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CASE REPORT

# The Role of *TP53* Mutations in the Malignant Progression of Mucinous Borderline Ovarian Tumors: A Case Report and Literature Review

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**Background:** Mucinous ovarian carcinoma (MOC) is characterized by aggressive behavior and limited responsiveness to standard chemotherapeutic regimens. The infrequent occurrence of MOC arising from mucinous borderline ovarian tumors (MBOTs) and the lack of readily identifiable diagnostic markers pose significant challenges to the development of effective treatment strategies. This report presents a case of a 26-year-old woman with MBOT progression to metastatic MOC despite aggressive surgical intervention and adjuvant chemotherapy, aiming to identify potential diagnostic and therapeutic improvements.

**Results:** A review of the literature revealed fewer than 30 comparable cases, underscoring the absence of established guidelines for diagnosing and treating the progression of MBOT to invasive MOC, particularly with respect to the role of *TP53* mutations. In our patient's case, we observed some changes in immunohistochemical marker expression between the MBOT and the subsequent invasive MOC, including altered p53 expression. Although these changes, considered in the context of existing literature, hint at a complex transformation process potentially involving genetic and epigenetic alterations, including *TP53* mutations, further detailed genomic or transcriptomic analyses would be required to confirm this in our specific case. The diagnostic process was further complicated by clinical and pathological similarities with gastrointestinal malignancies. Ultimately, disease progression necessitated adjustments to the treatment plan, despite the use of a multi-agent chemotherapy regimen consisting of paclitaxel, carboplatin, and bevacizumab.

**Conclusion:** The transition from MBOT to MOC is characterized by intricate genetic and epigenetic alterations, especially involving *TP53* mutations. This progression presents considerable diagnostic challenges due to similarities with gastrointestinal cancers. Therefore, given the strong correlation between *TP53* mutations and chemoresistance, there is a pressing need to develop targeted therapies and enhance diagnostic strategies.

**Keywords:** mucinous borderline ovarian tumors, mucinous ovarian carcinoma, *TP53* mutations, chemotherapy, targeted therapy

## Introduction

Mucinous borderline ovarian tumors (MBOTs) account for approximately 10% of ovarian neoplasms[1] and generally carry a favorable prognosis, particularly in younger women.[2] However, the malignant transformation to mucinous ovarian carcinoma (MOC), representing only 3–5% of ovarian cancers, poses significant clinical challenges.[3,4] The rarity of this progression (<5% of MBOT cases) severely limits the development and validation of effective treatment strategies due to small sample sizes in clinical trials.[5,6] Consequently, data on response rates and patient survival are scarce.[7] This study reviews

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the existing literature on the molecular mechanisms driving MBOT-to-MOC progression, associated diagnostic challenges, and treatment limitations, supplemented by a case report to understand further and identify areas for therapeutic improvement.

# Literature Review

## Studies Investigating MBOT to MOC Progression

MOCs exhibit a continuum of morphological changes where benign, borderline, and malignant lesions can coexist. However, the transition from an MBOT to an expansile MOC, and subsequently to an infiltrative MOC within the same patient is quite rare. To explore this phenomenon, we searched the PubMed/MEDLINE and SCOPUS databases using terms such as "malignant transformation", "malignant progression", "recurrence", "mucinous borderline ovarian tumors", and "mucinous ovarian carcinoma". As of September 20, 2024, our search identified only three case reports documenting the progression of MBOTs without stromal microinvasion to MOCs among a total of 528 papers; one of these reports lacked follow-up results. In addition to these three cases, we found nine additional articles that provided detailed information on 26 instances of progression from MBOTs to invasive mucinous carcinoma[5,6,8–15](see Table 1).

This analysis of reported cases reveals a patient population characterized by young age (mean 34.5 years), a preference for conservative surgery (80%, 16/20), a median time to recurrence of 40.7 months, and a predominance of intestinal-type tumors. The high mortality rate (approximately 50%, 13/26) and the persistence of disease in three cases highlight critical unmet needs. Further research is urgently required to optimize surgical approaches, understand the underlying genetic and molecular mechanisms driving tumorigenesis, and develop effective targeted therapies to improve patient outcomes.

## Molecular Mechanisms of Progression

The transformation of MBOTs into MOCs is a complex, multistep process marked by a gradual accumulation of molecular genetic alterations.[16–18] While the exact mechanisms involved are not fully understood, research indicates a significant shift in genetic profiles throughout these stages. MBOTs often carry mutations in genes such as *KRAS, CDKN2A, BRAF, ERBB2*, and *TP53*.[19–23] In contrast, MOCs exhibit a markedly higher frequency of *TP53* mutations (26–55%),[23] suggesting that inactivation of *TP53* plays a critical role in the malignant transformation process.[8,22,24] Data derived from the Caris CODEai™ database further corroborate these findings, showing that the *TP53*-mutant population in MOC has a substantially lower survival rate compared to the *TP53* wild-type population (refer to Figure 1). This evidence highlights the critical prognostic value of *TP53* status in MOCs. Moreover, MOCs show an increased prevalence of mutations in other genes, including *RNF43* and *PIK3CA*, as well as *ERBB2* amplification and various copy number variations, all pointing to the acquisition of multiple genetic drivers during progression.[25,26] Epigenetic modifications also play a significant role in this transformation. Studies have identified methylation defects within the proteasome system in MOCs, highlighting the importance of epigenetic dysregulation in tumorigenesis.[27] The interplay between genetic and epigenetic alterations warrants further investigation to thoroughly understand the mechanisms underlying this progression. Importantly, *TP53* mutations—especially in combination with *KRAS* mutations—have been strongly associated with resistance to platinum-based chemotherapy.[28] This insight suggests the potential for targeting specific genetic alterations as a means to counteract chemoresistance. For example, APR-246 (eprenetapopt), initially characterized as a *TP53*-reactivating agent, has demonstrated clinical promise in *TP53*-mutant ovarian cancer (NCT03268382), though its mechanism may also involve off-target redox modulation. Conversely, MBOTs harboring the *BRAFV600E* mutation appear to have a reduced risk of progression to invasive carcinoma.[29]

## Diagnostic Challenges

Accurate differentiation of primary MOC from other mucinous neoplasms, particularly those of gastrointestinal origin, poses a significant diagnostic challenge. Histopathological evaluation, especially during intraoperative frozen section analysis, can be hindered by the large size and variable differentiation of these tumors, often requiring extensive microscopic sampling.[30] The transition from MBOTs to MOCs involves significant IHC changes, complicating the definitive diagnosis.[19,20,22] While both MBOTs and MOCs share overlapping IHC profiles, historically cited distinctions—such as CK7 positivity/CK20 negativity in MBOTs versus CK20/CDX2 positivity in MOCs—have proven unreliable for definitive classification, as recent

**Table 1** The MBOTs Progressed to MOCs Reported in the Literature

| Authors | Case number | Age | Primary Treatment | Stage of MBOTs | Interval to Progression (Months) | Recurrent Surgery | Subtype of MOC | Adjuvant Treatment after Progress | Diagnosis (Recurrence) (Months) | Status |
|---|---|---|---|---|---|---|---|---|---|---|
| Wakazono E[8] | 1 | 73 | Conservative surgery (BSO) | Stage IC | 31 | Peritoneal and subcutaneous nodules sampling | NR | No | NR | NR |
| Salomon, L. J. et al[9] | 1 | 22 | Conservative surgery (cystectomy) | Stage I | 26 | Surgical resection and staging, | NR | Platinum-based chemotherapy. | NR | In treatment |
| Park, J. Y. et al[10] | 4 | 58 | Radical surgery | Stage IIIC | 123 | Tumor reduction surgery | NR | No | NR | DOD |
| | | 28 | Radical surgery | Stage IC | 7 | Tumor reduction surgery | NR | Paclitaxel+cisplatin | NR | DOD |
| | | 33 | Radical surgery | Stage IA | 21 | Tumor reduction surgery | NR | Paclitaxel+cisplatin | NR | NED |
| | | 15 | Conservative surgery (USO, UOC) | Stage IA | 82 | Biopsy | NR | No | NR | DOD |
| Uzan, C. et al[11] | 6 | 17 | Conservative surgery (USO) | Stage IA | 8 to the first MBOT recurrence | Surgery exploration | Intestinal | NR | NR | AWPD |
| | | 27 | Conservative surgery (UO) | Stage IA | 76 | Surgery exploration | Intestinal | NR | NR | AWPD |
| | | 41 | Conservative surgery (USO) | Stage IA | 30 | Surgery exploration | Intestinal | NR | NR | DOD |
| | | 50 | Conservative surgery (BSO) | STAGE IC | 14 | Surgery exploration | Intestinal | NR | NR | DOD |
| | | 27 | Conservative surgery (USO+CC) | Stage IA | 58.5 | Surgery exploration | Intestinal | NR | NR | NED |
| | | 23 | Conservative surgery (USO) | Stage IA | 27.4 | Surgery exploration | Intestinal | NR | NR | AWPD |
| Ifthikar, M. A. et al[6] | 5 | NR | Conservative surgery | Stage I | NR | NR | NR | Yes | NR | DOD, 4 NR, 1 |
| Ma, J. W. et al[12] | 1 | 53 | Radical surgery (cytoreductive surgery) | Incomplete stage due to the obscure diagnosis of the lung nodules. | 84 | NR | Intestinal type | NR | | NED |

(*Continued*)

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**Table 1** (Continued).

| Authors | Case number | Age | Primary Treatment | Stage of MBOTs | Interval to Progression (Months) | Recurrent Surgery | Subtype of MOC | Adjuvant Treatment after Progress | Diagnosis (Recurrence) (Months) | Status |
|---|---|---|---|---|---|---|---|---|---|---|
| Song, T. et al[5] | 2 | 18 | Conservative surgery | Stage IA | 26 | Radical surgery | Intestinal type | No | 38 | NED |
| | | 53 | Radical surgery (Complete staging surgery) | Stage IB | 18 | Surgery | Intestinal type | Yes | 18 | NED |
| Zanetta, G. et al[13] | 2 | 30 | Conservative surgery (Cystectomy) | Stage IC | 10 | TAH+BSO | NR | No | 13 | DOD |
| | | 27 | Conservative surgery (cystectomy) | Stage IA | 55 | TAH+BSO | NR | No | 41 | NED |
| Chen, R. F. et al[14] | 1 | 36 | Conservative surgery | Stage III | NR | Tumor reduction surgery | NR | Yes | 8 | DOD |
| Cao, D. Y. et al[15] | 3 | NR | NR | NR | <62 | NR | NR | NR | One is 102, one is 152 rom first diagnosis | 2 DOD, 1 NR |
| This case | 1 | 25 | Conservative surgery (cystectomy) | Stage I | 15 | 1st: conservative staging surgery<br>2nd: Tumor reduction surgery | Gastric | 1st: TC+Bev<br>2nd: albumin-bound paclitaxel+oxaliplatin, +capecitabine | 1st: 14<br>2nd:10 | DOD |

**Abbreviations**: NR, not reported; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy; UOC, unilateral ovarian cystectomy; UO, unilateral oophorectomy; USO+CC, Unilateral salpingo-oophorectomy+contralateral cystectomy; TAH, total abdominal hysterectomy; TC+Bev, paclitaxel+carboplatin+bevacizumab; NED, no evidence of disease; DOD, Died of disease; AWPD, Alive with persistent disease.


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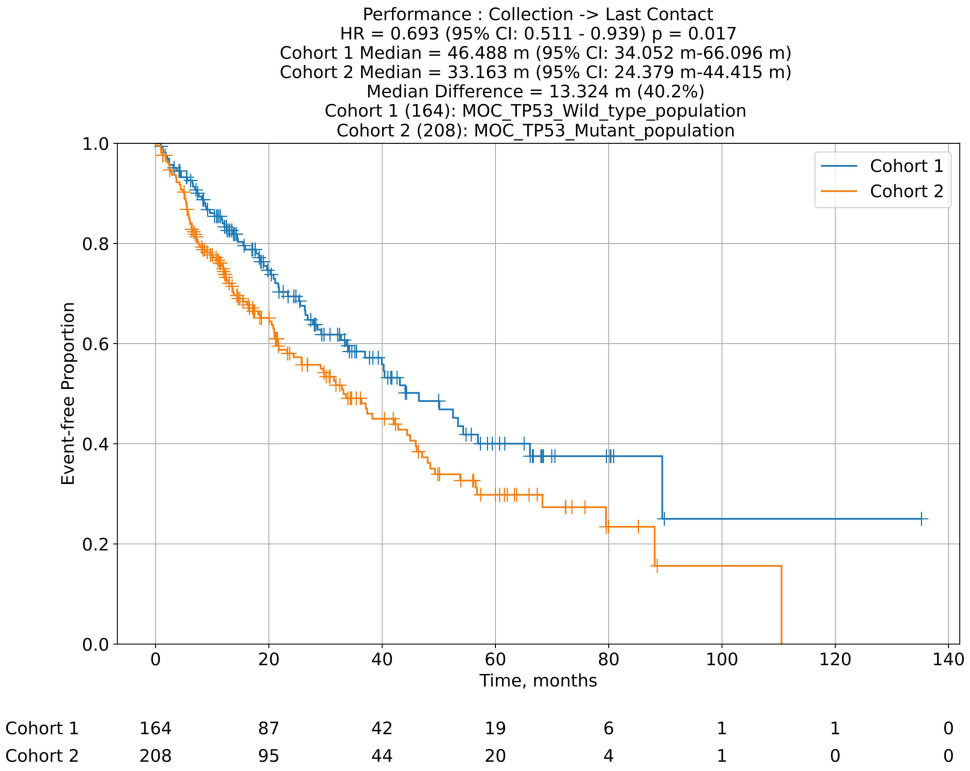


**Figure 1** Kaplan-Meier curve analysis of overall survival in MOC among *TP53*-mutant population compared to *TP 53* wild-type population, calculated from the time of tissue collection to the last contact (Data derived from the Caris CODEai™ database).

studies demonstrate minimal differences between these entities.[14,31] Instead, careful clinicopathologic correlation and exclusion of metastatic mimics (eg, gastrointestinal primaries) remain paramount in differential diagnosis. In contrast, MOCs often exhibit positivity for CK20 and CDX2, indicative of intestinal or gastric differentiation. Additionally, MOCs frequently show abnormal p53 accumulation, suggesting the presence of *TP53* mutations (refer to Table 2). Recent studies have also identified OCIAD2 as a cancer-related protein, with its expression increasing during malignant progression, making it a potential marker for evaluating the malignancy of ovarian mucinous tumors.[32] In the case presented, the shift in the IHC profile from MBOT to MOC provided the strongest diagnostic evidence. However, the differential diagnosis is further complicated by the fact that many tumors initially classified as primary MOC may actually be metastatic from gastrointestinal sources.[33] This emphasizes the importance of careful differentiation between primary MOC and metastatic disease, particularly in early-stage presentations, as primary ovarian mucinous tumors and gastrointestinal tumors often share similar immunophenotypes.[34] Studies have investigated the utility of various IHC markers to differentiate between primary MOC and gastrointestinal mucinous tumors. For example, CK7, when evaluated with a non-diffuse/diffuse cutoff, demonstrates 91.7% accuracy, while SATB2 shows 88.8% accuracy using a present/absent classification. A combined three-tiered interpretation of CK7 and SATB2 (absent, focal, diffuse) significantly enhances diagnostic accuracy to 95.3%, surpassing the accuracy of traditional panels that include CK7, CK20, and CDX2 (87.5% accuracy).[31] Additional markers, such as PAX8 (35% positivity in primary MOC and 0% positivity in gastric cancers) and CA125 (24% positivity in primary MOC and absent in gastric cancers), can assist in diagnosis; however, no single marker definitively identifies the tumor's origin.[35] In this case, despite the immunohistochemical profile not strongly indicating a primary mucinous ovarian carcinoma (CK7 positive, focal CK20 positive, CDX2 positive, PAX8 negative), negative results from gastroscopy and colonoscopy conclusively ruled out a gastrointestinal origin.

## Therapeutic Strategies

The management of MOC arising from MBOTs poses significant clinical challenges, primarily due to the rarity of this progression and the inherent heterogeneity of the tumors. Treatment necessitates a multidisciplinary approach that is

**Table 2** Comparative Immunohistochemical Profile of MBOT and MOC in This Patent

| IHC Marker | MBOT State | MOC State |
|---|---|---|
| **CK7** | Positive | Positive |
| **CK20** | Negative | Focal Positive |
| **CDX2** | Negative | Focal Positive |
| **p53** | Wild type | Partial missense mutation |
| **Ki 67** | 30% positive | 50%~60% positive |
| **PAX-8** | Negative | Negative |
| **Vim** | Negative | NR |
| **CEA** | Negative | NR |
| **p16** | Negative | NR |
| **ER (Estrogen Receptor)** | Negative | NR |
| **PR (Progesterone Receptor)** | Negative | NR |
| **WT-1** | Negative | NR |
| **Villin** | NR | Positive |
| **MUC-6** | NR | Focal Positive |
| **MUC-5AC** | NR | Positive |
| **DPC-4** | NR | Positive |

**Abbreviation**, NR, not reported.

tailored to the disease stage and individual patient factors. For early-stage MOC derived from MBOT, the primary treatment is surgical resection, with careful technique required to prevent tumor rupture. Mucin spillage during surgery can greatly increase the risk of peritoneal dissemination, resulting in recurrence, metastasis, and a poorer prognosis.[36]

Determining the optimal adjuvant therapy for early-stage MOC has been challenging due to the disease's infrequency and the limited available data. In advanced-stage MOC, the cornerstone of treatment is cytoreductive surgery aimed at achieving complete cytoreduction (R0 resection), as recommended by NCCN guidelines. However, achieving complete resection is often difficult due to the advanced nature of the disease when diagnosed. For patients with residual disease following cytoreduction, hyperthermic intraperitoneal chemotherapy (HIPEC) has been proposed as an adjunct therapy.[37,38] However, a comprehensive multicenter retrospective analysis found no survival advantage with the addition of HIPEC to cytoreductive surgery in MOC patients.[39]

Post-surgery, platinum-based chemotherapy regimens, such as carboplatin/paclitaxel or cisplatin/paclitaxel, are considered the standard of care. Nevertheless, response rates for MOCs often remain suboptimal compared to those seen in serous ovarian cancers. The shared pathological and molecular characteristics between MOCs and gastrointestinal malignancies have led to retrospective investigations into the efficacy of gastrointestinal-directed chemotherapy regimens, but the results thus far are inconclusive and necessitate further validation through prospective studies.[7,40,41] Notably, the pivotal randomized Gynecologic Oncology Group trial 0241, which aimed to compare a gastrointestinal chemotherapy regimen to standard platinum-based therapy, was terminated prematurely due to the rarity of this tumor subtype.[42]

The challenges associated with MOCs highlight the urgent need for innovative therapeutic strategies. Specific genetic alterations, particularly *TP53* and *KRAS* mutations, have been identified as factors influencing treatment responses and predicting chemoresistance.[20–22,24,29] As a result, current research efforts are focused on developing targeted therapies, such as agents that reactivate *TP53*,[28] along with other treatments including bevacizumab, AZD1775, sunitinib, and cediranib.[43] Additionally, immune checkpoint inhibitors are gaining interest; however, findings from IHC and immunofluorescence (IF) analyses indicate that the majority of MOCs (86%) exhibit an immune-depleted (cold) phenotype, while only a small proportion (14%) demonstrate an immune-inflamed (hot) phenotype characterized by T cell and PD-L1 infiltrates.[44] This suggests a potentially limited response to existing immunotherapies. Therefore, further exploration of combination therapies and personalized treatment approaches is essential to enhance clinical outcomes in this complex and rare disease.

# Case Presentation

## The First Progress from MBOT to expansile MOC

A 26-year-old woman with a history of a pelvic mass underwent laparoscopic right ovarian cystectomy in March 2021, where pathology confirmed an MBOT During a routine follow-up at our institution in June 2022, imaging revealed a right adnexal mass measuring 62×61 x 49 $mm^3$. The mass appeared sonographically anechoic and well-defined, with no Doppler flow detected. Serum tumor markers, including CA125, AFP, CEA, and β-hCG, were all negative. A CT scan confirmed the presence of a cystic-solid right adnexal mass, with normal-sized retroperitoneal lymph nodes and unremarkable findings in the chest. A pathological review of the initial cystectomy specimen reaffirmed the diagnosis of MBOT.

The patient was subsequently diagnosed with a recurrent MBOT and underwent laparoscopic right salpingo-oophorectomy with comprehensive surgical staging (excluding lymph node dissection) in June 2022. Intraoperative findings showed a normal appendix, while pathology revealed an MBOT with a focal area of well-differentiated MOC, measuring 7.5 mm in greatest diameter. The FIGO stage was determined to be 1C1 (pT1c1N0M0, G1), attributed to tumor rupture during surgical manipulation. Following this diagnosis, a consultation with a gynecologic oncologist recommended regular monitoring and consideration of adjuvant therapy; however, the patient did not return for follow-up appointments or treatment.

## The second Progress from expansile MOC to infiltrative MOC

In August 2023, the patient sought medical attention due to significant bloating and menstrual irregularities lasting one month. Pelvic MRI revealed a large abdominopelvic cystic-solid mass with ascites, as well as evidence of peritoneal implants and metastasis, including an abnormal signal in the left iliac bone. Elevated CA125 levels (735.7 U/mL) led to further investigation with PET/CT imaging, which confirmed extensive metastatic disease involving the liver capsule, gastrosplenic ligament, mesentery, peritoneum, multiple retroperitoneal and left diaphragmatic lymph nodes, and focal involvement of the bone marrow (Figure 2).

After a review by a multidisciplinary tumor board, the patient underwent a secondary cytoreductive surgical procedure that achieved R1 resection (left iliac bone and potential diaphragmatic lymph node residue).

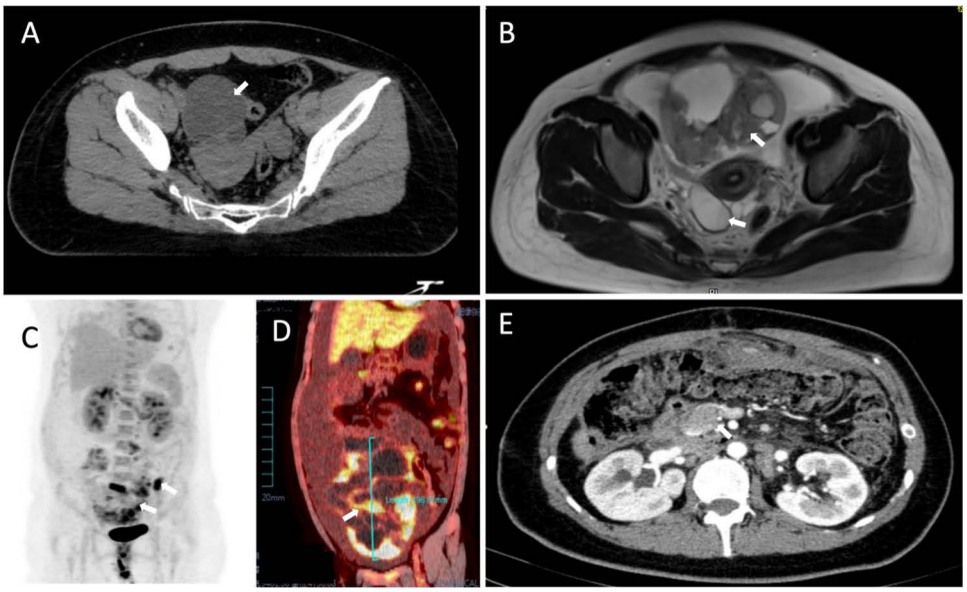


**Figure 2** Imaging findings at multiple intervals following initial diagnosis. (**A**) An unenhanced pelvic CT scan was conducted 15 months post-initial surgery, highlighting a right adnexal cystic-solid mass measuring 7.03×6.30 x 5.60 $cm^3$, indicated by the white arrow. (**B**) A pelvic contrast-enhanced MRI scan was performed 14 months following the second surgical procedure, with the white arrow indicating a sizable abdominopelvic cystic-solid mass accompanied by ascites. (**C** and **D**) PET/CT scans obtained 14 months after the second surgery revealed a significant abdominopelvic cystic-solid mass with extensive abdominal metastases and focal bone marrow involvement, as marked by the white arrow. (**E**) A contrast-enhanced abdominal CT scan, performed 6 months after the third surgical intervention, demonstrated several enlarged retroperitoneal lymph nodes, underscored by the white arrow.


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Histopathological examination of the resected specimen revealed gastric-type MOC involving the left fallopian tube, along with extensive peritoneal implants throughout the abdomen and pelvis. Notably, among the 63 lymph nodes examined, multiple sites showed metastatic involvement. Table 2 presents the immunohistochemical profiles for both the initial MBOT and the subsequent MOC, facilitating a direct comparison. Figure 3 illustrates the histopathological findings associated with the initial MBOT alongside those of the subsequent MOC.

Given the extent of the disease, a comprehensive adjuvant chemotherapy regimen was initiated 27 days post-surgery. Pre-operative gastrointestinal endoscopy, including gastroscopy and colonoscopy, ruled out any primary gastrointestinal malignancy. Genetic testing revealed no BRCA1 or BRCA2 mutations and confirmed the absence of homologous recombination deficiency (HRD). The initial three-cycle treatment regimen consisted of paclitaxel, carboplatin, and bevacizumab, administered every three weeks, with the inclusion of upfront intraperitoneal cisplatin. However, due to slow healing at the surgical site, the administration of bevacizumab was deferred until the third cycle.

A follow-up CT scan indicated a partial response, showing a reduction in the size of metastatic lesions in the liver, peritoneum, and omentum. Despite this, there was an enlargement of hilar, mesenteric, and posterior peritoneal lymph nodes, along with rising CA125 levels (as shown in Figure 4). As a result, the treatment regimen was modified to include albumin-bound paclitaxel, oxaliplatin, bevacizumab, and oral capecitabine (1000 mg/m² per day for two weeks followed by a one-week break) for five cycles, in consultation with a gastroenterologist. Narusobimab was also introduced for two

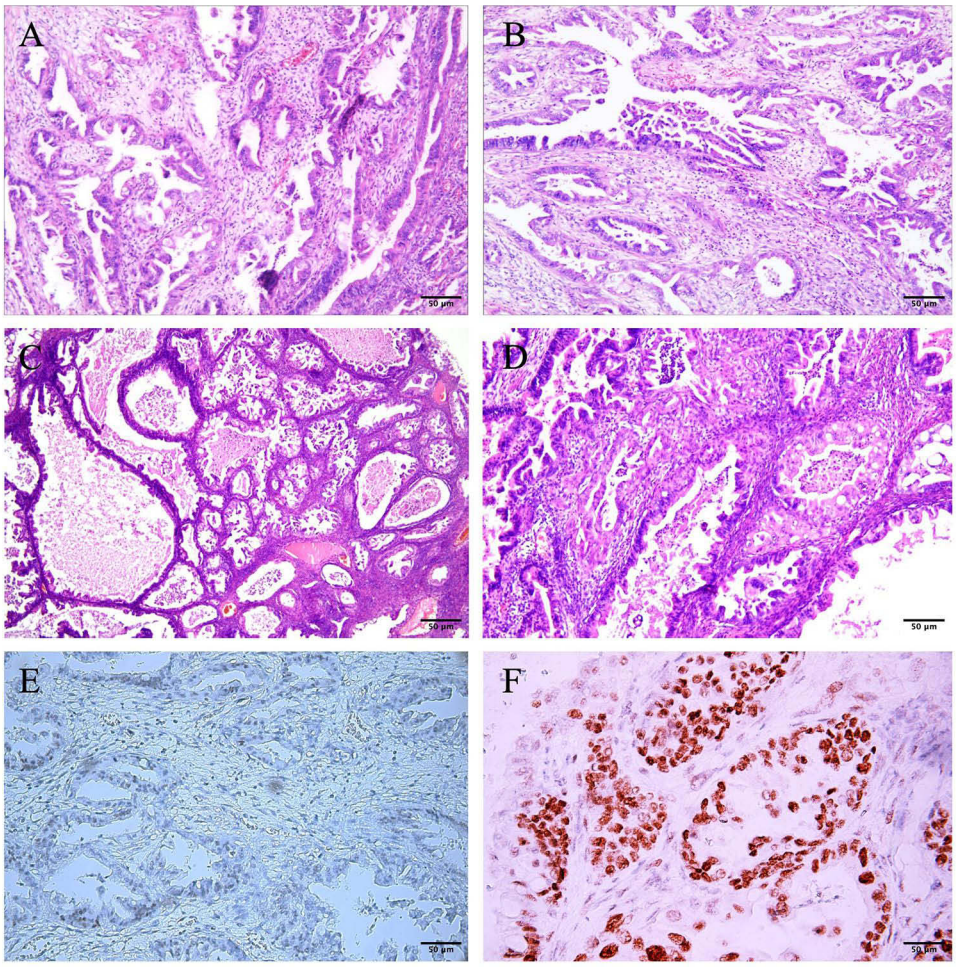


**Figure 3** Histopathological features of tumor progression. (**A** and **B**) H&E staining of the second surgical resection, demonstrating MBOT with a focus on well-differentiated MOC. (**C** and **D**) H&E staining of the third resection, showing infiltrative MOC. (**E** and **F**) IHC staining for p53. Panel (**E**) Second surgical resection, demonstrating wild-type p53 expression. Panel (**F**) Third surgical resection, revealing a partial missense p53 mutation.

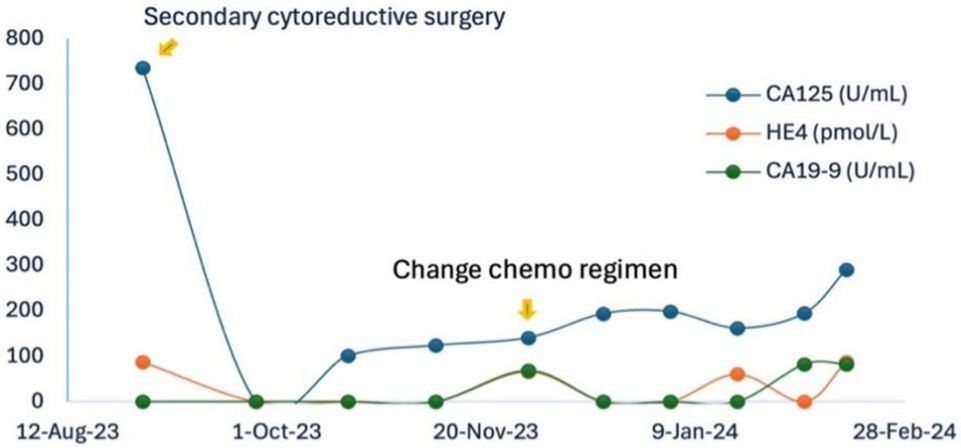


**Figure 4** The trend of tumor markers.

cycles to target the bone metastases. Unfortunately, despite this intensified treatment approach, the disease continued to progress, and the patient passed away ten months after the final surgical procedure.

Per the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

## Conclusions

The progression from MBOT to MOC is a complex process characterized by a multistep transformation involving genetic and epigenetic changes, with a marked increase in *TP53* mutations and abnormal p53 protein expression. This finding underscores the association between *TP53* mutations and chemoresistance, highlighting the urgent need for targeted therapies.

This study, while informative, is limited by the absence of whole-exome sequencing and the potential for misdiagnosis due to phenotypic overlap with gastrointestinal malignancies. Future research should focus on comprehensive genomic analyses, improved diagnostic markers, and the development of treatment strategies tailored to the specific molecular characteristics of this rare disease. Enhanced post-surgical surveillance is also essential for optimal patient management and improved outcomes.

## Clinical Trial Number

Not applicable.

## Data Sharing Statement

Datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval

This study involves human participants but as it is a case study, the patient's family consent was obtained.

## Patient Consent for Publication

In this case report, written consent could not be obtained from the patient due to her passing. Instead, verbal consent was obtained from the patient's aunt, who is legally authorized to make decisions on behalf of the patient. This consent was formally documented in the patient's medical records on 12/20/2024. The process of obtaining and documenting consent was conducted with careful adherence to ethical considerations and institutional guidelines.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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