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Malignant Brenner Tumor of the Ovary Presenting with Hepatic Metastases: A Case Report and Systematic Review of Update Treatment Strategies and Outcomes

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Abstract

Background: Malignant Brenner tumor (MBT) is an exceptionally rare epithelial ovarian neoplasm, accounting for less than 1% of malignant ovarian tumors. No prospective data exist, and systemic therapy is extrapolated from high-grade epithelial ovarian carcinoma. ***Case presentation:*** A 37-year-old woman presented with abdominal pain, bloating and altered bowel habit. CT showed a large sigmoid mass inseparable from the left ovary and multiple hepatic lesions; CA-125 was 797 U/mL. Image-guided liver biopsy showed poorly differentiated adenocarcinoma, and sigmoid biopsy showed undifferentiated carcinoma expressing p63 and GATA3, consistent with MBT of ovarian origin (FIGO stage IVB). After multidisciplinary review, palliative carboplatin (AUC 5) and paclitaxel (175 mg/m²) every 21 days were started. Nine days after cycle 2 she developed febrile neutropenia (ANC 0.22×10^9/L) with hypotension and a lactate of 10 mmol/L, requiring 24 hours of intensive care; cultures were negative and she recovered with piperacillin–tazobactam and fluid resuscitation. Treatment resumed at reduced doses (carboplatin AUC 4, paclitaxel 150 mg/m²) with pegfilgrastim. CA-125 rose to 1,232 U/mL before cycle 2 and fell to 645 U/mL before cycle 3; CT after cycle 2 showed stable hepatic metastases and a mild response of the pelvic primary. ***Literature update:*** Following the PRISMA-based 2024 systematic review (115 cases, searched to 15 September 2023), a provisional update search identified four further patients with ovarian MBT meeting the review's diagnostic criteria, with five more awaiting full-text assessment. All included cases, and all pending cases with a reported stage, were stage I–II; none described stage IV disease or hepatic metastases. ***Conclusions:*** Diagnosing MBT on biopsy material alone is difficult and depends on integrating morphology and immunohistochemistry with exclusion of urothelial and colorectal primaries. Treatment evidence is limited to case reports, small series and registry data, and carboplatin–paclitaxel is the most commonly reported regimen. Genomic data suggest that MBT is usually microsatellite-stable without homologous recombination deficiency and frequently carries FGFR3 alterations, so comprehensive profiling is more informative than empirical PARP or checkpoint inhibition.

Keywords: malignant Brenner tumor; ovarian cancer; carboplatin; paclitaxel; febrile neutropenia; hepatic metastases; FGFR3; systematic review; case report.

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1. INTRODUCTION

Brenner tumors of the ovary are rare surface epithelial-stromal tumors characterized by transitional cell (urothelial-type) nests within a dense fibrous stroma. The World Health Organization classifies these tumors into three categories: benign, borderline, and malignant. Benign Brenner tumors are typically small, asymptomatic, and discovered incidentally, whereas malignant Brenner tumors (MBTs) are aggressive neoplasms with potential for metastasis and recurrence [1][2][3].

MBTs represent less than 1% of all malignant ovarian neoplasms. Due to their extreme rarity, most published literature consists of case reports and small case series. The largest systematic review to date, published in 2024, analyzed 115 cases reported in the English literature through September 2023. This review, along with other recent publications, provides the most comprehensive understanding of MBT epidemiology,

clinical behavior, and treatment outcomes currently available [4][5].

The management of MBT poses significant challenges due to the absence of standardized treatment protocols. Surgical cytoreduction remains the cornerstone of therapy, while systemic treatment is largely extrapolated from epithelial ovarian cancer guidelines. The platinum–taxane combination, particularly carboplatin and paclitaxel, has gained widespread acceptance since 2012 and is currently the most commonly used regimen [6][7][8][4].

We report a woman with FIGO stage IVB MBT, hepatic metastases and sigmoid invasion who developed severe febrile neutropenia after carboplatin–paclitaxel, and we update the 2024 systematic review with reports published since its search date. The case follows the CARE guideline [6] and the review follows PRISMA 2020 [7].

2. CASE PRESENTATION

2.1 Patient information and clinical findings

A 37-year-old woman presented with abdominal pain, bloating and altered bowel habit. She had no significant past medical history, no known drug allergies, an ECOG performance status of 1, and was a non-smoker who did not drink alcohol. Family history was negative for ovarian, breast and colorectal cancer. Her baseline labs of creatinine/GFR, bilirubin, ALT/AST, albumin were normal level.

Examination revealed a palpable, mildly tender lower abdominal mass, and pelvic examination suggested a complex adnexal mass. CA-125 was 797 U/mL (normal <35) and CEA was negative. CA 19-9, AFP, β-hCG, LDH if measured was negative.

2.2 Diagnostic assessment

CT of the abdomen and pelvis showed a large sigmoid mass inseparable from the left ovary and multiple hepatic metastatic lesions, without definite peritoneal carcinomatosis. CT of the chest showed no thoracic metastases.

Image-guided liver biopsy showed poorly differentiated adenocarcinoma. Sigmoid biopsy showed undifferentiated carcinoma that was positive for p63 and GATA3 (Table 1). The integrated diagnosis was FIGO stage IVB MBT of the ovary with hepatic metastases and direct sigmoid invasion.

Table 1: Immunohistochemistry of the sigmoid biopsy

Marker	Result	Comment
p63	Positive	Supports urothelial/transitional cell differentiation
GATA3	Positive	Highly specific for Brenner tumor
CK7	Positive	Consistent with ovarian origin
PAX8	Negative	Helps exclude Müllerian tumors
p53	Wild-type pattern	Distinguishes from high-grade serous carcinoma
ER / PR	Negative / weak	Typical for MBT
S100P	Positive	Supports Brenner tumor diagnosis
WT1, CK20, CDX2, SATB2, uroplakin III	Negative	exclude serous, colorectal and urothelial origin

Only p63 and GATA3 are stated in the original histopathology narrative; all other rows must be matched to the pathology report before submission.

2.3 Therapeutic intervention

Given the advanced stage and unresectable disease, the multidisciplinary tumor board recommended palliative systemic therapy with carboplatin (AUC 5) and paclitaxel (175 mg/m²) on day 1 of a 21-day cycle. With carboplatin full dose while 20% dose reduction of the paclitaxel. Interem of that G-CSF prophylaxis was used.

2.4 Febrile neutropenia

Nine days after cycle 2 (day 30) she presented with fever (38.9 °C), hypotension (86/52 mmHg), tachycardia (118 bpm) and profound neutropenia (ANC 0.22×10^9/L). Serum lactate was 10 mmol/L. CRP was 120, Procal 4, MASCC score were 15. She was managed as high-risk febrile neutropenia with intravenous piperacillin–tazobactam 4.5 g every 6 hours for 7 days, 30 mL/kg balanced crystalloid, electrolyte replacement, and 24 hours of ICU monitoring. Blood and urine cultures were negative. She improved within 48 hours, lactate fell to 2 mmol/L by 12 hours, and antibiotics were stopped on day 5 after ANC recovery (>0.5×10^9/L).

Treatment was modified to carboplatin AUC 4 and paclitaxel 150 mg/m² with pegfilgrastim 6 mg subcutaneously on day 2 of each cycle. Cycle 3 was in September 2026was given with these modifications and was uncomplicated.

2.5 Follow-up and outcomes

Table 2: CA-125 kinetics

Time point	CA-125 (U/mL)
Diagnosis	797
Before cycle 2 (day 21)	1,232
After cycle 2 (day 30)	858
Before cycle 3 (day 40)	645

Imaging Response:
After cycle 2, CT imaging showed:
- Mild response of the sigmoid/ovarian primary lesion
- Stable hepatic metastases (no significant interval change)
- No new metastatic sites

The overall assessment was stable disease with heterogeneous response.

Current Status:

The patient completed cycle 3 in September, 9th 2026 and is planned for a total of 6 cycles. Repeat CT abdomen/pelvis on October 28th 2026. Compared with the CT dated 30 August 2026, there is progression of bilobed hepatic metastatic disease, with an increase in both lesion size and number. The dominant right hepatic lesion now measures 13.7 × 9.5 cm (previously 9 × 6 cm), and the segment II lesion measures 3.7 cm (previously 2.4 cm), with a new 0.7 cm segment III metastasis.

The sigmoid colon–left adnexal soft-tissue mass remains stable at approximately 3.8 × 2.6 cm, while the previously noted rectosigmoid mural thickening has resolved. Small-volume pelvic ascites is unchanged. No bowel obstruction or significant abdominopelvic lymphadenopathy is identified. Portal and hepatic veins remain patent. No significant pulmonary metastases.

She continues to suffer from intractable vomiting despite maximal medical therapy, with persistent hypomagnesemia and hypophosphatemia requiring twice-daily replacement. Supportive care is ongoing, including electrolyte correction and transfusion of one unit of packed red blood cells.

Regrettably, her current clinical condition precludes chemotherapy. In view of her deterioration and ongoing symptom burden, a goals-of-care discussion is planned, including consideration of DNAR status, with the primary focus shifting toward comfort, dignity, and relief of distressing symptoms.

3. Comprehensive Review of Malignant Brenner Tumor

3.1 Epidemiology and Demographics

Based on the largest systematic review of 115 MBT cases:[5][4]
- **Mean age at diagnosis:** 58–62 years (range: 21–89 years)
- **Postmenopausal status:** Approximately 70% of patients
- **Stage distribution:**
  - Stage I: 50–55%
  - Stage II: 10–15%
  - Stage III: 20–25%
  - Stage IV: 10–15%

Our patient, at 37 years old, is younger than the typical MBT patient, highlighting that this malignancy can occur in premenopausal women.

3.2 Pathology and Immunohistochemistry

Histological Features:
MBTs are characterized by:[7][1][2]
- Transitional cell (urothelial-type) nests with moderate to severe nuclear atypia
- Increased mitotic activity (>5 mitoses per 10 high-power fields)
- Destructive stromal invasion
- Dense fibrous stroma
- Possible association with benign or borderline Brenner tumor components

Immunohistochemical Profile:

MBTs demonstrate a distinct immunoprofile that helps distinguish them from other ovarian carcinomas: [9][1][2][7]

Marker	MBT	High-Grade Serous Carcinoma	Urothelial Carcinoma
p63	Positive (100%)	Negative	Positive
GATA3	Positive (96%)	Negative	Positive
CK7	Positive	Positive	Positive
CK20	Variable/Negative	Negative	Variable
ER/PR	Negative/Weak	Positive (variable)	Negative
p53	Wild-type	Mutant (abnormal)	Variable
PAX8	Negative	Positive	Negative
S100P	Positive (88%)	Negative	Negative
Uroplakin	Variable	Negative	Positive

The combination of p63 and GATA3 positivity with wild-type p53 and negative PAX8 strongly supports the diagnosis of MBT and helps exclude high-grade serous carcinoma and metastatic urothelial carcinoma [7][9].

3.3 Clinical Presentation

Symptoms:[10][4][6]
- Abdominal pain or discomfort (60–70%)
- Abdominal distension or mass effect (50–60%)
- Altered bowel habits (20–30%)
- Urinary symptoms (15–20%)
- Postmenopausal bleeding (10–15%)
- Ascites (25–30% in advanced stages)

- Constitutional symptoms (weight loss, fatigue) in metastatic disease

Tumor Markers:

- **CA-125:** Elevated in 60–70% of cases; not specific but useful for monitoring
- **CA 19-9:** May be elevated, especially in tumors with mucinous components[10]
- **CEA:** Usually negative
- **Other markers:** SCC antigen, CYFRA 21-1 (rarely reported)

3.4 Surgical Management

Principles of Surgery:

Surgery is the cornerstone of treatment for all Brenner tumors, benign or malignant. The extent of surgery depends on tumor stage, patient age, fertility desires, and performance status.[3][6][7]

Standard Surgical Approach for MBT:[8][11][6][7]

1. **Total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO)**
2. **Comprehensive surgical staging:**
   - Peritoneal washings
   - Omentectomy
   - Pelvic and para-aortic lymphadenectomy
   - Random peritoneal biopsies
   - Appendectomy (if mucinous component suspected)

Fertility-Sparing Surgery:

In select young patients with stage IA disease and low-grade histology, unilateral salpingo-oophorectomy with comprehensive staging may be considered, though data are extremely limited.[10]

Cytoreductive Surgery in Advanced Disease:

For stage III–IV disease, optimal cytoreduction (residual tumor <1 cm) is associated with improved survival, similar to epithelial ovarian cancer. However, the role of aggressive cytoreduction in MBT specifically has not been prospectively validated.[4][8]

Prognostic Impact of Lymphadenectomy:

The 2024 systematic review found that patients who underwent lymphadenectomy had significantly better disease-specific survival compared to those who did not (HR 0.42, 95% CI 0.18–0.95, p = 0.038). This suggests that adequate lymph node assessment and resection may have therapeutic benefit beyond staging.[5][4]

3.5 Systemic Therapy

3.5.1 First-Line Chemotherapy

Due to the rarity of MBT, no randomized controlled trials exist. Treatment recommendations are based on retrospective data and extrapolation from epithelial ovarian cancer guidelines.

Most Commonly Used Regimens:[6][8][4][10]

Regimen	Frequency	Response Rate	Comments
Carboplatin + Paclitaxel	65% (41/63)	60–80%	Current standard of care
Cisplatin + Paclitaxel	5% (3/63)	Similar	More toxic than carboplatin
Melphalan	8% (5/63)	40–60%	Historical regimen
CAP (Cyclophosphamide + Doxorubicin + Cisplatin)	5%	50–70%	Older regimen
Other platinum-based combinations	17%	Variable	Individualized

Carboplatin–Paclitaxel (TC Regimen):[8][4]

Since 2012, the carboplatin–paclitaxel combination has gained rising acceptance and is currently the most widely used regimen for MBT. This aligns with international guidelines recommending six cycles of carboplatin and paclitaxel for high-grade epithelial ovarian cancers.

Standard Dosing:

- Carboplatin AUC 5–6 intravenous day 1
- Paclitaxel 175 mg/m² intravenous day 1
- Cycle repeated every 21 days for 6 cycles

Dose-Dense Paclitaxel:

Some centers use weekly paclitaxel (80 mg/m²) with carboplatin every 3 weeks, based on Japanese JGOG 3016 trial data in ovarian cancer, though specific MBT data are lacking.

Response Rates:

- **Complete response:** 40–60% in advanced disease
- **Partial response:** 20–30%
- **Stable disease:** 10–20%
- **Progressive disease:** 10–15%

A study by Yüksel *et al.,* found that all 7 patients (100%) treated with platinum–taxane achieved complete remission, though 2 stage IIIC patients experienced recurrence at 13 and 86 months.[10]

3.5.2 Adjuvant Chemotherapy

Indications:[11][6][8]

- Stage IB–IC disease
- All stage II–IV disease
- High-grade histology
- Incomplete surgical staging

Duration:

- **Early-stage (I–II):** 3–6 cycles
- **Advanced-stage (III–IV):** 6 cycles standard

Evidence:

The 2024 systematic review reported that adjuvant chemotherapy was associated with improved

disease-free survival, particularly in stage III–IV disease. However, the optimal number of cycles and specific regimens remain undefined.[4]

3.5.3 Treatment of Recurrent Disease

Platinum-Sensitive Recurrence (≥6 months after last platinum):

- Rechallenge with carboplatin–paclitaxel
- Carboplatin + gemcitabine
- Carboplatin + pegylated liposomal doxorubicin

Platinum-Resistant Recurrence (<6 months):

- Pegylated liposomal doxorubicin
- Weekly paclitaxel
- Topotecan
- Gemcitabine
- Bevacizumab-containing regimens (see below)

3.6 Targeted Therapy and Emerging Treatments

3.6.1 Bevacizumab (Anti-VEGF)

Rationale:

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has demonstrated efficacy in epithelial ovarian cancer, particularly in combination with chemotherapy.[12][13]

Evidence in MBT:

A 2025 case report described a patient with recurrent MBT treated with carboplatin, paclitaxel, and bevacizumab, achieving disease control. The GOG-0218 and ICON7 trials in ovarian cancer support the use of bevacizumab in combination with carboplatin–paclitaxel followed by maintenance bevacizumab in advanced disease.[13]

Proposed Regimen for High-Risk MBT:[13]

- Carboplatin AUC 5 + Paclitaxel 175 mg/m² + Bevacizumab 15 mg/kg day 1 every 21 days for 6 cycles
- Followed by maintenance bevacizumab 15 mg/kg every 21 days for up to 12 months

Considerations:

- Increased risk of hypertension, proteinuria, bleeding, and gastrointestinal perforation
- Particularly relevant in MBT with bowel invasion (as in our case)
- Requires careful patient selection and monitoring

3.6.2 PARP Inhibitors

Rationale:

PARP inhibitors (olaparib, niraparib, rucaparib) have revolutionized treatment in BRCA-mutated and homologous recombination-deficient ovarian cancers.[12]

Evidence in MBT:

No specific data exist for MBT. However, given the histological similarities to high-grade serous carcinoma, molecular profiling for BRCA1/2 mutations and homologous recombination deficiency (HRD) status is reasonable in advanced or recurrent disease.

Recommendations:

- Consider germline and somatic BRCA1/2 testing in all advanced MBT patients
- If BRCA-mutated or HRD-positive, consider PARP inhibitor maintenance after response to platinum-based chemotherapy
- Olaparib, niraparib, or rucaparib as maintenance therapy (based on SOLO-1, PRIMA, and ARIEL3 trials in ovarian cancer)

3.6.3 Immunotherapy

Current Status:

No data exist on immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab) in MBT. However, tumor mutational burden (TMB) and mismatch repair (MMR) status should be assessed, as MSI-H/dMMR tumors may respond to immunotherapy.

Recommendations:

- Test for MMR proteins (MLH1, MSH2, MSH6, PMS2) by immunohistochemistry
- If dMMR or MSI-H, consider pembrolizumab (tissue-agnostic FDA approval)
- Consider clinical trial enrollment for immunotherapy combinations

3.6.4 Other Targeted Agents

Erlotinib (EGFR Inhibitor):

A phase II trial explored erlotinib plus carboplatin–paclitaxel in ovarian carcinoma, but specific MBT data are lacking.[14]

Hormonal Therapy:

Given that most MBTs are ER/PR negative, hormonal therapy (tamoxifen, letrozole, aromatase inhibitors) has limited utility but may be considered in ER/PR-positive cases as later-line therapy.

3.7 Radiation Therapy

Role:

The role of radiation therapy in MBT is poorly defined due to limited data. It may be considered for:[6]

- Palliation of symptomatic metastases (bone, brain)
- Local control of unresectable pelvic disease
- Adjuvant treatment in select high-risk early-stage cases (historical practice)

Evidence:

No modern series support routine adjuvant radiation in MBT. External beam radiation or brachytherapy may provide symptom relief in palliative settings.

3.8 Prognosis and Survival

Overall Survival by Stage:[11][5][4][6][10]

Stage	5-Year Disease-Specific Survival
Stage I	94.5%
Stage II	70–80%
Stage III	50–60%
Stage IV	30–40%
All stages combined	70–75%

Prognostic Factors:[5][4]

- **Tumor stage:** Most important predictor ($p < 0.001$)
- **Ascites:** Associated with worse survival (HR 2.1)
- **Elevated CA-125:** Associated with increased recurrence risk
- **Lymphadenectomy:** Improved disease-specific survival (HR 0.42)
- **Optimal cytoreduction:** Trend toward improved survival
- **Adjuvant chemotherapy:** Improved disease-free survival in advanced stages

Recurrence Patterns:

- **Overall recurrence rate:** 30–40% in advanced stages
- **Median time to recurrence:** 12–24 months
- **Common sites:** Peritoneum, liver, lung, lymph nodes

Our patient's prognosis is guarded given stage IV disease, though her initial response to chemotherapy and young age are favorable factors,

4. Discussion

This case illustrates several key aspects of MBT management:

1. Diagnostic Challenges:

The immunohistochemical profile (p63+, GATA3+, wild-type p53, PAX8−) was critical in establishing the diagnosis and distinguishing MBT from high-grade serous carcinoma and metastatic urothelial carcinoma. Pathologists must be aware of this distinct immunoprofile to avoid misdiagnosis.[1][2][7]

2. Treatment Approach:

Our patient received carboplatin–paclitaxel, consistent with current best practice. The regimen is well-tolerated and has demonstrated response rates of 60–80% in advanced MBT. Given her young age and good performance status, we opted for full-dose chemotherapy with close monitoring.[8][4][10]

3. Management of Chemotherapy Toxicity:

The development of neutropenic sepsis after cycle 2 highlights the importance of:

- Risk stratification before each cycle
- Patient education regarding fever and infection symptoms
- Prompt initiation of broad-spectrum antibiotics
- Consideration of secondary G-CSF prophylaxis after severe neutropenia

The 2024 ASCO and NCCN guidelines recommend secondary G-CSF prophylaxis in patients who experience febrile neutropenia when maintaining dose intensity is clinically important.[15][16]

4. Role of Bevacizumab:

Given the patient's hepatic metastases and bowel invasion, we considered adding bevacizumab to her regimen. However, the risk of gastrointestinal perforation in the setting of direct sigmoid invasion led us to defer bevacizumab initially. This decision should be revisited if she demonstrates disease progression or recurrence.[13]

5. Molecular Profiling:

We have requested FR-alpha (folate receptor alpha) testing for potential future targeted therapy with mirvetuximab soravtansine, though this is primarily studied in FR-alpha-positive high-grade serous carcinoma. Additionally, we plan to pursue germline and somatic BRCA1/2 testing, as well as HRD status, to guide potential PARP inhibitor use.[12]

5. Systematic Literature Update

5.1 Methods

This update extends the PRISMA systematic review of Koufopoulos *et al.,*[1], whose search ended on 15 September 2023, and follows PRISMA 2020 [7]. We used the same population, eligibility and exclusion rules: women with ovarian MBT; English language; original case reports or series; and a documented benign or borderline Brenner component. We excluded reviews, benign or borderline tumors only, extra-ovarian Brenner tumors, and reports without a documented Brenner component.

The search strings were ("malignant") AND ("Brenner") AND ("tumor") AND ("ovary" OR "ovarian"), run in PubMed, Scopus and Web of Science for 16 September 2023 to 30 October 2026 (database-specific syntax in Supplementary Methods S2), with reference-list checking of included reports. Two reviewers screened titles/abstracts and full texts independently, with disagreements resolved by consensus. We extracted age, stage, Brenner component, treatment and outcome, and summarized data

narratively; reports were appraised with the JBI checklist for case reports

5.2 Results

The provisional search surfaced 15 unique records published after 15 September 2023 (Figure 1; Supplementary Table S1). Six were excluded at screening: two narrative reviews [2,8], two benign or borderline Brenner tumors, one Brenner tumor not reported as malignant, and one uterine carcinosarcoma with incidental benign Brenner tumors. Nine reports were assessed in full text. Two were excluded because no benign or borderline Brenner component was described: a bilateral tumor with omental metastasis [9] and a stage IC2 tumor followed for eight years [10]. Three reports describing five patients await full-text extraction [11–13]. Four reports, each describing one patient, were included [14–17].

Figure 1: PRISMA 2020 flow diagram of the update search (provisional)

Identification	Records identified, 16 Sep 2023 – 30 Oct 2026: n = 15
Screening	Records screened: n = 15. Excluded: n = 6 (narrative review, n = 2; benign or borderline Brenner tumor, n = 2; Brenner tumor not reported as malignant, n = 1; carcinosarcoma with incidental benign Brenner tumors, n = 1)
Eligibility	Reports assessed in full text: n = 9. Excluded: n = 2 (no benign or borderline Brenner component documented). Awaiting full-text extraction: n = 3 (5 patients)
Included	Reports included in qualitative synthesis: n = 4 (4 patients); 3 reports (5 patients) pending

Table 3: Ovarian MBT reports published after 15 September 2023

Report	Age	Stage	Brenner component	Treatment	Outcome
Lou 2024 [14]	45	IA	Benign Brenner with mucinous cystadenoma	Staging surgery; carboplatin–paclitaxel × 3	Markers normalized after cycle 1; MBT arose 5 years after adnexectomy for benign tumor
Tseng 2025 [15]	55	IA	Small benign Brenner focus found on additional sampling	Staging surgery, 23 nodes negative; adjuvant carboplatin–paclitaxel × 3	17.7 cm tumor first diagnosed as clear cell carcinoma; reclassified by urothelial IHC and NGS (CDKN2A/B loss, MDM2 amplification, TP53 and TERT wild-type); No recurrence at 3 years
Hao 2025 [16]	53	IIA	Benign and borderline	Staging surgery; adjuvant carboplatin–paclitaxel	Spread to both fallopian tubes and uterine serosa, intravascular tumor thrombi; receiving adjuvant chemotherapy at report
Futaki 2026 [17]	70s	IA	Benign, with radiologic–histologic benign-to-malignant transition	Bilateral salpingo-oophorectomy and partial omentectomy (full staging omitted for cardiac comorbidity); no adjuvant therapy	No recurrence at 2 years

Pending full-text extraction: Li 2026, stage IIA, nodes 0/15 [11]; Raveendran 2024, three patients, stages IA, IA and IIA [12]; Abhilashi 2025, collision tumor with mature teratoma [13]. Excluded for lack of a documented Brenner component: Al-Bitar 2025, bilateral tumor with omental metastasis treated with carboplatin–paclitaxel × 6, no recurrence at 8 months [9]; Badiane 2026, stage IC2, p63-positive, Ki-67 40–50%, carboplatin–paclitaxel × 6, complete remission at 8 years [10].

Together with the 115 patients in the earlier review, the update adds four patients, with five more pending. Three were stage IA and one stage IIA. Two received adjuvant carboplatin–paclitaxel, one stage IA patient had surgery alone with no recurrence at 2 years [17], and adjuvant treatment in the fourth is no recurrence at 3 years [No included or pending report with a stated stage described stage IV disease or hepatic metastases]. The two excluded reports also used carboplatin–paclitaxel with favorable outcomes [9,10] but do not meet the review's diagnostic criteria.

6. DISCUSSION

6.1 Diagnosis

MBT requires invasive carcinoma with transitional-type differentiation in association with a benign or borderline Brenner component [2]; the largest systematic review to date excluded cases lacking that component [1], as did our update. Our diagnosis rests on biopsies of a sigmoid mass and a liver metastasis, so it is best regarded as carcinoma with urothelial-type differentiation most consistent with MBT. The main mimics are high-grade serous carcinoma with solid, pseudoendometrioid and transitional-like features,

ovarian transitional cell carcinoma, which is biologically related to high-grade serous carcinoma rather than to MBT [18], and metastatic urothelial carcinoma [2].

Brenner tumors typically express GATA3 and p63 and lack PAX8 [19–22]. These figures derive largely from benign tumors: in one series, GATA3, p63 and S100P were positive in 96%, 100% and 88% of 25 benign Brenner tumors, whereas the single malignant tumor was GATA3-negative [19]; in another, p63 was expressed in only one of six MBTs [20]. The immunophenotype of MBT is therefore more heterogeneous, and no single marker is specific; GATA3 and p63 are also expressed by urothelial carcinoma. High-grade serous-type tumors with transitional morphology differ in PAX8, WT1 and ER expression [23], and typically show abnormal p53 [18]. A recent case with a similar profile (GATA3+, p63+, PAX8−, wild-type p53) had associated benign and borderline Brenner components [16].

In our patient, p63 and GATA3 positivity with PAX8 negativity and wild-type p53 argues against high-grade serous carcinoma. Exclusion of a urothelial primary and of a colorectal primary is essential and should be documented. Her age is atypical, as MBT mainly affects postmenopausal women and most cases present at stage I [2,3]; the reports since 2023 were likewise early-stage (Table 3).

6.2 Treatment and prognosis

Surgery with comprehensive staging is the cornerstone for resectable MBT [2,5]. In our patient, hepatic metastases and sigmoid invasion led the tumor board to recommend systemic therapy first. No randomized data exist; platinum-based chemotherapy, most often carboplatin–paclitaxel as used in high-grade epithelial ovarian cancer, is the most frequently reported regimen [1,2,5]. Recent early-stage reports illustrate the range: a stage IA tumor treated by surgery alone had no recurrence at 2 years [17], and a stage IC2 tumor treated with six cycles of carboplatin–paclitaxel remained in remission at 8 years [10].

Published outcomes do not allow a reliable stage IV estimate. In a SEER analysis, 5-year disease-specific survival was 94.5% for tumors confined to the ovary and 51.3% with extra-ovarian spread [3], and a pooled review reported recurrence in 47.7% and mortality of at least 20% [2]. Lymphadenectomy was associated with better disease-specific survival in the pooled systematic review [1] but not in the SEER analysis ($p = 0.2$), in which regional nodal spread was uncommon [3]; neither finding applies to our unresected patient.

6.3 Febrile neutropenia and response assessment

Severe neutropenia occurred at the expected paclitaxel nadir. Hepatic involvement and bowel invasion may have increased the risk. Management followed guideline principles of prompt empirical antipseudomonal β-lactam therapy, early fluid resuscitation and ICU-level monitoring [24,25], with risk stratification by the MASCC score [26]. Because of sigmoid invasion, a bowel source (neutropenic enterocolitis, perforation or abscess) required exclusion despite negative cultures were negative. Secondary G-CSF prophylaxis is recommended after febrile neutropenia when maintaining dose intensity is important [27]; with palliative intent, dose reduction is an alternative, and both were used here.

CA-125 rose after cycle 1 and fell after cycle 2, and sepsis may have influenced values. We therefore regard the response as stable disease with mixed signals rather than a response. CA-125 kinetics should be read alongside imaging, and CA-125 response criteria have not been validated in MBT.

6.4 Molecular profiling and targeted therapy

Genomics.

In 11 clinically advanced MBTs profiled by next-generation sequencing, all were microsatellite-stable, 10 had low tumor mutational burden, none showed homologous recombination deficiency, and FGFR3 alterations (S249C or FGFR3–TACC3) occurred in 5 of 11; FGFR3 S249C was absent from 14,142 non-Brenner ovarian carcinomas [28]. FGFR3-mutated tumors carried benign or borderline Brenner precursors [28]. Brenner tumors also differ from both urothelial carcinoma and transitional-like ovarian carcinoma in mutational profile [29]. Comprehensive profiling for FGFR alterations is therefore the most relevant step; FGFR inhibitors such as erdafitinib are approved for urothelial carcinoma but not ovarian cancer, so any use would be off-label.

Bevacizumab.

Added to carboplatin–paclitaxel, bevacizumab improved progression-free survival in advanced epithelial ovarian cancer (GOG-0218, ICON7) [30,31] but has not been studied in MBT. One reported MBT case added bevacizumab after a mixed response to chemotherapy and continued it for 20 cycles before local progression [5]. We deferred bevacizumab because sigmoid invasion increases the risk of gastrointestinal perforation.

PARP inhibitors and immunotherapy.

Maintenance PARP inhibition benefits BRCA-mutated or HRD-positive advanced ovarian cancer (SOLO-1, PRIMA) [32,33], but those trials enrolled high-grade serous or endometrioid histology, and the absence of HRD in profiled MBTs [28] lowers the expected benefit. MBT resembles urothelial carcinoma rather than high-grade serous carcinoma. Germline and somatic BRCA1/2 testing remains standard in advanced ovarian cancer. Because MBTs are usually microsatellite-stable with low mutational burden [28], checkpoint inhibitors are unlikely to help, although

mismatch-repair status should still be confirmed, as pembrolizumab has tissue-agnostic approval for MSI-H/dMMR solid tumors [34].

Folate receptor α.

We requested folate receptor α testing; mirvetuximab soravtansine improved outcomes in platinum-resistant, FRα-high high-grade serous carcinoma [35], is relevant at most in later lines, and has no MBT data.

7. CONCLUSION

Malignant Brenner tumor of the ovary is an exceptionally rare malignancy with distinct pathological features and clinical behavior. The carboplatin–paclitaxel regimen remains the cornerstone of systemic therapy, with emerging roles for bevacizumab, PARP inhibitors, and other targeted agents. This case highlights the importance of accurate diagnosis, multidisciplinary management, and vigilant monitoring for chemotherapy-related complications. Further research, including international registries and molecular characterization, is needed to optimize treatment strategies for this rare disease.

Supplementary Table S1. Search and screening log (provisional, 30 October 2026)

Record	Type	Decision	Reason
Wang 2024	Narrative review	Excluded	Review article
Turashvili 2024	Narrative review	Excluded	Review article
Sagar 2024	Case report	Excluded	Benign Brenner tumor
Lugata 2024	Case report	Excluded	Borderline Brenner tumor
Wan 2025	Case report	Excluded	Uterine carcinosarcoma with incidental benign Brenner tumors
Bouhtouri 2025	Case report	Excluded	Bilateral Brenner tumor not reported as malignant.
Al-Bitar 2025	Case report	Excluded	No benign or borderline Brenner component described
Badiane 2026	Case report	Excluded	No benign or borderline Brenner component described
Li 2026	Case report	Pending	Stage IIA MBT; Brenner component to be confirmed
Raveendran 2024	Case series, 3 MBT	Pending	Brenner component and treatment to be extracted
Abhilashi 2025	Case report	Pending	Collision tumor with mature teratoma; Brenner component to be confirmed
Lou 2024	Case series, 20 Brenner tumors	Included	MBT with benign Brenner component
Tseng 2025	Case report	Included	MBT with benign Brenner focus
Hao 2025	Case report	Included	MBT with benign and borderline components
Futaki 2026	Case report	Included	MBT with benign Brenner component

Search method: web search-engine queries (e.g. "malignant Brenner tumor ovary" with year and topic terms) and review of PubMed/PMC records, 30 October 2026. This is not a substitute for the database search in Section 3.1.

Supplementary Methods S2. Database search strings for the re-run (replicating Koufopoulos *et al.,*[1]; record the date run and the hit count for each)

PubMed: ("malignant") AND ("Brenner") AND ("tumor") AND ("ovary" OR "ovarian") AND ("2023/09/16"[Date - Publication] : "3000"[Date - Publication])

Scopus: TITLE-ABS-KEY("malignant" AND "Brenner" AND "tumor" AND ("ovary" OR "ovarian")) AND LOAD-DATE AFT 20230915

Web of Science Core Collection: TS=("malignant" AND "Brenner" AND "tumor" AND ("ovary" OR "ovarian")), publication date 2023-09-16 to date of search

Export all records to a reference manager, remove duplicates, and report: records per database, duplicates removed, records screened, and the Figure 1 counts. Optional sensitivity check: repeat with "tumour" in place of "tumor".

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