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*Review Article*

# Mucinous neoplasms of the appendix and ovary: confusing terminology and clinical impact

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**Abstract:** Mucinous tumors may arise from a variety of anatomic locations; however, their clinical behavior varies considerably depending on their origin. When mucinous tumors involve the abdominal cavity, it may lead to mucinous ascites, clinically known as pseudomyxoma peritonei. While most cases are derived from the appendix, it may arise from a mucinous tumor of the ovary. However, the biological potential of these lesions vary, which is reflected by their recently updated classification schemes. This article is intended to clarify the different classifications of the mucinous tumors derived from the appendix and those derived from the ovary, and to provide therapeutic guidance for clinicians. This may facilitate better communication between pathologists and clinicians, and optimize therapeutic decision making.

**Keywords:** Pseudomyxoma peritonei, appendix, ovary, mucinous tumors

## Introduction

Mucinous neoplasms may arise from a variety of anatomic locations, including the appendix, colorectal tract, pancreas, and ovary. Historically, up until perhaps 15 years ago, no differentiation was made amongst Pathologists between neoplastic and non-neoplastic, or gastrointestinal vs gynecologic origins of mucinous ascites, clinically described as *pseudomyxoma peritonei* [1]. Despite common morphologic and cytologic appearances, however, the clinical behavior varies tremendously depending on the primary organ system from which these tumors derive. Despite numerous classification schemes proposed for mucinous neoplasms of both the gastrointestinal and gynecological systems, confusion still persists in regard to deciphering the origin of widely disseminated mucinous lesions in the setting of pseudomyxoma peritonei, and especially regarding the terminology that is most appropriate for optimal clinical management. Here, our aim is to provide a brief review of the current understanding of the neoplasms derived from the appendix and ovary, their clinical significance, and to provide a '*quick reference guide*' to the most up to date and most widely accepted classification schemes and terminology.

## Appendix

Primary mucinous neoplasms of the appendix are found in less than 2% of surgically resected appendices [2]. Despite the rare incidence of these lesions, they account for the vast majority of cases of mucinous ascites, even in women with concomitant ovarian mucinous tumors. Furthermore, as data has accumulated over the last two decades, the proper classification of these lesions has revealed paramount in clinical management. The major considerations regarding these lesions are location, degree of peritoneal spread, and cytologic morphology of the epithelium (if present) [2]. As regards location and spread, the questions to be answered are whether or not the lesion is limited to the lumen of the appendix, whether it has invaded the appendiceal wall, extended beyond the appendiceal serosa but limited to the right lower quadrant, or whether it has spread to involve the entire peritoneal cavity and viscera.

**Table 1.** Classification and associated treatments for mucinous tumors of the appendix

| Categories | Diagnostic criteria | Management |
|---|---|---|
| Adenoma | All mucinous tumors confined to the appendix (Regardless of cytologic appearance) | Appendectomy, with complete microscopic evaluation |
| Invasive mucinous adenocarcinoma | Mucinous neoplastic epithelium within the wall of the appendix | |
| Low-grade mucinous adenocarcinoma | Low-grade mucinous epithelium within peritoneal mucin | Cytoreductive surgery and chemotherapy |
| High-grade mucinous adenocarcinoma | High-grade mucinous epithelium within peritoneal mucin | Systemic chemotherapy |

A recent review of mucinous neoplasms of the appendix and peritoneum by Panarelli and Yantiss [2] provides an excellent overview of these lesions, and the clinical data supporting a variety of classification schemes, there being up to 6 classification schemes described in the literature. In reference to the cumulative data available in the literature, we currently support and employ the classification scheme devised by The American Joint Commission on Cancer (AJCC) and the World Health Organization (WHO) in 2010 [3, 4].

In this classification scheme, lesions limited to the appendix are referred to as adenomas (mucinous), regardless of cytologic appearance or the status of the surgical margin. Only when tumor is seen within the appendiceal wall is the lesion referred to as Invasive Mucinous Adenocarcinoma.

Before addressing the final classification categories that involve extra-appendiceal spread of mucinous neoplasms, it must be recognized that acellular mucin can be found within the peritoneum in cases of clinical pseudomyxoma peritonei that is not derived from a neoplastic process. Practically speaking, any segment of the gastrointestinal tract beyond the proximal foregut contains mucin-secreting cells. Thus, rupture of the alimentary tract along these segments, regardless of etiology, may lead to spilling of mucin into the peritoneum, and involve the abdominal viscera. Therefore, the classification of mucinous *neoplasms* is predicated on the histological identification of neoplastic epithelium within the mucinous aggregates of the peritoneum. In such circumstances, the cytologic grading is either low- or high-grade. These cytologic distinctions are made on the basis of cell size, pleomorphism, and nuclear atypia.

Classification schemes must serve a purpose. In the case of neoplastic processes, it is their variety of biological potential and/or response to treatments that must be differentiated. The following table, adapted from Panarelli and Yantiss, provides an up to date classification system advocated by the AJCC and the WHO [3, 4], and the corresponding clinical actions that appear the most practical and/or efficacious [2] (**Table 1**).

### Ovary

Mucinous ovarian tumors are epithelial tumors whose cells, like those of the appendiceal neoplasms, contain intracytoplasmic mucin. They account for approximately 15% of all primary ovarian tumors and are separated into three categories based on the World Health Organization [5] classification system: benign, borderline and malignant [6-8]. It is common to have a mural nodule of neoplastic growth [9] in either a benign or borderline lesion and, therefore, ample sectioning for microscopic evaluation is imperative (1 section per centimeter of tumor) [10].

Benign tumors account for 75% of mucinous tumors and are categorized into cystadenoma (most common), cystadenofibroma and adenofibroma types. Grossly, these tumors are unilateral [11] and large, ranging from 15-30 cm and 2,000-4,000 g [12]. The cystadenomas are typically multilocular or unilocular cysts filled with mucoid material, whereas the cystadenofibroma and adenofibroma types can be completely solid. Histologically, the cysts are lined by mucinous columnar epithelium with well organized, non-stratified epithelial architecture and minimal nuclear atypia [5].

Borderline mucinous tumors are characterized by greater epithelial stratification and cytologic atypia than benign lesions, but are differentiated from adenocarcinomas by lack of stromal invasion. They are divided into intestinal type and endocervical-like (Mullerian) type by histologic examination [7]. The intestinal type accounts for 85-90% of borderline tumors and are unilateral 95% of the time. Like benign

lesions, they are large, unilocular or multilocular and the cysts are filled with a mucoid substance. However, unlike benign lesions, these may be hemorrhagic or harbor foci of necrosis. The intestinal type generally resembles a hyperplastic colonic polyp and goblet cells are almost always seen. Areas with malignant cytologic features and papillary or cribriform cellular stratification of more than four cell layers should be labeled as borderline with intraepithelial carcinoma [5]. The endocervical-like type comprises the other 10-15% of borderline tumors and, like the intestinal type, is characterized by increased cellularity and lack of invasion. These tumors are generally smaller than the intestinal type and are bilateral in 40% of cases, a unique feature of this subtype of mucinous tumors. They are also associated with endometriosis of the involved ovary. Histologically, they exhibit papillary architecture, with endocervical-like mucinous epithelium with many acute inflammatory cells [5].

Ovarian mucinous adenocarcinoma is defined by having histologic or gross evidence of stromal invasion. These tumors are large, unilateral in 95% of cases and cystic or solid with areas of hemorrhage and necrosis. Stromal invasion can be demonstrated microscopically or is assumed if there are of areas of packed glands with malignant cells and little to no stroma that are at least 10 $mm^2$ and 3 mm in each of 2 linear dimensions [5, 8]. Histologically, these cancers can mimic mucinous borderline tumors or even have areas of benign appearing cytology, making carful and thorough sectioning of the gross specimen extremely important. The incidence of primary mucinous carcinoma of the ovary comprises less than 3% of the ovarian epithelial cancers [13].

One of the most important differentiations when diagnosing a mucinous tumor is the delineation between primary and metastatic lesions [9, 14]. Metastatic tumors usually originate in the appendix or other parts of the GI tract. As borderline tumors and invasive mucinous adenocarcinomas are unilateral 95% of the time, features that favor metastasis are multiple lesions, bilateral tumors, surface implants and vascular invasion [5, 15]. Thus, as previously mentioned, pseudomyxoma peritonei with ovarian involvement or a widely disseminated presentation almost exclusively occurs in the setting of metastatic cancer from an appendiceal primary tumor and a high index of suspicion must be maintained [9, 10, 15]. Furthermore, pseudomyxoma peritonei can sometimes be minimal, and clinicians should carefully rule out this possibility in cases of either unilateral or bilateral presentation.

Ovarian epithelial cancers, including mucinous carcinomas, are surgically treated and staged by the examination of biopsies from all commonly involved sites of metastasis, including the omentum, mesentery, diaphragm, peritoneal surfaces, pelvic nodes and para-aortic nodes [3]. Primary staging is by the method developed by FIGO, and the stage of ovarian mucinous neoplasms corresponds to their prognosis, and thus should be treated appropriately. Stage I tumors without an extraovarian focus have excellent prognosis with a 90.8% 5-year disease free survival [10] while extraovarian spread denotes a very poor prognosis. The majority present as FIGO stage I or II [6], are limited to the ovary, and have excellent prognosis. However, these tumors are notoriously resistant to chemotherapy, especially platinum based methods [16, 17], and mucinous tumors have thus far been widely underrepresented in randomized controlled trials aimed at developing new chemotherapy regimens for these patients [10].

## Conclusions

The clinical setting of mucinous ascites can be challenging enough for clinicians, and rendering an accurate diagnosis of the etiology by Pathologists can dramatically influence the subsequent clinical decisions made by Oncologists. Therefore, when faced with specimens from the peritoneum with abundant mucin, all General, Gastrointestinal, and Gynecologic pathologists should always maintain a differential diagnosis that includes both appendiceal (or other GI) and ovarian primary tumors. The use of immunohistochemistry can easily facilitate this distinction. As an initial immunohistochemical panel, cytokeratin 7 (CK7) and CK20 can aid in the differentiation but should be utilized with caution, and not in isolation. Primary ovarian lesions are generally CK7 positive and either CK20 negative or only express weak and focal positivity; on the other hand, appendiceal primaries are CK7 negative and CK20 strongly positive [10]. The addition of immunostains against CDX2 and PAX-8 can greatly assist in

the distinction. CDX2, a transcription factor involved in embryologic development of alimentary structures, is strongly positive in appendiceal neoplasms, and negative in those derived from the ovary in the majority of the cases. Conversely, PAX-8, a marker of Mullerian differentiation, is strongly positive in ovarian neoplasms, and negative in those derived from the GI tract.

## Disclosure of conflict of interest

None.

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