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Unmasking the complexities of mucinous ovarian carcinoma

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Abstract

Objective—Most collaborative studies for the treatment of primary and recurrent ovarian cancer have grouped all epithelial ovarian cancers together, leading to a common therapeutic approach to all the different subtypes. Emerging data, however, support the hypothesis that primary mucinous ovarian cancers are unique histologically, molecularly, and clinically from other epithelial subtypes. The objective of our review was to identify and synthesize the most current information on mucinous ovarian carcinoma with regard to pathologic, molecular, and clinical distinctions.

Methods—We searched PubMed for English-language articles with the MeSH term “mucinous ovarian carcinoma” published between 1990 and 2009.

Results—On pathologic examination, primary invasive mucinous ovarian cancer often can be seen next to areas of benign and borderline mucinous histology, suggesting a continuum to malignant progression not observed in the other epithelial ovarian lesions. When compared to serous ovarian tumors, primary mucinous ovarian tumors have a significantly higher prevalence of KRAS mutations and a lower frequency of BRCA and p53 abnormalities. In addition, metastatic primary disease and recurrent mucinous cancers have a substantially worse prognosis than other epithelial ovarian cancers and are largely platinum and taxane resistant.

Conclusions—Primary mucinous ovarian cancer should be considered separate from the other epithelial ovarian cancers. Ongoing clinical trials in this disease will likely offer improvements in chemotherapeutic agents used to treat women with primary and recurrent mucinous ovarian cancer.

Keywords

ovary; mucinous; carcinoma; tumor; neoplasm

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Introduction

Epithelial tumors of the ovary are thought to arise from the surface of the ovary – a single layer of mesothelial cells. Traditionally, all carcinomas arising from the surface epithelial layer of the ovary have been grouped together. This grouping has led to a single therapeutic strategy that is used for all epithelial ovarian cancers. Histologically, however, epithelial ovarian cancers represent a wide variety of tumor subtypes. On the basis of clinical and molecular observations, there is growing consensus that many of these histological subtypes are unique entities that do not respond to conventional cytotoxic agents uniformly and merit exploration of novel therapeutic approaches tailored to histological subtype is warranted. Many authors have suggested reclassifying the epithelial ovarian cancers. Gilks [1] has suggested considering these tumors not as a single subtype but as 6 different subtypes based on their clinical behavior and pathologic findings. As part of this schema, mucinous borderline and invasive cancers of the ovary are within the same continuum and completely separate from serous borderline and low-grade serous cancers, which in turn are different from high-grade serous malignancies. Several pathologic, molecular, and clinical studies support this interpretation.

In 2004, Hess et al. [2] showed that women with advanced-stage mucinous ovarian cancer had a worse prognosis than women with nonmucinous epithelial ovarian cancers. In fact, these authors reported that women with stage III and IV nonmucinous epithelial ovarian cancers lived over 3 times longer than women with mucinous ovarian cancer matched for stage and other prognostic factors [2]. This startling difference in prognosis has led many researchers to investigate how mucinous tumors differ from other epithelial cancers. The objectives of this review are to 1) discuss why all epithelial tumors have traditionally been treated similarly, 2) describe the current literature on the pathologic, molecular, and clinical differences between mucinous ovarian cancer and other epithelial ovarian cancers, with particular attention to serous cancers of the ovary, the most epithelial ovarian cancer, and 3) describe ongoing international clinical trials for the treatment of mucinous ovarian cancer.

Past Chemotherapy Trials for Epithelial Ovarian Cancer

In the past, collaborative groups have included all epithelial ovarian tumors in their phase III trials and have not analyzed results by tumor histological subtype. Mucinous tumors have always accounted for only a small percentage of patients enrolled in these trials. For example, in Gynecologic Oncology Group (GOG) trial 111 (cisplatin and cyclophosphamide vs. cisplatin and paclitaxel), only 3.4% of the patients enrolled (14 of 410) had mucinous tumors [3]. In intergroup trial IV-10 (cisplatin and cyclophosphamide vs. cisplatin and paclitaxel), only 4.4% of the patients enrolled (30 of 680) had mucinous tumors [4]. And, in GOG trial 132 (cisplatin vs. paclitaxel vs. cisplatin and paclitaxel), only 2.6% of the patients enrolled (16 of 614) had mucinous tumors [5]. Most recently, GOG trial 182 compared standard-of-care paclitaxel and carboplatin to 4 other platinum-based regimens as adjuvant chemotherapy in women with stage III or IV epithelial ovarian cancer. This study, one of the largest to date, enrolled 4312 patients with primary epithelial ovarian cancer after debulking surgery. Of those women enrolled, only 1.6% (71 of 4312) had primary mucinous ovarian

cancer [6]. Surprisingly, current standard treatment of mucinous ovarian cancer is based on these large studies with very limited numbers of patients with this histological subtype.

Incidence of Mucinous Ovarian Carcinoma

Although the proportion of patients with mucinous tumors in the collaborative groups' large phase III studies of epithelial ovarian cancer ranged from 2% to 4%, much of the historical literature puts the incidence of mucinous ovarian cancer as a subgroup of the epithelial ovarian cancers at almost 11%. Recent reviews of the proportion of ovarian cancers that are mucinous have supported the lower rates reflected in the collaborative group studies. Seidman et al. [7] carefully re-reviewed the pathology of 220 consecutive cases of epithelial ovarian cancer at their community hospital. After excluding carcinosarcomas and primary peritoneal cancers, they found the incidence of primary mucinous ovarian cancer to be 3.4%.

In another review of mucinous ovarian cancers, Shimada et al. [8] reviewed 1400 cases of epithelial ovarian cancer from 14 centers in Japan. In this large group, 16% patients had an initial diagnosis of invasive primary mucinous ovarian cancer. However after a careful pathologic review, only 4.9% had invasive primary ovarian cancer with the remainder reclassified as were either mucinous intraepithelial carcinoma, mucinous borderline tumors, or metastases from another site.

So what accounts for this large discrepancy between the incidence in the historical literature and the incidence in the collaborative group studies and these single- and multi-institutional reviews of consecutive cases? Seidman et al. [7] argue that these lower estimates are likely a more accurate reflection of the incidence of mucinous ovarian cancer because the following problems were more likely in the historical literature: 1) misclassification of a gastrointestinal primary tumor as an ovarian primary tumor (80% of mucinous epithelial tumors found in the ovary are extraovarian in origin); 2) misclassification of a mucinous borderline tumor as an invasive cancer; and 3) classification of pseudomyxoma peritoneii as being of ovarian origin when it is now standard to consider all such cases as intestinal in origin [7]. To this list of reasons, we would add that 4) much of the historical literature is from tertiary referral centers, which often get sent difficult cases for second opinions. Patients with serous ovarian cancers are less likely to be referred because these tumors are easier to diagnose than mucinous tumors for the reasons outlined above. Tertiary referral centers, therefore, are likely to have patient populations highly enriched in patients with mucinous tumors, leading to a selection bias in their resultant publications.

Pathologic Features of Mucinous Ovarian Tumors

Ovarian mucinous carcinoma is divided into intraepithelial (non-invasive) carcinoma and invasive carcinoma. Intraepithelial (non-invasive) mucinous carcinoma is characterized by the presence of marked epithelial atypia in the absence of stromal invasion (Figure 2). Invasive mucinous carcinoma is diagnosed once stromal invasion measuring more than 5 mm or more than 10 mm^2 is detected. Two types of invasive mucinous carcinoma are recognized: 1) expansile (confluent) type and 2) infiltrative type. The former is characterized by a confluent glandular growth uninterrupted by normal ovarian parenchyma (Figure 3) while the latter demonstrates the presence of small glands, nests or individual cells

infiltrating the stroma (Figure 4). Intraepithelial (non-invasive) mucinous carcinoma, FIGO stage I, has a recurrence rate of 5.8% [9]. Invasive mucinous carcinoma, FIGO stage 1, has a 5-year survival rate of 91% with patients having advanced stage tumor usually dying of disease [10]. Invasive mucinous carcinoma with an infiltrative pattern has a more aggressive course than mucinous carcinoma with an expansile pattern [9, 11]. Interestingly, invasive mucinous carcinoma of the ovary often coexist alongside areas of mucinous borderline lesions and benign mucinous cystadenomas, suggesting that these lesions may be precursors to invasive tumors.

Molecular Features

Genetic Alterations

The role of the *KRAS* oncogene has been extensively explored in epithelial ovarian carcinomas. The *RAS* family of G proteins is part of the pathway that signals cell division. Mutations in the *RAS* genes have been found to stimulate cell growth [12]. One study found that 50% of mucinous ovarian carcinomas had *KRAS* mutations, compared to only 5% of serous ovarian carcinomas, 10% of endometrioid ovarian carcinomas, and 0% of clear cell ovarian carcinomas [13]. This finding was highly statistically significant. Interestingly, the same *KRAS* mutations found in invasive mucinous tumors are also found in adjacent borderline and benign mucinous lesions in the same specimens [14].

In contrast to *KRAS* mutations, *BRCA1* and *BRCA2* mutations are thought to play a significant role in the development of serous ovarian carcinomas but not mucinous ovarian carcinomas. *BRCA1* and *BRCA2* are tumor suppressor genes that help to repair damaged DNA and are commonly mutated not only in inherited serous ovarian carcinomas but also in many cases of sporadic serous ovarian cancer. Tonin et al. [15] reviewed the histopathologic subtypes of ovarian carcinomas in 58 families with hereditary breast and ovarian carcinomas. In these patients with known *BRCA* mutations, 64% had serous ovarian carcinomas, and only 2% had mucinous ovarian carcinomas. In contrast, among women with *BRCA* mutation-negative ovarian cancer, 29% of women had mucinous ovarian cancer, and this proportion was significantly higher than among the *BRCA* mutation-positive women. Similarly, in a review of the literature that included 636 *BRCA* mutation-positive women with ovarian cancer, only 2% were found to have mucinous subtypes [16].

Another tumor suppressor gene, *p53*, also seems to play a prominent role in carcinogenesis of serous ovarian tumors but not mucinous ovarian tumors. The *p53* gene codes for a transcription factor that regulates the cell cycle by 1) activating DNA repair proteins when DNA has sustained damage, 2) inducing growth arrest by holding the cell cycle at the G1/S regulation point, and 3) initiating apoptosis if the DNA damage proves to be irreparable. Mutations in *p53* are have been found in almost 60% of serous tumors but only 16% of mucinous tumors [17].

Gene Expression Analyses

Mutations in *KRAS*, *BRCA*, and *p53* are the most commonly studied single gene alterations in ovarian cancer pathogenesis. Some investigators have gone beyond analysis of single gene mutations and used gene expression analysis to evaluate differences between serous

and mucinous ovarian carcinomas. Marchini et al. [18] carried out genomic analyses using a microarray chip with 16,000 genes and found that serous and mucinous tumors were easily distinguishable from one another on the basis of expression profiles. Using a probe set of 59,000 genes, Heinzelmann-Schwarz et al. [19] likewise found clear separation in expression profiles between serous and mucinous tumors of the ovary.

Immunohistochemical Studies

The expression of multiple individual proteins has been examined in serous and mucinous tumor specimens using immunohistochemical stains. Compared to serous tumors, mucinous tumors are more likely to express E-cadherin (62% vs. 4%, $p<0.001$) and less likely to stain positive for N-cadherin (8% vs. 68%, $p<0.001$) [20]. The cadherin family of glycoproteins helps cells establish contact with other cells and stabilize tissue architecture. The matrix metalloproteinases, which also play a role cell migration and adhesion, have also been found to be expressed differently between serous and mucinous tumors [21]. Kobel et al. [22] evaluated 21 proteins with immunohistochemistry in 500 ovarian cancer specimens. They found differential expression between serous and mucinous subtypes in 20 of the 21 biomarkers examined, including tp53, cadherin, metalloproteinase, CA125, and WT-1. Collectively, these and other molecular studies point toward a distinct pathogenesis of mucinous ovarian carcinomas compared to other histological subtypes of ovarian cancer.

Serum Markers

Carcinoembryonic antigen (CEA) is a well known serum tumor marker for gastrointestinal carcinomas. CEA has been noted to be elevated in almost one third of all ovarian carcinomas. However, CEA is much more likely to be elevated in mucinous ovarian carcinomas than in nonmucinous ovarian carcinomas (88% vs. 19%) [23, 24].

Nolen *et al*. [25] compared the levels of 58 serum biomarkers in serous ovarian carcinomas and mucinous, clear cell, and endometrioid ovarian carcinomas. Using immunoassays, they found significant differences between the 2 groups for 10 (17%) of the biomarkers examined. Serous tumors had significantly higher levels of CA125, follicle-stimulating hormone, luteinizing hormone, and SMRP. Mucinous tumors had higher levels of CA72-4, matrix metalloproteinase-9, CD40L, insulin-like growth factor-binding protein-1, myeloperoxidase, and tissue plasminogen activator-1.

Clinical Features

Several clinical differences have been noted between serous and mucinous tumors of the ovary, including differences with respect to stage at diagnosis, laterality, prognosis, and response rates to platinum-based therapy.

Stage at Diagnosis and Laterality

Eighty-three percent of mucinous ovarian carcinomas but only 4% of serous ovarian carcinomas are stage I at diagnosis [7]. Seventy-nine percent of mucinous tumors are unilateral, and the mean size of mucinous tumors at diagnosis is 18 cm [10]. When a mucinous tumor is grossly limited to the ovary, there is little chance of occult lymph node

metastasis. Cho et al. [26] reviewed 26 cases of mucinous ovarian cancer noted to be stage I grossly intraoperatively. All of these patients underwent lymphadenectomy as part of their staging procedures, and none were found to have lymph node disease. In contrast, 10% of patients with apparent stage I serous carcinoma of the ovary have been reported to have occult nodal metastasis at the time of diagnosis [27].

Prognosis

As the majority of primary mucinous ovarian carcinomas are stage I at diagnosis, it follows that as a group (all stages), women with mucinous carcinomas have a better prognosis than women with serous ovarian cancer, in whom stage I disease is less common. Using the Swedish Family Center Database of over 6000 women with a diagnosis of ovarian cancer (all stages), Ji et al. [28] found that the average overall survival was 34 months in women with serous subtypes, compared to 70 months for women with mucinous subtypes. In addition, the hazard ratio for cause-specific survival for mucinous carcinomas compared to serous carcinomas was 0.49 (95% confidence interval, 0.41-0.57); the corresponding hazard ratio for overall survival was 0.56 (95% confidence interval, 0.48-0.64).

Although most mucinous ovarian carcinomas are stage I at diagnosis, 17% of women with mucinous ovarian cancer have advanced-stage disease at diagnosis, and these women do decidedly worse than their nonmucinous counterparts with stage III or IV serous disease. The fact that advanced-stage mucinous ovarian cancer has a much worse prognosis than advanced-stage serous ovarian cancer is felt to be due to mucinous ovarian carcinomas' being largely platinum resistant. Unfortunately, all major studies in patients that have included mucinous ovarian tumors have been with platinum-based regimens.

As previously mentioned, Hess et al. [2] were the first to show that women with advanced-stage mucinous ovarian cancer had a worse prognosis than women with nonmucinous epithelial ovarian carcinomas. The authors matched 27 patients with mucinous ovarian cancer to 54 patients with nonmucinous ovarian cancer (2:1 match), all of whom had stage III or IV disease and had undergone primary cytoreductive surgery followed by platinum-based adjuvant therapy. There was no difference between patients with mucinous tumors and those with nonmucinous tumors with regard to histological grade, stage, optimal or suboptimal debulking, chemotherapy regimen, or length of follow-up. Patients with advanced mucinous ovarian cancer had a progression-free survival of 5.7 months, compared to 14.1 months for patients with nonmucinous ovarian cancer ($p < 0.001$), and an overall survival of 12.0 months, compared to 36.7 months ($P<0.001$) [2].

Winter et al. [29] reviewed the data from 6 GOG phase III trials of adjuvant chemotherapy with cisplatin and paclitaxel in women with stage III epithelial ovarian cancer after primary debulking surgery, both optimal and suboptimal. Of the 1895 patients included in these 6 studies, 74% had serous ovarian cancer, while only 2% had mucinous ovarian cancer. The authors found that women with mucinous tumors had a progression-free survival of 10.5 months, compared to 16.9 months for women with serous tumors. Women with mucinous ovarian cancer had a relative risk of progression of 2.18 compared to their serous counterparts ($p < 0.001$). Another highly significant finding was the difference in overall survival: women with mucinous ovarian cancer had a median survival of 14.8 months,

compared to 45.2 months for women with serous ovarian cancer. The relative risk of death from mucinous cancer for mucinous cancer compared to serous cancer was 4.14 ($p<0.001$) [29].

Response to Platinum-based Chemotherapy

In a smaller study, Shimada *et al*. [8] compared 24 women with primary mucinous ovarian cancer to 189 women with serous ovarian cancer and found response rates to platinum-based regimens of 12.5% and 67.7%, respectively. In a 2:1 matched study, Pectasides et al. [30] compared 47 women with advanced-stage primary mucinous ovarian cancer and 94 women with advanced-stage serous ovarian cancer, all of whom had received a platinum-based regimen in 1 of 9 Hellenic Cooperative Oncology Group studies. The authors found a better response rate in women with serous cancer (70% for serous vs. 38.5% for mucinous), although this did not translate into survival differences between the 2 groups.

Like primary mucinous ovarian tumors, recurrent mucinous ovarian tumors are also seemingly platinum resistant. Pignata et al. [31] reviewed their retrospective data on recurrent, platinum- sensitive epithelial ovarian carcinomas collected as part of the SOCRATES (Study of an Ovarian Cancer cohort Recurred After first-line Treatment: a rEtrospective Survey) study. Compared to recurrent nonmucinous ovarian carcinomas, recurrent mucinous ovarian carcinomas were less likely to respond to platinum-based regimens (36% vs. 63%, $p=0.04$). Progression-free survival after recurrence was 4.5 months for the mucinous carcinomas, compared to 8 months for the nonmucinous carcinomas ($p=0.03$), and overall survival was 17.9 months for the mucinous carcinomas, compared to 28.8 months for the nonmucinous carcinomas ($p=0.003$) [31].

Differentiating Primary from Metastatic Disease

Gross Differentiation

Most mucinous carcinomas involving the ovary prove to be metastases as opposed to ovarian primary carcinomas. Therefore, surgeons and pathologists must have a high index of suspicion for metastatic disease when considering the origin of mucinous carcinomas found in the ovary. Seidman et al. [32] found that only 23% of invasive mucinous carcinomas of the ovary were primary ovarian cancer. Most clinicians typically assume that metastases to the ovary are gastrointestinal in origin. However, although gastrointestinal tract tumors are the most common source of ovarian metastases, accounting for 45% of such tumors, ovarian metastases from primary tumors of the pancreas (accounting for 20% of ovarian metastases), cervix (13%), breast (8%), and uterus (5%) are also seen. The remaining 10% of ovarian metastases are from unknown primary tumors.

At surgical exploration, a working differential diagnosis can be developed on the basis of tumor size and laterality. Among unilateral tumors, more than 80% of those larger than 10 cm are ovarian primary tumors, while 88% of those smaller than 10 cm are metastases. Bilateral mucinous ovarian tumors are metastatic in 94% of cases [32]. This algorithm has been retrospectively validated by other investigators, who showed it to be correct 84% of the time in differentiating primary from metastatic mucinous carcinomas of the ovary [33]. Other authors have also found this algorithm useful in predicting site of origin for ovarian

carcinomas [34, 35].In addition, primary ovarian carcinomas tend to have a smooth capsule, while ovarian metastases often involve the ovarian surface grossly. However, the above mentioned algorithm and the status of the ovarian surface should be applied clinically with caution as in one study, up to 24% of the cases of colonic adenocarcinoma metastatic to the ovary showed unilateral ovarian involvement with tumor measurements of at least 10 cm. In the same study, 46% of the cases with available information on gross intraoperative appearance had a smooth capsule [36].

Although gross examination of the adnexae can often predict site of origin, both ovarian and extraovarian sources of primary disease should be explored. Intraoperatively, the surgeon should perform a careful exploration of potential gastro-intestinal sources including palpating the pancreas and running the entire small and large bowel. Postoperatively, the surgeon should consider a colonoscopy and mammogram if these screening tests have not been performed within the year prior to diagnosis.

Microscopic Differentiation

Although the presence of certain histological features can favor the diagnosis of primary mucinous carcinoma over metastasis, there are cases where a definitive diagnosis cannot be provided due to the presence of discordant or overlapping features. Microscopic features that favor the diagnosis of primary ovarian mucinous carcinoma include the coexistence of a borderline and benign mucinous component, an expansile (confluent) pattern of invasion, and a coexisting ovarian teratoma, Brenner tumor or mural nodule. In contrast, the following microscopic features favor the diagnosis of metastatic adenocarcinoma to the ovary: 1) prominent desmoplastic response, 2) nodular pattern of invasion (i.e., tumor nodules among structures indigenous to the ovarian parenchyma), 3) small clusters of tumor cells within corpora lutea or albicantia, 4) numerous pools of mucin dissecting the ovarian stroma (i.e., pseudomyxoma ovarii) in the absence of a coexistent ovarian teratoma, 5) an extensive signet-ring cell pattern, 6) ovarian surface involvement, 7)vascular invasion, 8) hilar involvement, and 9) an extensive infiltrative pattern of invasion [37, 38].

Immunohistochemistry may assist in determining the primary site of a mucinous carcinoma. Primary ovarian mucinous carcinomas tend to be positive for CK7 and CK20 with a predominance of CK7 expression while colorectal primaries tend to express CK20 only. In addition, colorectal cancers usually express racemase and β-catenin while primary mucinous ovarian cancers do not. In regards to other gynecological primaries metastatic to the ovary, it is worthy to mention that HPV *in situ* hybridization is useful in confirming an endocervical origin since most of the endocervical adenocarcinoma are HPV related. P16 immunostaining is useful only in well differentiated adenocarcinoma cases where a diffuse staining will be in keeping with an endocervical origin. Attention has to be paid to the fact that high grade ovarian mucinous or endometrioid adenocarcinomas can be positive for p16. Estrogen and progesterone receptors are usually express in endometrioid carcinomas either metastatic from the endometrium or primary in the ovary. Metastatic endocervical adenocarcinomas to the ovary cannot be distinguished from a primary mucinous carcinoma of the ovary since both tumors are progesterone receptor negative and usually estrogen receptor negative, although they can have variable expression for the latter (weak/diffuse or strong/focal

staining) [39]. When trying to differentiate primary ovarian tumors from metastasis from the pancreas, the presence of mesothelin, fascin, and prostate stem cell antigen (PSCA) favor a pancreatic primary while the presence of Dpc4 expression favors an ovarian primary. [40] Most breast cancers are CK7 positive/CK20 negative unlike ovarian primaries which typically express both. In addition, breast cancers almost always express estrogen receptors as well as gross cystic disease fluid protein (GCDFP)-15. [41] Mucinous ovarian carcinomas are unlikely to express these markers.

Future Directions

Realizing that mucinous ovarian cancer is a distinct disease from serous ovarian cancer, several collaborative groups have proposed innovative prospective chemotherapy protocols for patients with advanced or recurrent mucinous ovarian cancer. Recently, Sato et al. from Japan evaluated 6 different cytotoxic agents in 5 different primary mucinous ovarian cancer cell lines [42]. All 5 cell lines were resistant to platinum agents and taxanes given as single agents. However, 2 of the 5 cell lines showed sensitivity to oxaliplatin, etoposide, and 5-fluorouracil (5-FU) as single agents. The investigators then treated the cell lines with oxaliplatin plus etoposide and with oxaliplatin plus 5-FU and found that the combination of oxaliplatin and 5-FU was significantly inhibitory in 4 of the 5 cell lines (and almost significantly inhibitory in the fifth) whereas the combination of oxaliplatin and etoposide had activity in only 1 of the 5 cell lines. In addition, the combination of oxaliplatin and 5-FU produced significantly more inhibition than either drug alone and appeared to be synergistic. The authors then applied the cell line results to a mucinous ovarian cancer xenograft mouse model and found that mice treated with the combination of oxaliplatin and 5-FU survived significantly longer than mice treated with either agent alone or control mice treated with placebo [42].

On the basis of their own *in vitro* and *in vivo* studies, these same Japanese researchers are currently enrolling women with advanced or recurrent mucinous ovarian cancer in a single-arm phase II trial of S-1 and oxaliplatin. S-1 is an orally active drug made by Taiho Pharmaceuticals that combines 3 separate molecules. The first is tegafur, a prodrug that is converted to fluorouracil in cells. Next is gimeracil, an inhibitor of dihydropyrimidine dehydrogenase, an enzyme that degrades fluorouracil. The third component is oteracil, a molecule that inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, reducing gastrointestinal toxicity. The primary endpoint of the study is response rate; secondary endpoints are toxicity, progression-free survival, and overall survival.

The GOG and the Gynecologic Cancer Intergroup are about to begin accrual to a 4-arm, phase III randomized study comparing carboplatin and paclitaxel with and without bevacizumab to oxaliplatin and capecitabine with and without bevacizumab in women with stage II-IV or recurrent, untreated stage I primary mucinous ovarian or fallopian tube cancer (Figure 5). The primary endpoint will be overall survival; secondary endpoints will be progression-free survival, response rate, toxicity, and quality of life. Translational endpoints —*KRAS* mutations and expression of vascular endothelial growth factor and epidermal growth factor—are also included. The targeted accrual for the study is 322 patients.

The concept for this study was developed in 2004. At that time, prior to publication of most of the data described above, we felt that mucinous ovarian cancer pathologically and clinically mimicked colorectal cancer more than other types of epithelial carcinomas. For that reason, the experimental arm was chosen on the basis of the standard treatment of colorectal carcinomas at that time: capecitabine and oxaliplatin with or without bevacizumab. The Sato et al. pre-clinical studies [42] validate this choice of chemotherapeutic regimens.

Conclusions

Historically, primary mucinous ovarian carcinomas have been treated in the same manner as serous and other epithelial ovarian carcinomas. Over the last 5 years, however, several pathologic, molecular, and clinical studies have been published supporting the concept that mucinous ovarian carcinoma is likely completely separate from other subtypes of epithelial ovarian carcinoma. Collaborative groups in the United States, Europe, and Japan are currently undertaking prospective studies with chemotherapy and biologically targeted therapies in an effort to improve the traditionally poor outcome of patients with advanced or recurrent mucinous ovarian cancer.

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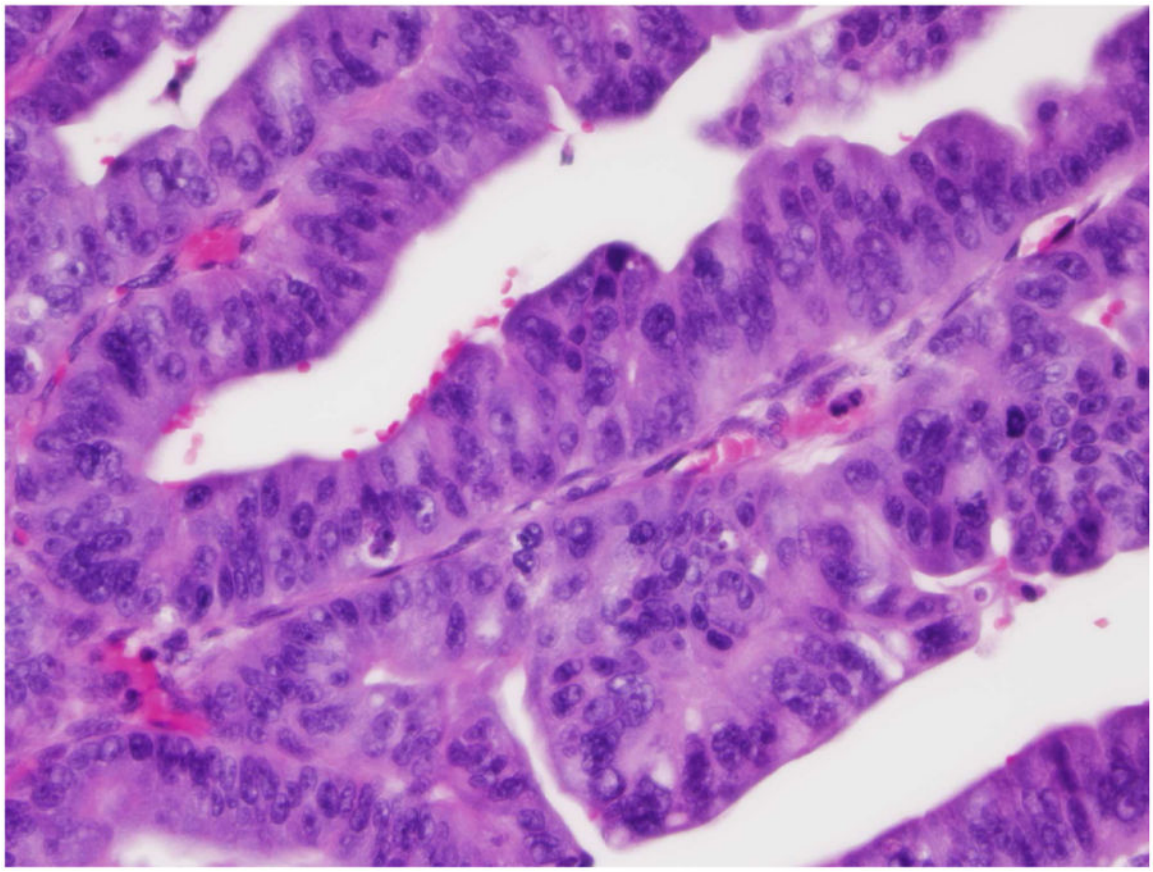

Figure 1. Intraepithelial (non-invasive) mucinous carcinoma

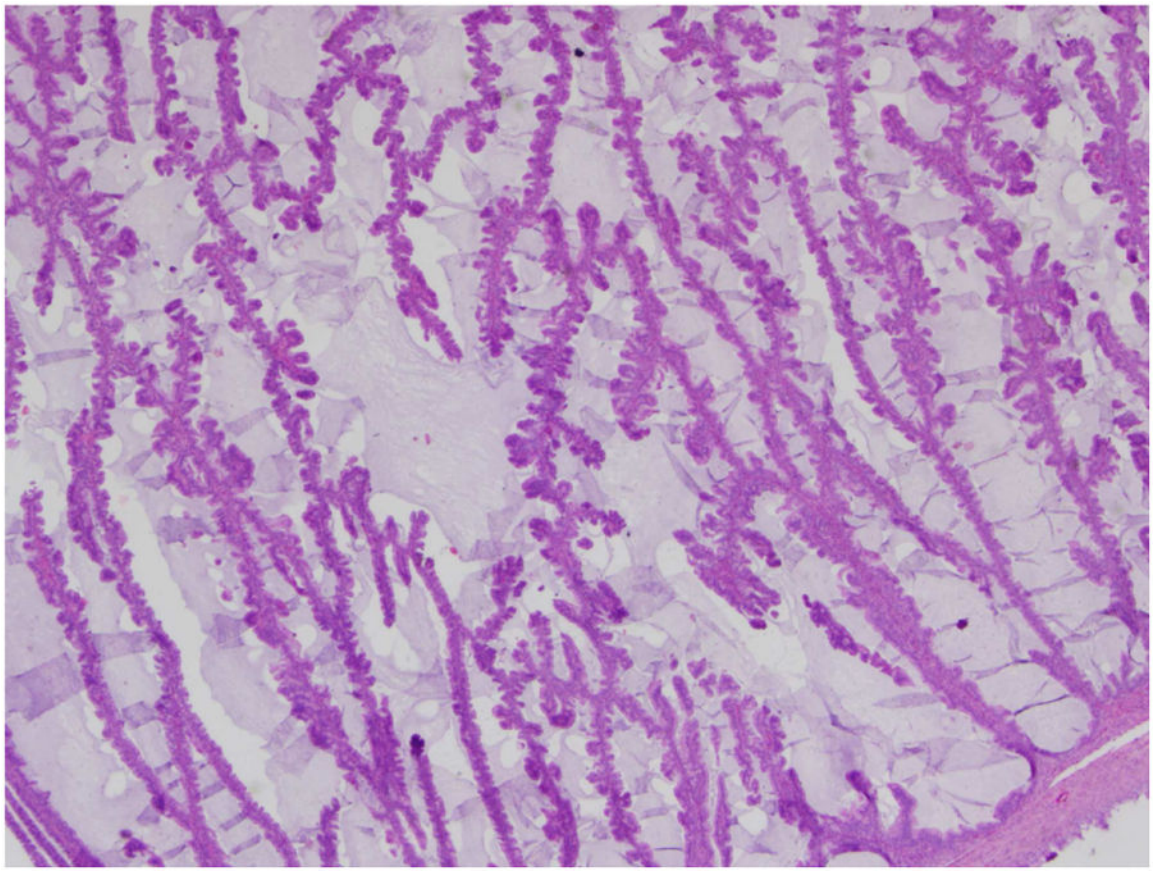

Figure 2. Expansile (confluent) invasive mucinous carcinoma

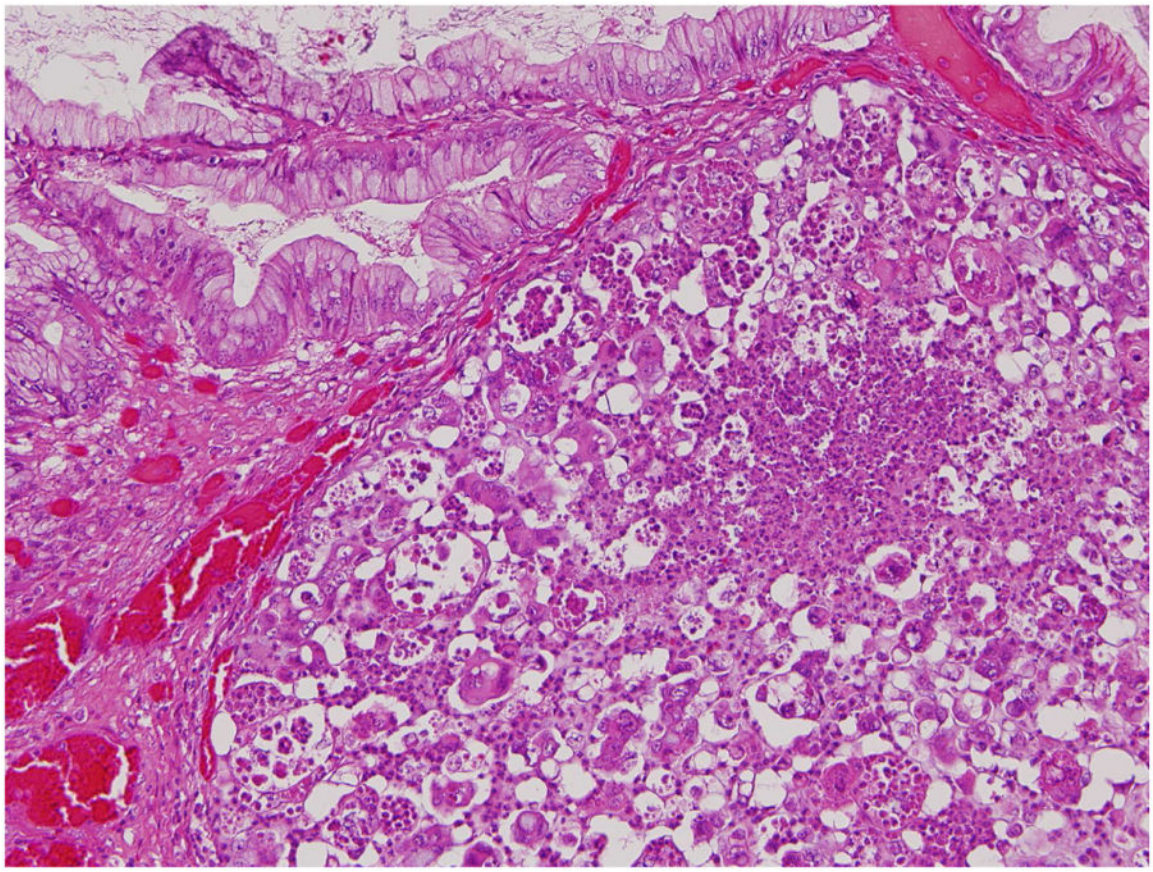

Figure 3. Infiltrative invasive mucinous carcinoma

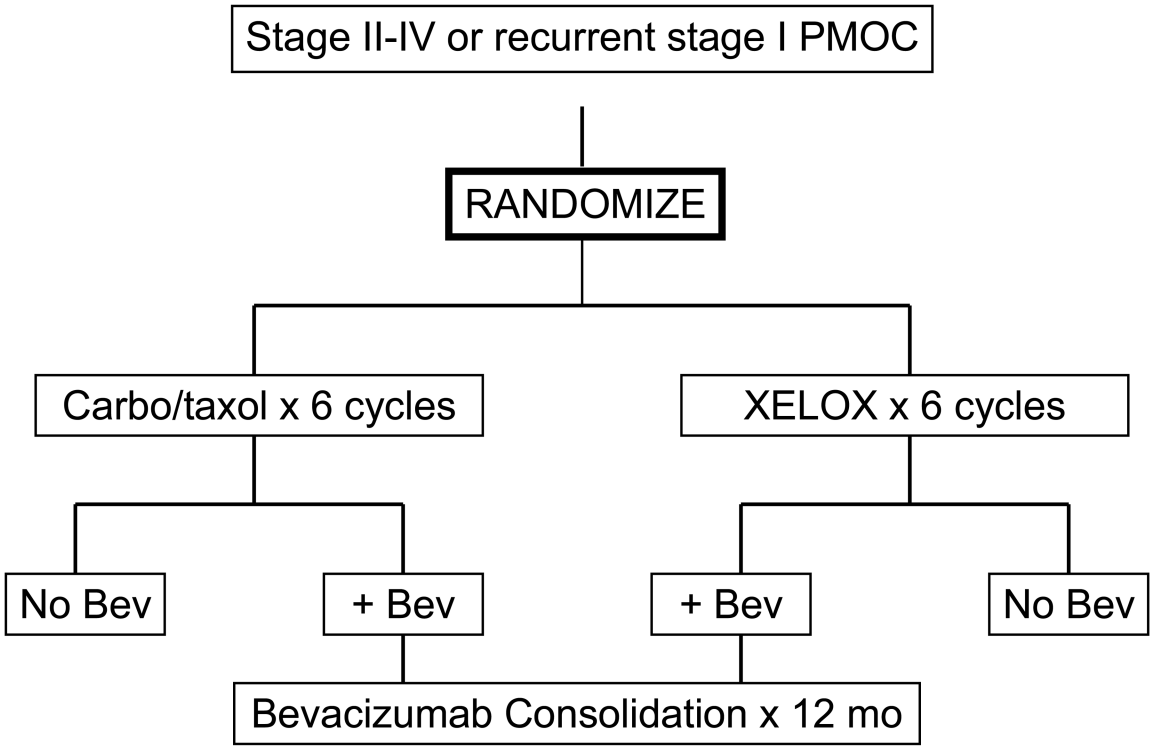

Figure 4. Schema for Gynecologic Oncology Group/Gynecologic Cancer Intergroup Study for women with advanced or recurrent mucinous ovarian cancer