Mucinous ovarian cancer

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Mucinous epithelial ovarian cancer (mEOC) accounts for approximately 10% of EOCs. Patients presenting with early-stage disease have an excellent prognosis, however, those with advanced disease have a poor outcome with relative resistance to standard ovarian cancer chemotherapy. Molecular and genetic studies demonstrate differences between mucinous and serous EOC supporting the concept that these tumors develop along separate pathways. Together with the observed differences in clinical behavior and outcome for mEOC, there is a need to develop specific therapeutic strategies for this histologic subtype. The relative rarity of advanced mEOC has resulted in few patients enrolled in major ovarian cancer trials. The results of such trials may not necessarily reflect those specific to mEOC. Separate trials testing alternative chemotherapeutics are required. Metastatic mucinous tumors from other sites such as the gastrointestinal tract may present with ovarian involvement. For all mucinous tumors of the ovary, establishing primary as opposed to metastatic cancers is important. Clinical presentation, tumor markers, histologic, and immunohistochemical features are helpful in distinguishing most cases.

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Invasive mucinous carcinoma of the ovary accounts for approximately 10% of epithelial ovarian cancers (EOC)(1). Despite the infrequency of this subtype, 27% of patients with stage I EOC have mucinous pathology as opposed to less than 10% of patients presenting with stage III/IV tumors(2,3). They appear to have a different natural history from the other histologic types in terms of presentation, response to therapy, and outcome.

In an analysis of prognostic factors for FIGO stage I invasive ovarian cancers, 410 patients with mucinous epithelial ovarian cancer (mEOC) were included and the 5-year disease-free survival was 90.8%. The hazard ratio for recurrence was 0.37 (95% CI, 0.25–0.53) for mEOC compared to other histologic types. Mucinous pathology was not a significant prognostic factor on multivariate analysis, with degree of differentiation as the most important independent prognostic variable(2). Most mEOC are either well or moderately differentiated and this contributes to the low risk of relapse for FIGO stage I tumors.

In contrast, patients with advanced mEOC have a poor response to chemotherapy with relative resistance to platinum-based therapy, and an inferior outcome is well recognized. Case-control studies have highlighted differences in response and survival for mEOC compared to other histologic types for standard therapies. Furthermore, molecular studies support the hypothesis that mEOC should be considered as a biologically distinct entity.

Tumors with mucinous pathology are underrepresented in randomized clinical trials of first-line chemotherapy in advanced disease, and usually account for less than 5% of all patients. Furthermore, in studies of second- and third-line chemotherapy, the percentage of patients with mEOC is often not specified. These trials tend to mainly include patients with serous and endometrioid tumors and, therefore, the results are not generally applicable to patients with mucinous tumors. However, in the absence of alternative data to guide management, standard treatment of ovarian cancer with debulking surgery and platinum-based chemotherapy is given to patients with mEOC.

Pathology

Mucinous tumors of the ovary are categorized according to the World Health Organization classification.
They include cystadenomas, borderline tumors (intestinal and endocervical types), noninvasive (intraglandular and intraepithelial) carcinomas, invasive carcinomas, and metastatic from other sites. Mucinous tumors are often heterogeneous in composition and thorough pathologic examination with extensive sampling is required. It is recommended that at a minimum, one block per centimeter of tumor is sampled.

Invasive mucinous carcinomas commonly have an expansive growth pattern, are usually stage I at diagnosis, and have an excellent prognosis. An infiltrative expansive growth pattern is less frequent but appears to follow a more aggressive course, accounting for most of the cases of advanced-stage mucinous tumors (4–6).

Nuclear grade has been identified as an adverse prognostic feature. For stage I mucinous tumors, one study found tumor grade to be an independent predictive factor for relapse (6), although this has not been found consistently (4,5). It should be acknowledged that numbers in these retrospective studies are limited and follow-up data are not always complete.

DNA ploidy, which looks at the DNA content of a cell, has been identified as a prognostic marker of survival in EOC (7), however, there is little data on this specific for invasive mucinous tumors (6).

Within mucinous tumors mural nodules may be appreciated, and these are distinct from the underlying tumor. There are conflicting reports on the prognostic importance of nodules of anaplastic carcinoma (6,9). These nodules may occur in either borderline or invasive mucinous tumors and may not be an adverse feature in stage IA tumors (6). Their presence should not influence the management of early-staged tumors.

Mucinous tumors arising in the ovary need to be distinguished from metastatic ovarian involvement from other primary sites. These are most commonly from the lower gastrointestinal tract and appendix but may also arise from the stomach, small bowel, pancreas, biliary tree, cervix, endometrium, and breast. The primary may not be apparent at diagnosis (10–12). There are several features that may suggest a non-ovarian primary including preoperative tumor markers, size of the ovarian tumor, and whether there is unilateral or bilateral ovarian involvement. Light microscopy findings and immunohistochemistry profile may help to distinguish between primary and metastatic disease, although diagnostic uncertainty may remain.

Primary mEOC are typically larger and more frequently unilateral than metastatic mucinous adenocarcinomas. In comparative studies, the mean size of mEOC was 16.4–20.0 cm (range 5–48 cm) and for metastatic involvement 10.6–11.7 cm (range 2–24 cm). Size alone is not sufficient to distinguish between the two clinical scenarios, as 32–48% of metastatic tumors were found to be greater than 10 cm. Bilateral tumors were found in 0–17% of cases for mEOC compared to 75–77% of cases for metastatic involvement (10–12).

Seidman et al. proposed an algorithm incorporating these two factors and used a cutoff of greater or less than 10 cm. Based on tumor size being greater than 10 cm and unilateral involvement, mEOC was correctly predicted in 82% of cases. For tumor size less than 10 cm and bilateral involvement, metastatic mucinous adenocarcinoma was correctly predicted in 95% of cases (10). Others have suggested that for unilateral tumors, size greater than 15 cm may be more accurate. In a retrospective sample of patients with unilateral tumors greater than 10 cm, a primary ovarian tumor was diagnosed in 50% and 69% for size 10–15 cm and greater than 15 cm, respectively (11).

Histologic features are helpful in differentiating primary and metastatic mucinous adenocarcinomas of the ovary. Primary mEOC is more likely to have an expansile pattern of invasion, complex papillary pattern, microscopic cysts, and necrotic luminal debris. The presence of a coexisting ovarian lesion supports the diagnosis of a primary ovarian tumor, although it should be noted that these deceptively benign appearances may be seen in tumors metastatic to the ovary. Factors supportive of metastatic involvement include nodular growth pattern, ovarian surface involvement by epithelial cells (surface implants), an infiltrative invasive pattern, single cell infiltration, hilar involvement, and signet ring cells (12). These histologic features may be helpful, however, they are not specific and intraobserver variability exists. The presence of so-called “dirty necrosis” and segmental necrosis of tumoral glands are characteristic for metastatic colorectal carcinoma and suggest this diagnosis when present.

Immunohistochemistry may assist in distinguishing the primary site, and cytokeratin (CK) stains are routinely used. An immunoprofile of CK 7 positive/CK 20 negative favor a primary ovarian tumor, while CK 7 negative/CK 20 positive suggest metastatic involvement (Figs. 1 and 2). Primary mucinous ovarian tumors can stain positively for CK 20, although this is usually weak and focal. Likewise colorectal tumors, which typically are strongly CK 20 positive, may be negative particularly in right-sided or poorly differentiated tumors. Mucinous tumors from the appendix and upper gastrointestinal tract may stain CK 7 positive. We can therefore not rely on the CK 7/CK 20 immunoprofile alone. Other immunohistochemical markers may be helpful (13–18) (Table 1).
Molecular studies

Molecular differences in mEOC and serous epithelial ovarian cancer (sEOC) have been observed suggesting that these tumors should be regarded as separate entities. These studies have identified overexpression of the k-ras oncogene and a relative absence of mutations of the tumor suppressor gene p53 for mEOC in contrast to sEOC where the converse is seen (19,20). Interestingly, mucinous tumors of gastrointestinal origin, such as colorectal and pancreatic cancers, are also known to have overexpression of the k-ras oncogene (21,22).

There is data supporting the development of mEOC through an adenoma–carcinoma sequence originating from cystadenomas and mucinous borderline tumors. Normal epithelium and sites of transitional epithelium may be seen adjacent to borderline or invasive mucinous tumors (23). Mutations in k-ras are likely to represent an early genetic lesion in the development of mEOC. Increasing frequency of k-ras mutations in benign, borderline, and malignant mucinous tumors have been demonstrated (24), and similar k-ras mutations in adjacent benign and borderline areas of grade 1 mucinous adenocarcinomas have been observed (25).

Gene expression profiling of mucinous tumors demonstrate a hierarchical clustering relationship between grade 1 mucinous adenocarcinomas and borderline tumors, which is distinct from cystadenomas and normal ovarian surface epithelium. Binary tree analysis showed that there are a number of co-regulated genes.
shared between cystadenomas and other mucinous tumors (26). These data are consistent with the other molecular studies that have demonstrated a link among the various mucinous tumors and support the hypothesis that invasive tumors may evolve from their benign counterparts.

Genetic abnormalities

The majority of women with hereditary ovarian cancer have a germline mutation in either BRCA1 or BRCA2. Approximately 10% of women diagnosed with invasive EOC will carry a mutation in one of these genes. BRCA1 and BRCA2 ovarian cancers have predominantly serous pathology and present with advanced disease. mEOC is not associated with these mutations, again illustrating that these tumors develop along separate pathways (27).

Tumor markers

The tumor marker profile at presentation, in particular the ratio of the serum CA125 and carcinoembryonic antigen (CEA) levels, has been identified as a useful diagnostic aid to identify patients who warrant investigation of the gastrointestinal tract preoperatively. A serum CA125/CEA ratio of greater than 25 has been found to have the highest discriminative value in distinguishing ovarian and colorectal primaries (28). Among the histologic types of EOC, case-control studies have shown that absolute values of CA125 at diagnosis were lower for patients with mEOC compared with sEOC (29,30). Additionally, CEA levels are frequently raised in the mEOC (31) (Table 1). Therefore this model, which relates to the preoperative assessment using tumor markers to differentiate between an ovarian or gastrointestinal primary prior to a histologic diagnosis, is likely to be less discriminatory for mEOC.

Clinical studies

Small retrospective studies have reported response rates of 26–42% to platinum-based first-line chemotherapy confirming platinum resistance for most mucinous ovarian tumors (29,30,32) (Table 2). In view of the rarity of this histologic subtype in patients with advanced disease, phase III trials of chemotherapy typically include too few patients with mEOC to allow a meaningful analysis of the outcome for these patients.

The International Collaborative Ovarian Neoplasm Group 1 and Adjuvant ChemoTherapy in Ovarian Neoplasms studies were performed in parallel and analyzed together. They investigated the role of adjuvant platinum-based chemotherapy in patients with stage I EOC, randomizing patients between immediate treatment and observation. There were 180 of 925 (19.5%) patients with mEOC included in this trial and subgroup analysis for mucinous pathology did not find a statistically significant difference in outcome between adjuvant chemotherapy versus observation in this group. Thirty-three patients (18.3%) experienced disease relapse, which is greater than would be anticipated for stage I mucinous tumors. For patients with sEOC, overall 20% relapsed (33). Less stringent surgical requirements with only one-sixth of patients being optimally surgically staged resulted in an unknown percentage with occult stage II or III disease. This may have affected the results and probably explains why there was an unusually high relapse rate for the patients with stage I mEOC in this trial (33).

The only large randomized clinical trial for advanced EOC which performed a separate analysis for mEOC was the International Collaborative Ovarian Neoplasm 3 study. One hundred forty-eight of 2074 patients (7%) had mucinous pathology. They did not find a difference in progression-free survival (PFS) or overall survival (OS) for patients with mucinous pathology based on treatment received, carboplatin or paclitaxel. Their analysis was limited in that they did not report outcome for response rate, PFS or OS for patients with mEOC compared to the other pathologic types. Therefore, based on this study, we cannot conclude whether patients with mEOC have an inferior outcome compared with sEOC to standard adjuvant chemotherapy (3).
were analyzed, 47 with mucinous pathology and 94 with serous pathology. The response rates were 38.5% (95% CI, 23.4–55.4%) versus 70% (95% CI, 58.5–80.3%) for mEOC and sEOC, respectively (P = .001). Complete remission was 18% versus 47%. They did not find a significant difference in time to progression 11.8 months (95% CI, 7.2–16.4 months) versus 20.0 months (95% CI, 15.7–24.2 months) or OS 33.2 months (95% CI, 23.3–43.1 months) versus 38.0 months (95% CI, 26.8–49.2 months) for mEOC and sEOC, respectively, although there was a trend to a worse survival for patients with mEOC (P = .46).30

A retrospective study of 21 patients reviewed the response to first-line chemotherapy for patients with mEOC; 19 patients had evaluable disease (12 with measurable disease and 7 assessed with second-look laparotomy). Eight (42%) patients with evaluable disease responded to first-line platinum-based chemotherapy.32

A small phase II trial enrolled 25 patients with platinum-refractory mucinous and clear cell ovarian cancer. Patients were treated with irinotecan and mitomycin C, and the authors reported a response rate of 52% (95% CI, 32.4–71.6%), with 5 (20%) complete responses (95% CI, 4.3–35.7%). The median OS was 15.3 months.34

Future directions

There is a rationale for using the molecular and histopathologic characteristics of a tumor rather than its issue of origin, as a basis for making treatment decisions. The latter consideration is well exemplified by the data on the behavior of advanced-stage mEOC. At present, chemotherapy for all histologic subtypes of EOC is similar despite suggestions that there are real differences in response and outcome for patients with mEOC and indeed other subtypes such as clear cell tumors.

At present, there is an interest in investigating oxaliplatin in combination with either 5-fluorouracil or capcitabine. Oxaliplatin and 5-fluorouracil has been documented to have modest activity in platinum-resistant ovarian cancer.35,36 There has not been further exploration of irinotecan despite a promising response rate in combination with mitomycin C in this tumor type. Another potential strategy would include the addition of an anti-angiogenic agent such as bevacizumab. In addition to demonstrating single-agent activity in platinum-resistant ovarian cancer,37,38 bevacizumab has successfully been incorporated with chemotherapy in several tumor types, including colon cancer39,40. The efficacy of these agents is yet to be established for mEOC. There is an urgent need for prospective data from randomized studies to be generated and for such trials to have a translational component to better define the molecular characteristics and potential predictive factors for response in patients with mEOC.

References

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