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Therapy-Based Analysis in Ovarian Small Cell Neuroendocrine Carcinoma: A Case Series on Surgical, Chemotherapeutic, and Immunotherapeutic Outcomes

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Abstract

Background:

Neuroendocrine neoplasms (NENs) of the female reproductive tract are extremely rare, accounting for 1–2% of gynecological malignancies. Primary ovarian small cell neuroendocrine carcinoma (SCNEC) is an aggressive subtype with uncertain origin, early metastasis, and poor prognosis.

Methods:

We retrospectively analyzed seven cases of primary ovarian SCNEC diagnosed at Yunnan Cancer Hospital between August 2015 and January 2025, focusing on clinical features, treatment, and outcomes.

Results:

The median age was 47 years (14–72). Clinical stages were I (1), III (3), and IV (3). Common symptoms included abdominal pain, distension, and painless masses. Median tumor diameter was 12 cm (6–19), and all patients had elevated CA-125 and NSE. All underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy; five received postoperative platinum-based chemotherapy. One HRD/BRCA-negative stage IVB patient progressed after EP and TC combined with tislelizumab; another IVB patient developed brain metastases after EP plus bevacizumab and received whole-brain radiotherapy. At follow-up, 2 were disease-free, 2 lost to follow-up, 2 recurred, and 1 died of disease progression.

Conclusion:

Primary ovarian SCNEC is highly aggressive with poor prognosis. Despite surgery and chemotherapy, recurrence is common, and immunotherapy may be ineffective in advanced cases. Early detection and novel treatment strategies are urgently needed.

Background

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from neuroendocrine cells, most commonly arising in the gastrointestinal tract and lungs, while they are relatively rare in the head and neck region and reproductive system. Among gynecological malignancies, ovarian neuroendocrine tumors are exceedingly rare, accounting for approximately 0.1% of all ovarian tumors and less than 5% of all neuroendocrine neoplasms[1]. Primary ovarian neuroendocrine carcinomas (NECs) are particularly uncommon, and their pathogenesis remains largely unclear. Some reports suggest that a small proportion of cases may arise from mature teratomas[2].Due to limited understanding and experience in pathological diagnosis, NECs are currently classified into carcinoid, atypical carcinoid, small cell NEC, and large cell NEC. According to the 2017 World Health Organization (WHO) classification of neuroendocrine tumors of the female reproductive system, ovarian small cell carcinoma can be divided into two subtypes: small cell carcinoma of pulmonary type (SCCOP) and hypercalcemic type (SCCOHT)[3].Notably, SCCOHT may not belong to the neuroendocrine tumor family, and its pathogenesis appears to be associated with germline and somatic inactivating mutations of the SMARCA4 gene[4, 5].Primary ovarian small cell neuroendocrine carcinoma is an extremely rare and highly malignant ovarian tumor, characterized by uncertain tissue origin, aggressive behavior, early metastasis, frequent recurrence, and very poor prognosis. Its 1-year and 5-year survival rates are approximately 50% and 10%, respectively (Small Cell Carcinoma of the Ovary). Diagnosis of NECs relies primarily on histopathology, including immunohistochemistry, with common markers such as chromogranin A (Cg-A), synaptophysin (Syn), neuron-specific enolase (NSE), and CD56[6].Most studies on ovarian small cell carcinoma are based on case reports, and current treatment guidelines remain limited.

Through a retrospective analysis of 7 cases of ovarian small cell neuroendocrine carcinoma at our center, focusing on clinicopathological features, treatment strategies, and survival outcomes, this study aims to enhance understanding of this rare and highly aggressive malignancy and to improve clinical diagnostic and therapeutic approaches.

Case 1

In September 2022, a 14-year-old girl presented with abdominal distension and enlargement for more than one month. She had no history of sexual activity. Physical examination was inconclusive, but a large solid abdominal mass was palpable. Serum tumor markers showed NSE 168 μg/L, CA19-9 40.17 KU/L, and CA-125 340 KU/L. Pelvic MRI revealed bilateral adnexal mixed cystic-solid masses (left: 14.1 × 8.4 cm; right: 10.3 × 7.0 cm) (Fig. 1), suggesting ovarian malignancy. Diffuse thickening of the peritoneum, omentum, and mesentery with multiple nodules and masses was observed, along with hepatic nodules and enlarged pelvic and retroperitoneal lymph nodes, indicating possible metastases (Fig. 2).The patient underwent cytoreductive surgery, including bilateral adnexectomy and omentectomy. Grossly, the left adnexal mass measured 19 × 14 × 6 cm, with a gray-white to reddish cut surface, partly cystic, and showing serosal invasion involving the omentum and bladder peritoneum. Histopathology confirmed small cell neuroendocrine carcinoma (SCNEC) of the ovary. Immunohistochemistry revealed CD56(+), CD99(+), vimentin(+), partial synaptophysin(+), Ki-67 index of 40%, and negative chromogranin A, EMA, and LCA. Expert pathology review confirmed the diagnosis of ovarian SCNEC, stage IVA.Postoperatively, the patient received four cycles of etoposide plus cisplatin chemotherapy. Grade II myelosuppression developed during treatment. The patient and her family discontinued therapy and were discharged. Despite follow-up, she unfortunately died one year later.

Case 2

A 64-year-old postmenopausal woman (G4P2) presented to Yunnan Cancer Hospital on April 23, 2024, with a 2-week history of abdominal distension and pain. Physical examination revealed bilateral adnexal masses with unclear borders (approximately 11 × 6 cm). Serum tumor markers showed CA-125 of 599 U/mL, CA19-9 of 43 U/mL, and HE4 of 67 pmol/L. Abdominal CT revealed multiple pelvic masses, peritoneal and omental metastases, ascites, and enlarged lymph nodes. Cytologic examination of ascites showed suspicious adenocarcinoma cells. A biopsy of the pelvic mass revealed malignant tumor cells positive for synaptophysin (SYN), chromogranin A (CgA), and CD56, with Ki-67 index of approximately 90%(Fig. 3), consistent with small cell neuroendocrine carcinoma (SCNEC).Given extensive disease, primary cytoreductive surgery was not feasible, and the patient received two cycles of neoadjuvant TC chemotherapy (paclitaxel plus carboplatin). Follow-up CT on June 13 demonstrated a significant reduction in tumor size and serum marker levels. On June 15, interval debulking surgery was performed, including total hysterectomy, bilateral salpingo-oophorectomy, peritonectomy, diaphragmatic resection, omentectomy, and lymphadenectomy. Histopathology confirmed bilateral ovarian SCNEC with poor differentiation involving the diaphragm, peritoneum, omentum, and one para-aortic lymph node (FIGO stage IIIC).

Postoperatively, CA-125 was 109 U/mL. CT in early July revealed new nodules on the peritoneum and hepatic capsule, as well as enlarged lymph nodes and pleural effusion, suggesting recurrence. Two cycles of EP chemotherapy (etoposide + cisplatin) were administered until September 3, but subsequent imaging showed disease progression (PD).From September 4, the regimen was changed to tislelizumab (a PD-1 inhibitor) combined with TC chemotherapy. After two cycles, the patient reported symptom relief; CA-125 normalized, and CT on September 26 demonstrated reduced peritoneal lesions and fewer pulmonary nodules, achieving partial response (PR). Genetic testing revealed negative BRCA/HRD status but positive mutations in TP53, CDK12, and FANCA.However, on October 17, serum CA-125 rose to 30.4 U/mL and neuron-specific enolase (NSE) to 251 ng/mL. CT showed enlarged peritoneal and omental nodules, confirming disease progression(Fig. 4). Combination therapy with tislelizumab plus IP regimen or addition of niraparib was recommended, but the patient declined further treatment.

From August 2019 to December 2025, we conducted a retrospective review of the hospital database of the Gynecology Department of Yunnan Cancer Hospital and identified a total of 7 patients with primary small cell neuroendocrine carcinoma of the ovary (SCCO).All cases were confirmed by senior pathologists through re-examination of pathological sections.The follow-up period was defined as the interval from the initial diagnosis to the last contact or date of death. Follow-up procedures included routine gynecological examinations, contrast-enhanced CT and PET-CT scans, and assessments of tumor markers (CA-125, HE4, and CA-199). Tumor staging was performed according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) criteria for ovarian cancer. The final follow-up date was December 5, 2025. This study was approved by the Ethics Committee of Yunnan Cancer Hospital. We conducted a comprehensive analysis of the clinical and pathological characteristics, treatment modalities, and survival outcomes of these seven patients. Subsequent sections will present the research findings.

Result

The median age at the initial diagnosis of patients in this center was 48 years (range: 14 to 72 years)(Table 1). The most common clinical symptoms were abdominal distension (42.8%, 3 cases), followed by abdominal pain (28.6%, 2 cases), pelvic mass (28.6%, 2 cases), and abnormal vaginal bleeding (14.3%, 1 case).According to the International Federation of Gynecology and Obstetrics (FIGO)

staging, the distribution of the 7 patients was as follows: 3 cases were stage IV, 1 case was stage I, and 3 cases were stage III. All patients underwent abdominal ultrasound (US) and computed tomography (CT) examinations. The maximum diameter of the ovarian tumors was 19 cm, ranging from 1.5 to 19 cm. Among them, 5 cases were unilateral tumors and 2 cases were bilateral tumors.In a cohort of seven patients who underwent initial surgery, three received neoadjuvant chemotherapy. Seven patients underwent bilateral salpingo-oophorectomy (BSO) and hysterectomy; notably, one patient (Case 4) preserved her fertility. Additionally, three patients underwent para-aortic lymphadenectomy, all of whom exhibited lymph node metastasis. To achieve optimal tumor volume reduction, all seven patients underwent omentectomy; among them, three also had appendectomy performed.Immunohistochemical staining results revealed that all seven cases demonstrated positive staining for synaptophysin (SYN), with a positivity rate of 100%. Among the seven samples analyzed, two case was positive for chromogranin A (CgA) (28.6%), while two cases showed partial positivity for CgA (28.6%). Furthermore, five out of the seven samples were positive for CD56 (71.4%), and two exhibited partial positivity for CD56 (28.6%). Four samples tested positive for vimentin (VIM) at a rate of 57.1%.Postoperative, five patients received adjuvant therapy:Case 3 completed 4 cycles of EP regimen chemotherapy before switching to 9 cycles of TC regimen chemotherapy.Case 4 completed 4 cycles of EP regimen chemotherapy but developed grade II myelosuppression, after which the patient refused further treatment.Case 5 received 2 cycles of EP regimen chemotherapy before switching to the TEP regimen.Case 6 completed 5 cycles of EP regimen combined with bevacizumab, followed by single-agent bevacizumab maintenance therapy for 8 cycles, until brain metastasis was detected. The patient then underwent VMAT radiotherapy with the following plan: PTV 30 Gy/10 fractions, with local boost to the metastatic lesions (PGTV1-6: 36 Gy/10 fractions). After radiotherapy, bevacizumab maintenance therapy was continued for an additional 5 cycles until March 5, 2025.Case 7 received 2 cycles of EP regimen treatment, but tumor markers showed no significant decline, accompanied by mesenteric and peritoneal thickening with nodules (suggestive of possible metastasis). The regimen was switched to "tislelizumab + TC" for 2 cycles, after which pulmonary metastatic lesions appeared, along with multiple metastases involving the hepatic capsule, splenic capsule, peritoneum, omentum, and mesentery.

Table 1
Clinical presentation, tumour characteristics and treatment analysis of the included cases

Age	Clinical stage	Symptoms	CA-125	NSE	Laterality,size	Operation	Adjuvant therapy	Outcome
27	IV	Abdominal pain Painfuless mass	227.8	60.96	left, 9cm	BSO + TAH+OM	NO	NA
72	IIIC	Abdominal pain	154.4	104.7	right, 12cm	BSO + TAH + OM + AP+LN	NO	NA
42	IA	Abdominal bloating	274.1	26.64	left, 6cm right, 4cm	NACT + BSO+TAH + OM + AP+LN	4EP+9TC	NED24m
14	IV	Painfuless mass	340	168	right, 19cm	BSO + OM	4EP	DOD 8m
56	IIIA	Abdominal bloating	660	82.1	right, 14cm	BSO + TAH+OM	2EP+4TEP	NED26m
60	IVB	Vaginal bleeding	77.2	152	left, 10cm right, 3cm	NACT + BSO+TAH + OM	5(EP+Bevacizumab)+9(Bevacizumab) + 10Whole-brain radiotherapy +5(Bevacizumab)	AWD20m
64	IIIC	Abdominal bloating Abdominal pain	599	108	right, 12cm	NACT + BSO+TAH + OM+LN + AP	2EP + 2(TC+Tislelizumab)	AWD10m

AWD alive with disease, NED no evidence of disease, NA information not available,NA information not available.

All seven patients were followed up until April 2025. Two patients were lost to follow-up, while the remaining five had follow-up durations ranging from 8 to 26 months, with a median follow-up of 18 months. At the last follow-up, one patient had died due to disease progression, and four patients were alive. During the follow-up period, two patients experienced disease progression, including one case

of brain metastasis.Owing to the limited number of cases, the impact of clinical stage, histological subtype, and different treatment regimens on prognosis could not be adequately evaluated.

Discussion

This study presents a retrospective analysis of the diagnostic and therapeutic experiences in seven patients with primary small cell neuroendocrine carcinoma of the ovary, pulmonary type (SCCOPT). Despite the limited sample size, the observed heterogeneity in clinical outcomes and variable responses to treatment offer valuable insights into the clinical behavior of this rare and aggressive malignancy, underscoring both current therapeutic challenges and potential avenues for future investigation.

Currently, the mainstay of treatment for SCCOPT consists of surgery combined with adjuvant chemotherapy. Early-stage patients typically undergo radical surgery followed by chemotherapy, whereas advanced-stage disease requires maximal cytoreductive surgery. The role of lymphadenectomy remains controversial, as previous studies have reported inconsistent results regarding its prognostic value[7, 8], indicating that the decision should be individualized. Radiotherapy may play a role in controlling regional lymph node metastases and potentially improving outcomes[9]; however, its precise role in the management of SCCOPT warrants further investigation.

In recent years, advances in molecular profiling and immunotherapy have catalyzed the investigation of combination strategies involving immune checkpoint inhibitors (ICIs) and cytotoxic chemotherapy. The U.S. Food and Drug Administration (FDA) approved nivolumab and pembrolizumab for the treatment of small cell lung cancer (SCLC) between 2018 and 2019, based on pivotal findings from the CheckMate-032, KEYNOTE-028, and KEYNOTE-158 trials[10]. Subsequently, the IMpower133 and CASPIAN phase III trials demonstrated that first-line treatment with atezolizumab or durvalumab in combination with platinum-based chemotherapy significantly improved overall survival in patients with extensive-stage SCLC, leading to a Class I recommendation in the CSCO clinical guidelines[11].To date, clinical evidence regarding the use of ICIs in gynecologic neuroendocrine carcinomas remains sparse, limited primarily to isolated case reports. For example, a patient with ovarian small cell neuroendocrine carcinoma (SCNEC) achieved a partial response following six cycles of tislelizumab combined with etoposide and cisplatin (EP), followed by two cycles of tislelizumab maintenance therapy; however, this was accompanied by severe multi-organ immune-related adverse events (irAEs). Notably, the patient remained free of disease progression for over one year after completion of treatment[12].

Although immune checkpoint inhibitors (ICIs) have become a standard component in the treatment of extensive-stage small cell lung cancer (ES-SCLC) and are increasingly applied in gynecological neuroendocrine cancers, there remain significant differences and challenges in their clinical benefits and application strategies, evidence supporting their efficacy in small cell carcinoma of the ovary, pulmonary type, remains exceedingly limited[13]. The clinical course of Case 7 (FIGO stage IIIC) in this study provides a critical counterexample. Following disease progression on platinum-based chemotherapy, the patient was transitioned to tislelizumab in combination with chemotherapy; however, definitive disease progression (PD) was observed after only two cycles, indicating rapid primary resistance. This outcome stands in stark contrast to the occasional reports of immunotherapy benefit documented in the literature[12], strongly implying that SCCOPT may harbor distinct immunological features compared to SCLC. We hypothesize that the lack of response in this patient may result from a confluence of adverse factors, including an exceptionally high tumor burden, physical and immunosuppressive barriers imposed by widespread peritoneal carcinomatosis, and specific genomic alterations-such as TP53 and CDK12 mutations-that may collectively foster a profoundly immunosuppressive "cold tumor" microenvironment, thereby blunting the antitumor activity of ICIs[14, 15]. This case underscores that directly extrapolating immunotherapy paradigms from SCLC to SCCOPT is likely inadequate. Instead, there is an urgent need to develop biomarker-driven patient selection strategies-incorporating assessments of tumor mutational burden (TMB), PD-L1 expression, and tumor-infiltrating lymphocyte profiles-to identify the subset of patients who may genuinely derive clinical benefit from immune-based therapies.

In contrast to the limited efficacy of immunotherapy, the treatment course of Case 6 (FIGO IVB stage) in this study suggests that anti-angiogenic therapy may have certain clinical value in SCCOPT. This patient received EP regimen combined with bevacizumab after surgery and continued maintenance treatment. Although brain metastasis occurred during follow-up, it was controlled after whole brain radiotherapy. The total progression-free survival (PFS) still reached 20 months, and the patient maintained a tumor-bearing survival. Compared with the rapid progression of most advanced cases in this group, this patient achieved relatively long-lasting disease control. SCCOPT usually has the biological characteristics of rich blood supply and often accompanied by a large amount of ascites in the advanced stage, indicating active angiogenesis. The case of Case 6 indirectly supports the potential role of the VEGF pathway in the progression of SCCOPT and provides preliminary clinical evidence for future exploration of bevacizumab or other anti-angiogenic drugs combined with chemotherapy.

Although new therapeutic strategies have been constantly explored, this study still indicates that maximal cytoreductive surgery combined with platinum/etoposide-based chemotherapy remains the cornerstone of treatment for small cell carcinoma of the ovary, hypercalcemic type (SCCOPT). The timing of treatment and the initial treatment response have a significant impact on prognosis. Case 3 (FIGO IA stage) achieved a 24-month disease-free survival (NED) after primary surgery and adjuvant chemotherapy (4 cycles of EP regimen combined with 9 cycles of TC regimen); while Case 1 (14 years old, FIGO IVA stage), despite undergoing cytoreductive surgery and 4 cycles of EP chemotherapy, died within 8 months due to disease progression because of large tumor burden and advanced stage. The contrasting outcomes of the two patients highlight the importance of early diagnosis and satisfactory cytoreductive surgery, and also indicate that there are significant individual differences in the sensitivity of SCCOPT to conventional chemotherapy, and the mechanism of drug resistance still needs further clarification.

Conclusion

Overall, despite the wide age range of affected patients, clinical outcomes were uniformly unfavorable, underscoring the lack of effective treatment strategies for ovarian neuroendocrine carcinoma. The main limitations of this study include the small sample size, absence of comprehensive molecular profiling, and limited follow-up, which preclude definitive conclusions. Nevertheless, this report provides valuable real-world evidence and suggests that immunotherapy and targeted therapy may have potential value in carefully selected patients. Future multicenter studies incorporating molecular classification and immune-related biomarkers are warranted to enable more precise and individualized treatment approaches.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Yunnan Cancer Hospital approved this study.Patients signed informed consent for their data to be used for scientificpurposes.

Consent for publication

Written informed consent was obtained from all participants, explicitly permitting the collection and use of clinical data for academic research.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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Author Contribution

DF, XXJ and ZL:Study design. DF and XT: Data extraction, case analysis, and manuscript writing,they contributed equally to this work. SJL: Case analysis. and MW: Diagnosis approach design. ZL: Manuscript editing. All authors approved the final version of the manuscript.

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Availability of data and materials

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

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Figures

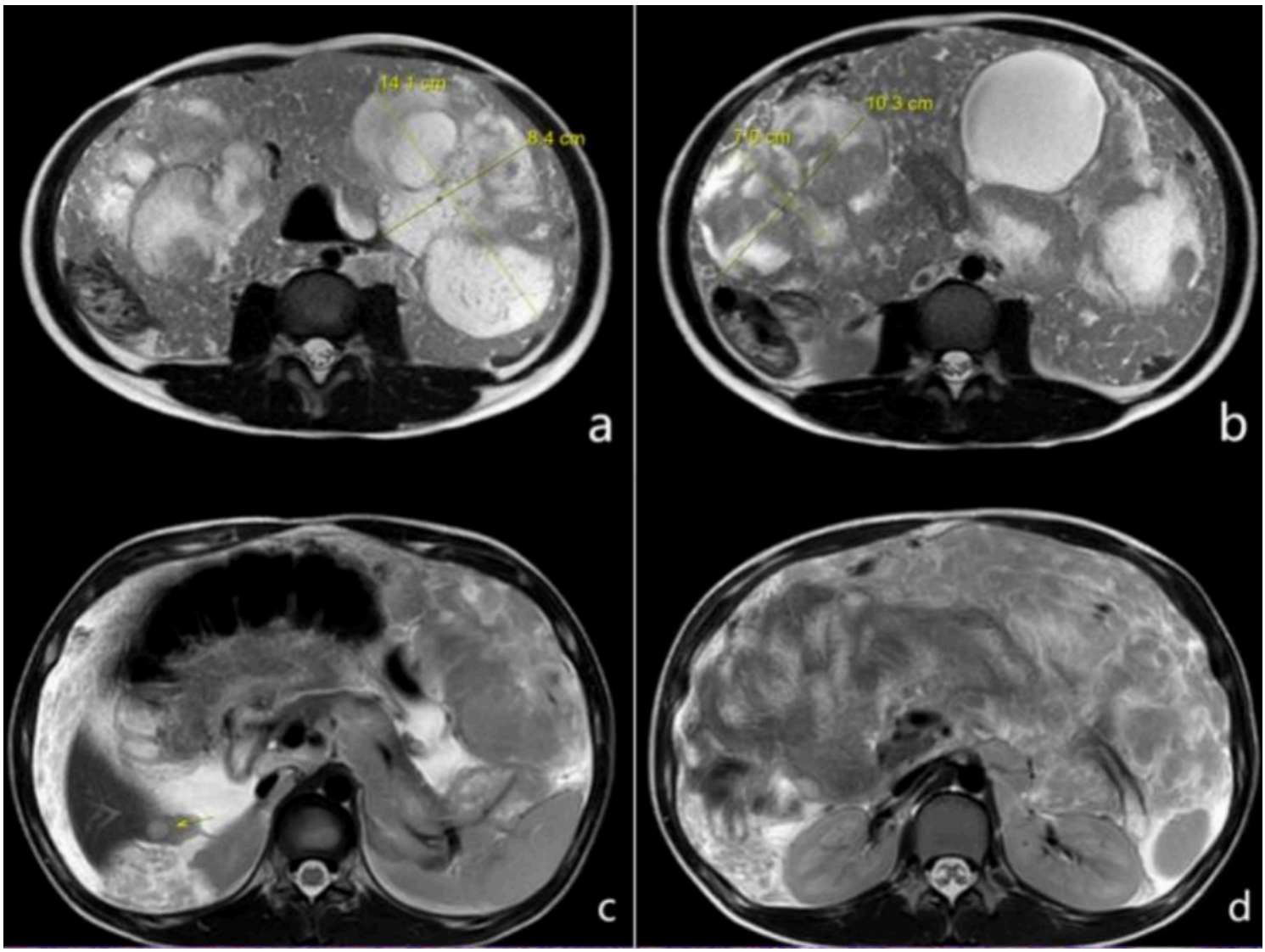


Figure 1

Pelvic-abdominal MRI (a-d): T2-weighted images show bilateral adnexal cystic-solid mixed masses, with (a) the left mass measuring 14.1x8.4 cm, (b) the right mass approximately 10.3x7.1 cm, (c) liver metastases, and (d) multiple tumors and metastases in the pelvic-abdominal cavity.

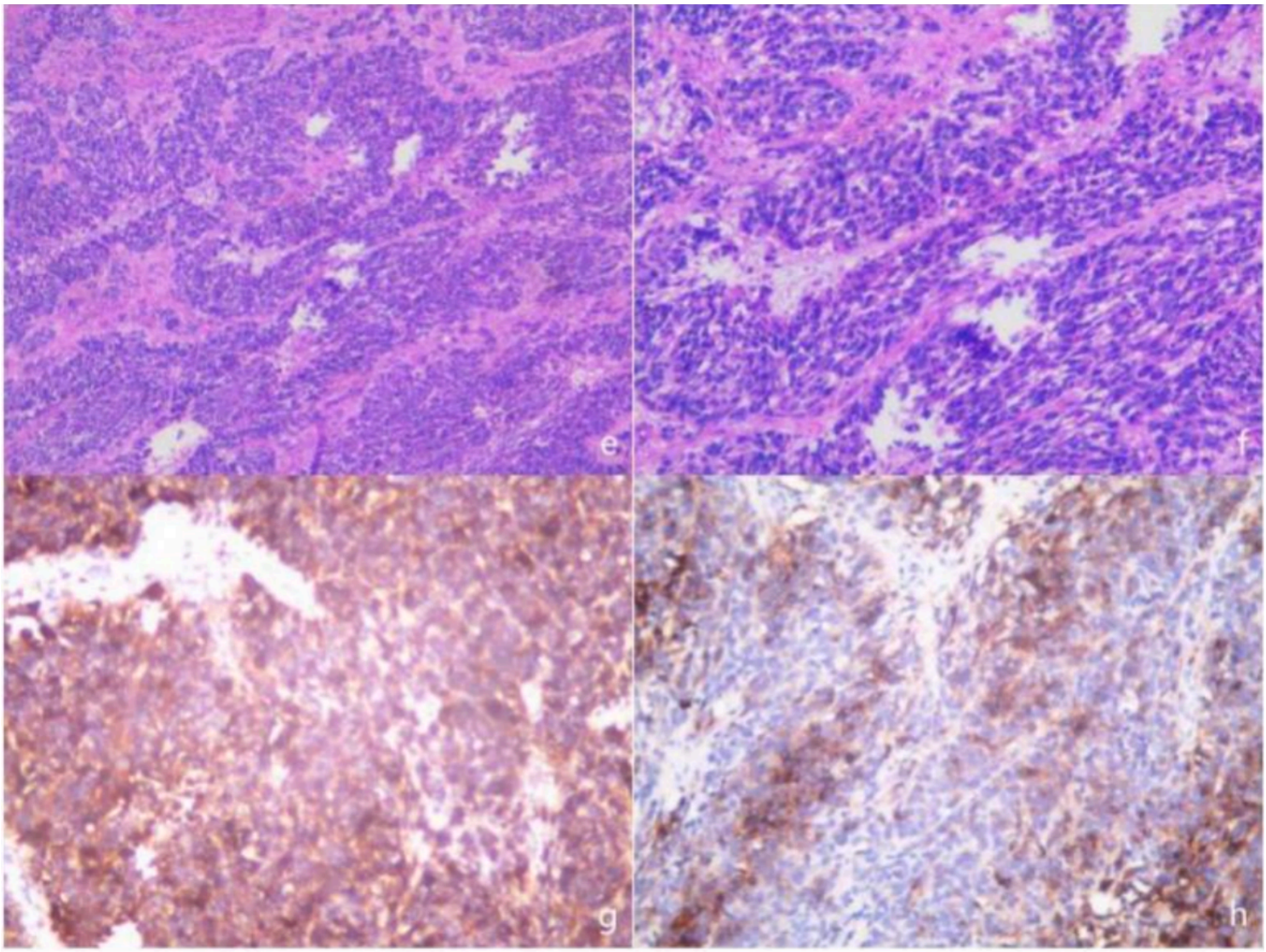


Figure 2

H&E staining as shown in (e) - HE X 5 and (f) - HE X 10 reveals cells of relatively uniform size, with a homogeneous appearance and round or ovoid nuclei. Immunohistochemistry: (g) CD56+, (h) partially SYN+.

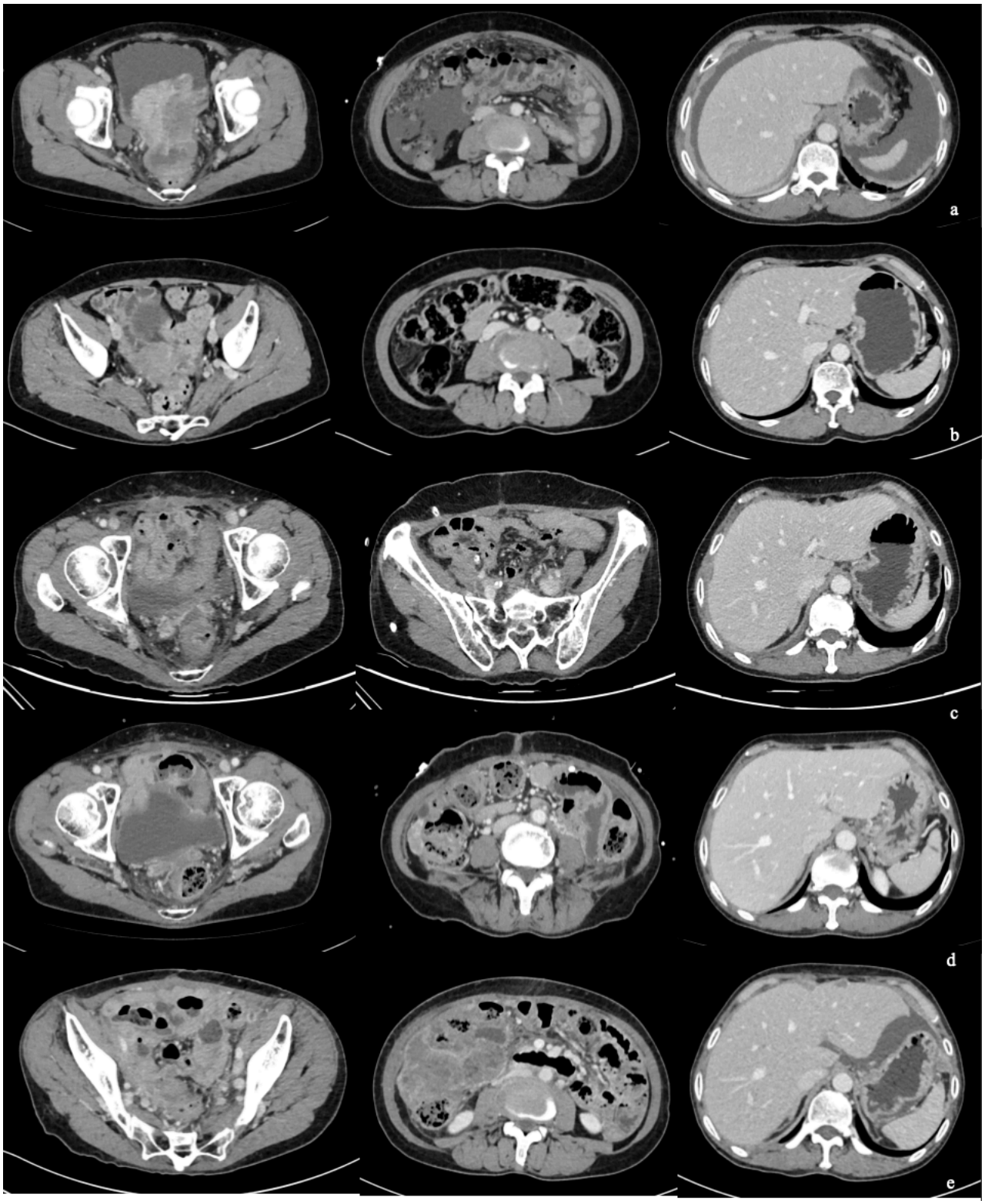


Figure 3

Longitudinal CT imaging demonstrating disease response and subsequent progression. a. 2024-04-25: Baseline CT showed a pelvic mass with omental and peritoneal metastases and associated ascites. b. 2024-06-12 Follow-up CT demonstrated a marked reduction in the pelvic mass, decreased peritoneal and omental disease, and reduced ascites. c. 2024-07-04: Approximately two weeks postoperatively, CT revealed vaginal stump soft-tissue thickening, postoperative lymphocele, peritoneal thickening, hepatic capsular thickening, and newly developed nodular lesions. d. 2024-08-30:The vaginal stump remained stable. The postoperative lymphocele persisted. Peritoneal thickening with nodules showed mixed changes, with partial progression and stability. Hepatic capsular lesions showed partial regression. e. 2024-01-15: CT demonstrated marked disease progression, with enlarging peritoneal nodules and mass

lesions invading adjacent bowel walls, as well as newly developed hepatic capsular thickening and nodules. The vaginal stump remained stable, and the lymphocele was nearly completely resolved.

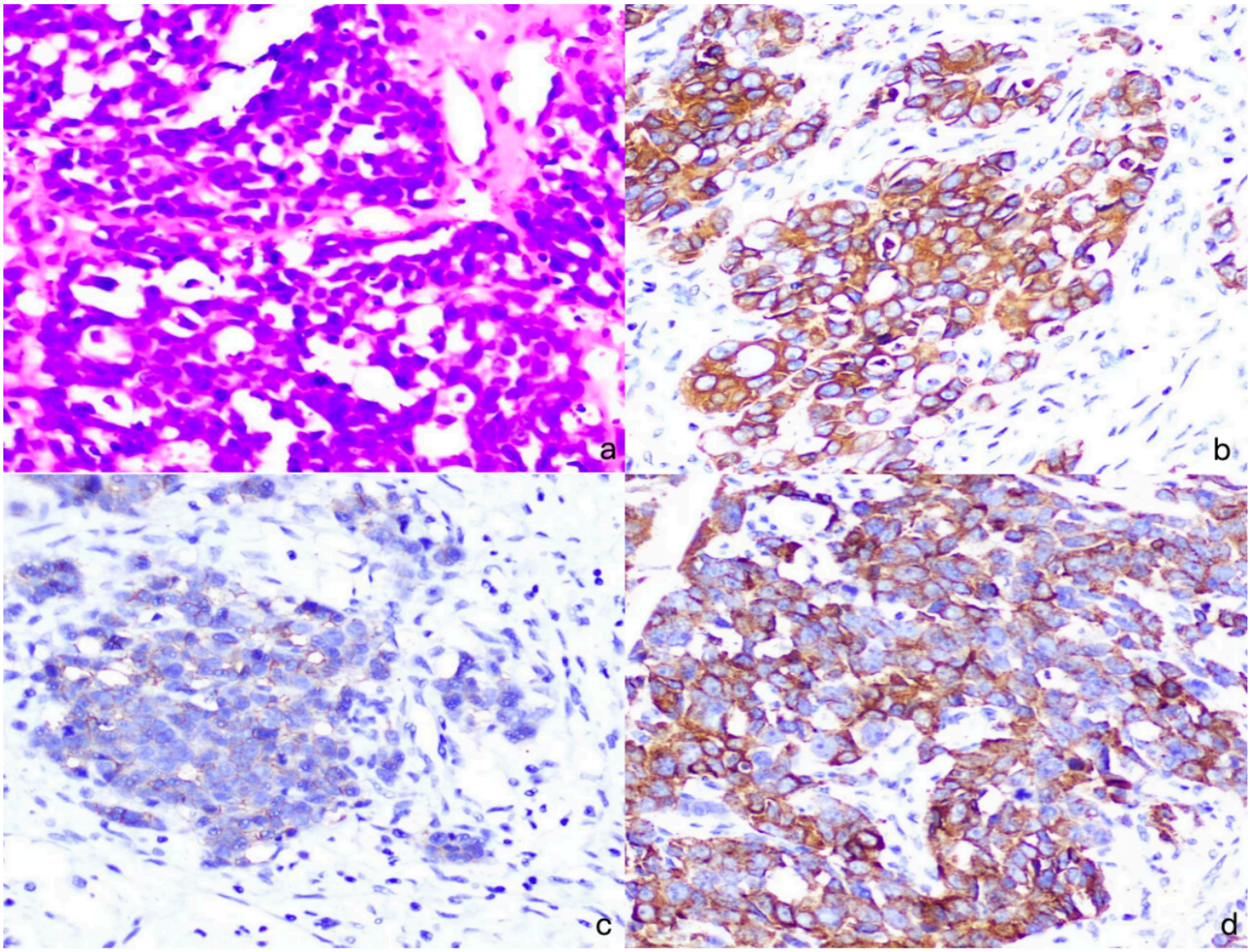


Figure 4

shows the results of histopathological and immunohistochemical staining. a. CK (200×; H&E staining); b. Positive staining for SYN (200×); c. Positive staining for CD56 (200×); d. Positive staining for CGA (200×).