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Early stage mucinous ovarian cancer: A review

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HIGHLIGHTS

- Mucinous ovarian carcinoma (MOC) is a distinct clinically and pathologically.
- Pathologic confirmation of primary MOC is complex but essential for treatment.
- Stage IA MOC can be observed after surgery.
- More advanced MOCs are treated with oxaliplatin and carboplatin +/− bevacizumab.

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ABSTRACT

Mucinous ovarian carcinomas (MOCs) are an uncommon subset of epithelial neoplasms, both clinically and molecularly distinct from other ovarian cancers. Pathologic diagnosis proves challenging, and metastatic disease from other sites—especially the digestive tract—must be excluded. Fortunately, most patients are diagnosed at an early stage of disease and often present with large, unilateral adnexal masses. Survival for patients with stage IA disease approaches over 90%, and surgery alone is sufficient. Patients with stage IB-II disease should receive adjuvant treatment but the specific regimen is controversial. In the following review, we provide an overview of mucinous ovarian carcinomas, with a particular focus on the treatment of patients with early stage disease.

1. Introduction

Mucinous ovarian carcinomas (MOCs) are rare entities, often erroneously cited as comprising 5–10% of epithelial ovarian cancers [1–3]. However, owing to diagnostic challenges, the true incidence is <5% [4]. Most patients present with an enlarging unilateral adnexal mass which leads to surgical intervention; as such, most patients are diagnosed at an early stage when disease is confined to the ovary. While overall survival is excellent for early-stage disease and is >90% [3,5], presentation at advanced stage is associated with poor survival. Outcomes for patients presenting with advanced stage disease are worse than those for serous histology when compared by stage-specific survival [3,6,7].

Surgery is often curative for patients with early stage disease (International Federation of Gynecologic Oncology (FIGO) stage I). For the small subset of patients with early stage disease who require adjuvant treatment, the recommended regimen remains controversial. Compared to the more common high grade serous ovarian carcinomas, MOCs have lower response rates to the traditional carboplatin/taxane-based regimen and have worse stage-specific outcomes [5,8,9]. Given the phenotypic and molecular similarity to gastrointestinal (GI) malignancies, some have opted to treat MOCs with a GI regimen. While preclinical rationale exists [10], proof of clinical efficacy is difficult to achieve since small study numbers and inconsistent pathology readings have thwarted randomized trials.

The following review describes the clinical and molecular characteristics of MOCs, recommends appropriate treatment options for patients with early stage disease, and presents the data which support current management guidelines.

2. Epidemiology

Mucinous ovarian carcinomas are a rare entity, comprising <5% of epithelial ovarian tumors [1,2,7]. Incidence published in comprehensive reviews incorporating tumor registry data ranges from 11 to 14%, but this appears to be inflated due to inclusion of tumors that are not ovarian in origin [2,3]. A more accurate reflection of the true incidence is provided by detailed pathological reviews, in which the incidence approaches 5% or less [1,2,11]. For example, a general SEER database review of 40,571 women with epithelial ovarian cancer described an 11.9% incidence of primary MOC [3]. When Seidman and colleagues

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re-reviewed 52 cases of mucinous carcinomas of the ovary, they found that 77% were in fact metastatic carcinomas from other sites (45% were GI in origin, 20% were pancreatic), and only 23% represented primary ovarian tumors [1]. Among the 12 primary MOCs, only 9 were invasive mucinous carcinomas, while 3 were microinvasive carcinomas [1]. In a larger central pathologic review of 1400 patients diagnosed with epithelial ovarian carcinomas, 16% of whom had initially been diagnosed with MOCs, Shimada et al. reclassified the true incidence of MOCs at 4.9% [2]. Most were reclassified as mucinous borderline tumors (22%), metastases (7%), or mucinous intraepithelial carcinomas (24%).

The importance of central pathologic review was unfortunately demonstrated in Gynecologic Oncology Group (GOG) 241, a trial designed to validate the efficacy of a GI-based regimen in patients with MOCs. In this trial, patients were randomized to receive a standard ovarian regimen with paclitaxel and carboplatin versus oxaliplatin and capecitabine, with and without bevacizumab. In 36 cases available for pathologic review, 17 were reclassified as having non-primary MOCs, most of which represented metastatic disease from other sites, and the trial was closed [12].

Reasons for overreporting are multiple; the majority stem from pathologic misdiagnosis from metastatic gastrointestinal tumors or from misclassification as mucinous borderline tumors. Frumovitz and colleagues also point out that tertiary referral centers see disproportionately more difficult cases, thereby enriching the MOC patient population in reports from academic centers [7]. Nonetheless, accurate diagnosis is paramount for these patients and has critical implications for both diagnosis and treatment.

3. Pathology

Mucinous epithelial ovarian tumors range from benign to malignant, and they are divided into invasive and non-invasive subtypes. Mucinous cystadenomas are classified as benign, while borderline and intraepithelial tumors comprise the non-invasive malignant components. Reports have described benign mucinous cystadenomas adjacent to borderline and intraepithelial non-invasive tumors, all of which may abut invasive mucinous carcinomas, suggesting a mechanism of pathogenesis and implying a continuum of disease [13,14].

Noninvasive intraepithelial carcinomas harbor atypia but lack stromal invasion [14], whereas classification as an invasive MOC requires stromal invasion >5 mm or 10 mm^2 (Fig. 1) [4]. Invasive MOC is further subdivided into expansile and infiltrative subtypes; an infiltrative pattern is associated with a worse prognosis [15,16]. Histologically, the expansile type exhibits confluent glands with no interposed stroma, and the infiltrative type displays "an infiltrative pattern of small glands, nests of cells, or individual cells haphazardly infiltrating the stroma" [14]. Diagnosis can be challenging, and metastatic disease must be excluded. Bilateral tumors, surface involvement, signet ring cells, lymphvascular invasion, desmoplastic reaction, hilar involvement, and a nodular growth pattern are more consistent with metastatic disease; while unilateral involvement, larger size (typically >10 cm), and coexisting borderline, Brenner, or dermoid tumors suggest a primary MOC [1,17–19].

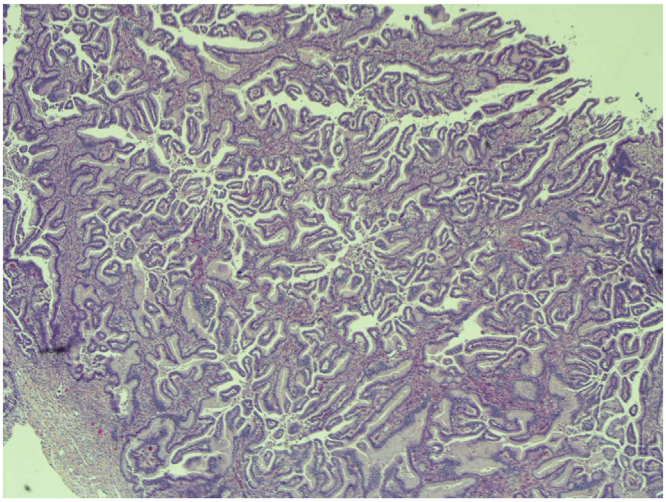

Fig. 1. H&E image of mucinous ovarian adenocarcinoma. (Credit: Tucker Burks, MD).

Immunohistochemistry has limitations but can aid in distinguishing between metastatic disease and primary MOC (Table 1). Mucinous ovarian carcinomas typically express cytokeratin (CK) 7 and 20, while colorectal cancers express only CK20 and breast carcinomas express only CK7 [14]. Appendiceal and upper GI malignancies may express both CK20 and CK7. The addition of special AT-rich sequence-binding protein 2 (SATB2) staining to CK20 immunostaining may further distinguish appendiceal neoplasm from MOCs, as glandular cells of lower gastrointestinal tract malignancies retain expression in metastatic foci, and SATB2 staining is negative in primary MOCs [20]. Pancreatic ductal carcinomas lack SMAD4/Dpc4 expression, while this is preserved in MOCs [17]. Diffuse p16 or human papilloma virus positivity may help differentiate between primary MOCs and metastatic endocervical adenocarcinomas, although MOCs may display some p16 expression [4]. Expression of E-cadherin and absence of N-cadherin can also help discern mucinous from serous carcinomas [21]. While serous tumors express both E- and N-cadherin, mucinous tumors strongly express E-cadherin but not N-cadherin.

4. Molecular characteristics

It is generally accepted that mucinous ovarian carcinomas are distinct histologic entities and arise from a molecular pathway that is separate from other histologic subtypes of epithelial ovarian cancer. While high grade serous ovarian carcinomas have a 96% frequency of *TP53* mutations, fewer MOCs harbor *TP53* mutations, with reports ranging from 16 to 52% [22,23]. Additionally, approximately 25% of high grade serous ovarian cancers are associated with either germline or somatic *BRCA* mutations, but mucinous ovarian carcinomas are not [24–26]. In contrast, *KRAS* mutations have been reported in 40–50% of MOCs [13,27] and may play a role in progression from benign to malignant phenotypes [28]. In an analysis of benign, borderline, and malignant MOCs, the frequency of *KRAS* mutations were 57%, 90%, and 76%, respectively [28]. *KRAS* mutations lead to activation of the EGFR pathway, which in turn promotes cell division and growth. HER2 amplification has also been reported in 20–30% of mucinous ovarian carcinomas, and 6% of mucinous borderline tumors [29–31]. IMP3 has recently been described as potentially promoting tumor progression from borderline tumors to invasive MOCs [32].

In the era of more rapid and widely available genome sequencing, reports are now emerging detailing molecular profiles of MOCs. While informative for future efforts at targeted treatment, limitations include unknown functions of certain genes and consequent therapeutic effects, and limited agents targeting the identified mutations. One report of exomic sequencing in MOCs revealed frequent mutations in *BRAF*, *KRAS*, and *NRAS* (68.3% collectively) [22]. However, they discovered a higher rate of *TP53* mutations in MOC than previously reported (52%), as compared to benign (9.1%) and borderline (13.8%) tumors, suggesting *TP53* mutation is a late event in tumorigenesis. RNF43, ELF3, ERBB3, and KLF5 mutations were also described (all ≤7% frequency) although sample size was small [22]. Another larger study detailed molecular profiling results on 304 cases of MOC and found frequent *KRAS* mutations (49%), as well as mTOR pathway alterations (18%), EGFR amplification (50%), HER2 amplification (11%), and PD-1/PD-L1 (43%/14%) positivity [33]. Interestingly, *TP53* mutant (53%) versus wildtype tumors differed significantly in ER, PR, and HER2 expression and BRAF, PIK3CA, and PTEN mutation prevalence.

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