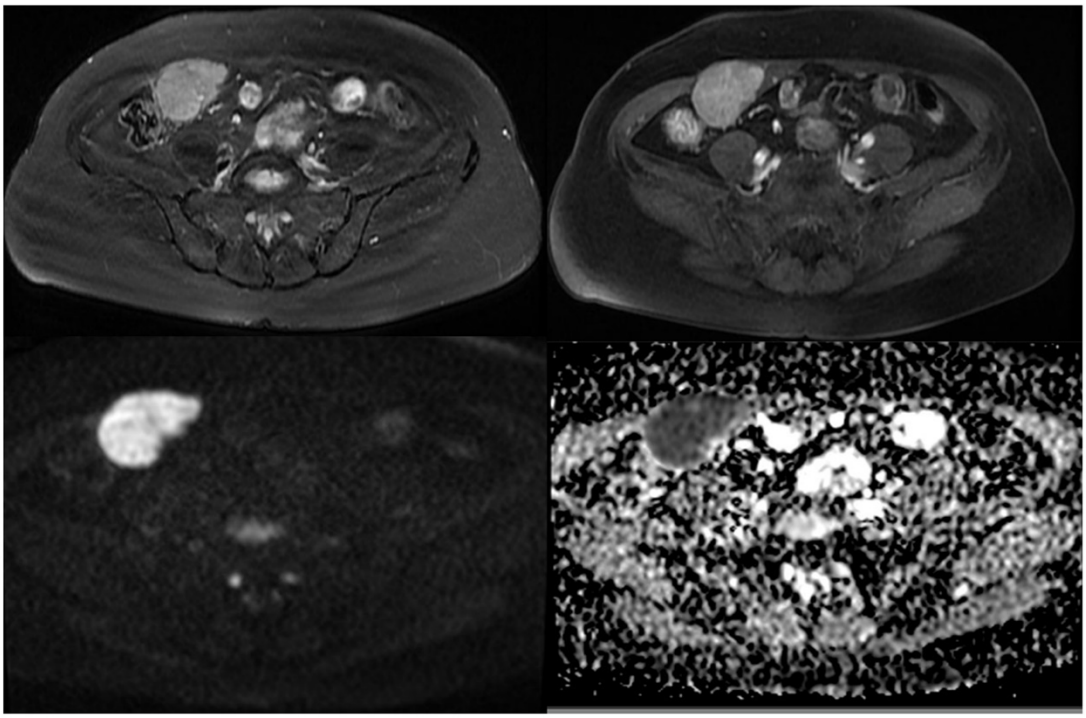

Figure 3. Preoperative PET-CT in 2020

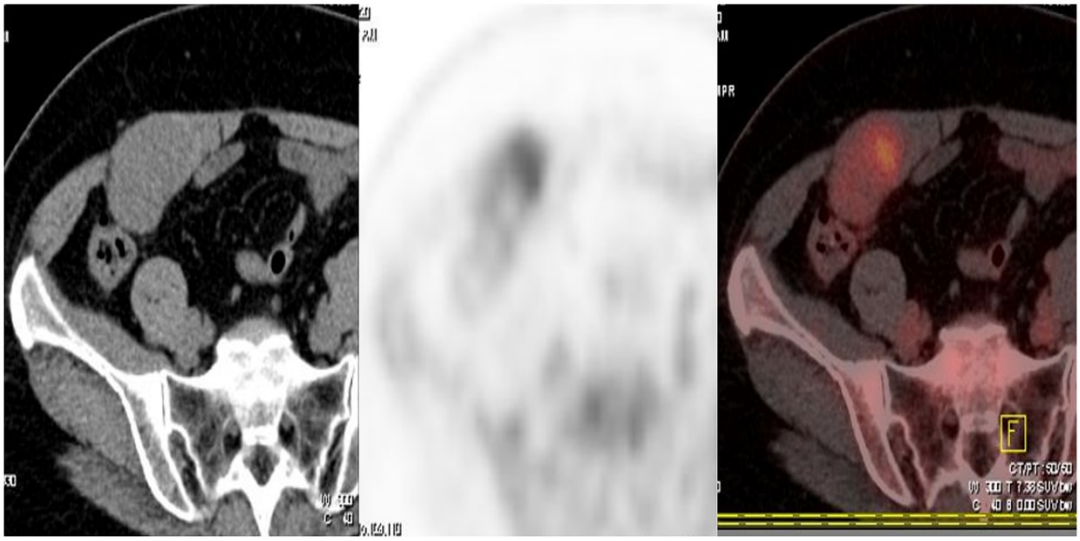

Figure 4. Surgical pathology in 2020

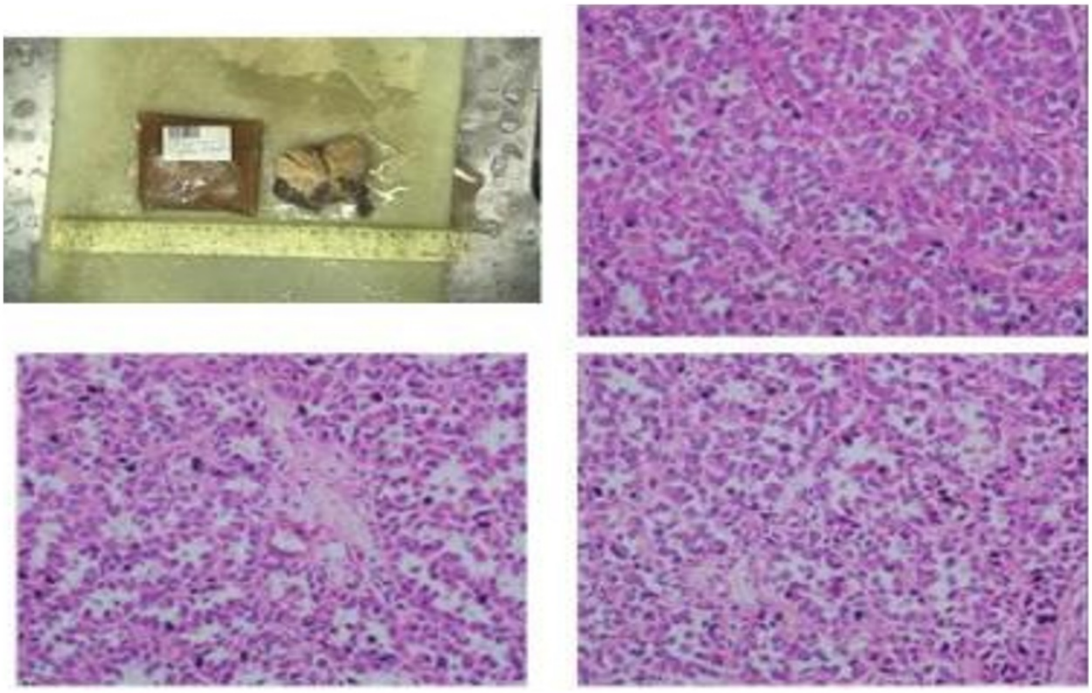

Figure 5. Follow-up of chest CT. A. 2021 chest CT showed the tumor was growing; B. 2022 chest CT showed the tumor volume was stable