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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms

Chicago Consensus Working Group

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ABSTRACT The Chicago Consensus Working Group provides multidisciplinary recommendations for the management of appendiceal neoplasms specifically related to the management of peritoneal surface malignancies. These guidelines are developed with input from leading experts including surgical oncologists, medical oncologists, pathologists, radiologists, palliative care physicians, and pharmacists. These guidelines recognize and address the emerging need for increased awareness in the appropriate management of peritoneal surface disease. They are not intended to replace the quest for higher levels of evidence.

APPENDICEAL NEOPLASMS WITH PERITONEAL METASTASES

This article provides multidisciplinary recommendations for the management of peritoneal surface malignancies of appendiceal origin and constitutes 1 article in a series composed by the Chicago Consensus Working Group for the Management of Peritoneal Surface Malignancies.[1–10] Information regarding formation of the Chicago Consensus Group and explanation of the working group's consensus methodology is discussed.[1,2]

The peritoneum is the most common site of metastasis of appendiceal neoplasms. Peritoneal metastases frequently occur as synchronous metastases but can also be seen as metachronous metastases. The incidence of peritoneal metastases varies depending on the histologic characteristics of the primary appendiceal neoplasm and the presence of perforation and has been reported to range from 5 to $> 50\%$.[11]

In the initial evaluation of these patients, the histologic subtype of the tumor, the burden of disease on the peritoneal surfaces, and the presence of nonperitoneal metastatic sites must be assessed. A thorough evaluation of the resected primary tumor and/or biopsy specimens of peritoneal metastatic sites should be performed by an experienced pathologist. Cross-sectional imaging with contrast-enhanced computed tomography (CT) or magnetic resonance imaging is the preferred imaging modality to evaluate the peritoneal burden of disease, although significant limitations exist in the ability of any imaging modality to detect small-volume disease. Additional staging imaging such as chest CT is recommended for staging of advanced and/or recurrent low-grade mucinous tumors and for high-grade tumors, including goblet cell adenocarcinoma (GCA). Positron emission tomography is not recommended for the evaluation of mucinous tumors. Levels of CEA, CRP, Ca 19-9, CA-125, and chromogranin A (for GCA only) are often elevated, and their measurement can be useful in patients with peritoneal metastases from appendiceal neoplasms.[12–18] See Figs. 1, 2 and 3, management pathways for goblet cell adenocarcinoma, low-grade appendiceal mucinous neoplasm, and appendiceal adenocarcinoma.

Principles of Pathology

The histologic evaluation of a peritoneal biopsy specimen and/or the primary tumor provides the basis for determining the specific subtype of appendiceal neoplasm

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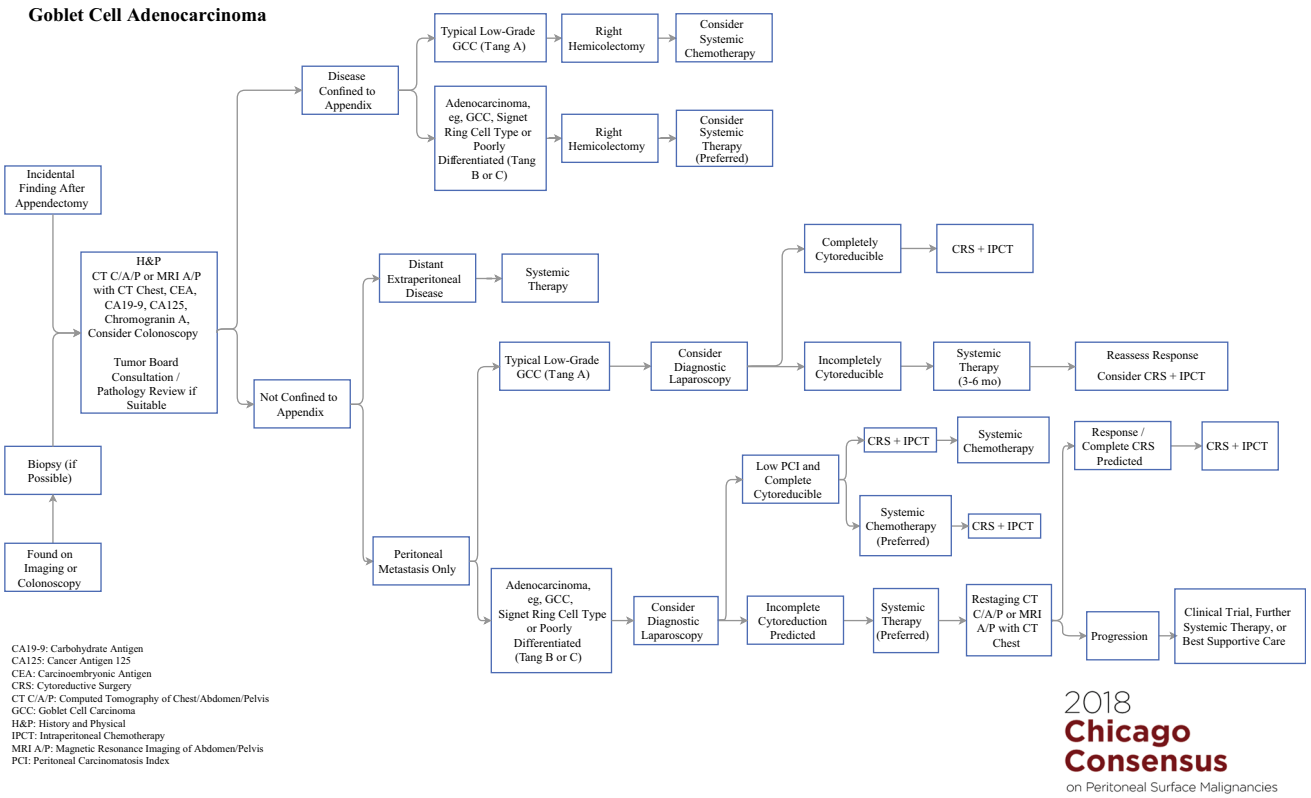

FIG. 1 Goblet cell adenocarcinoma management pathway

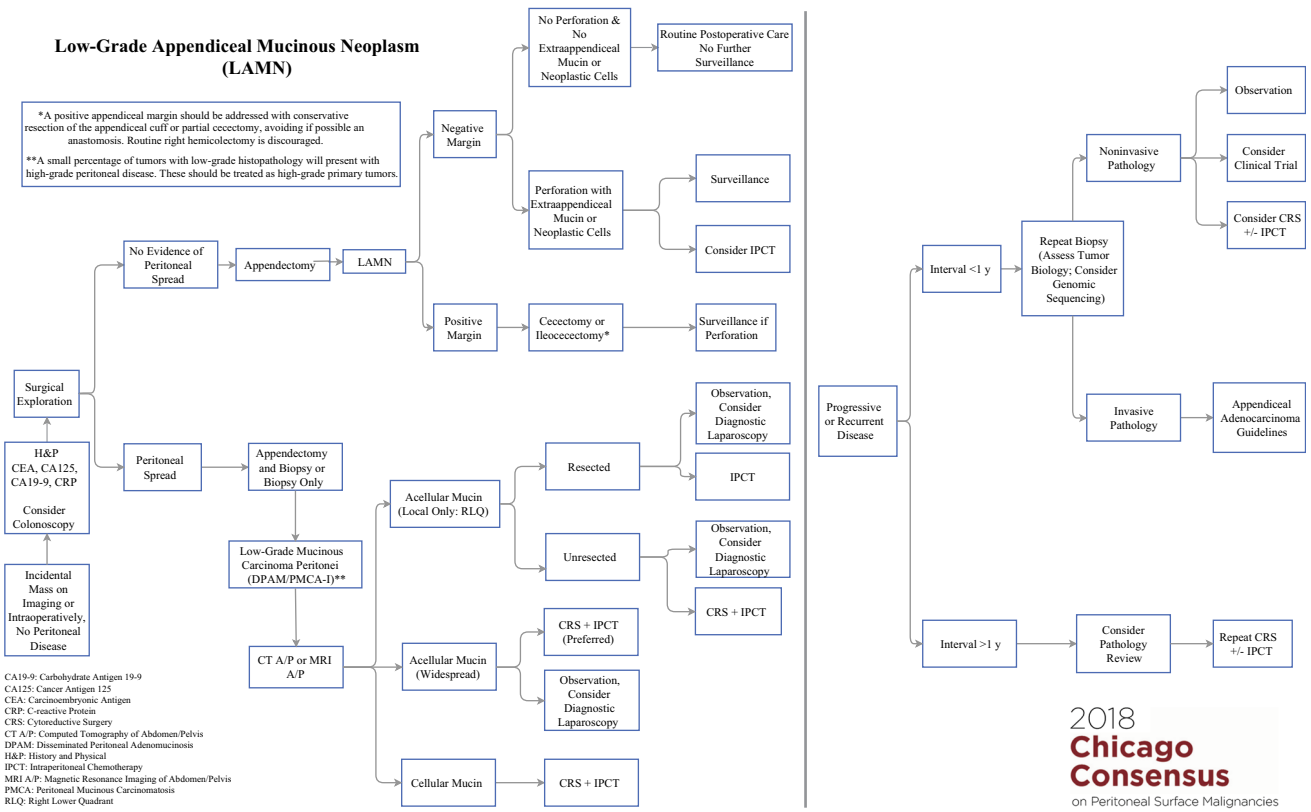

FIG. 2 Low-grade appendiceal mucinous neoplasm management pathway

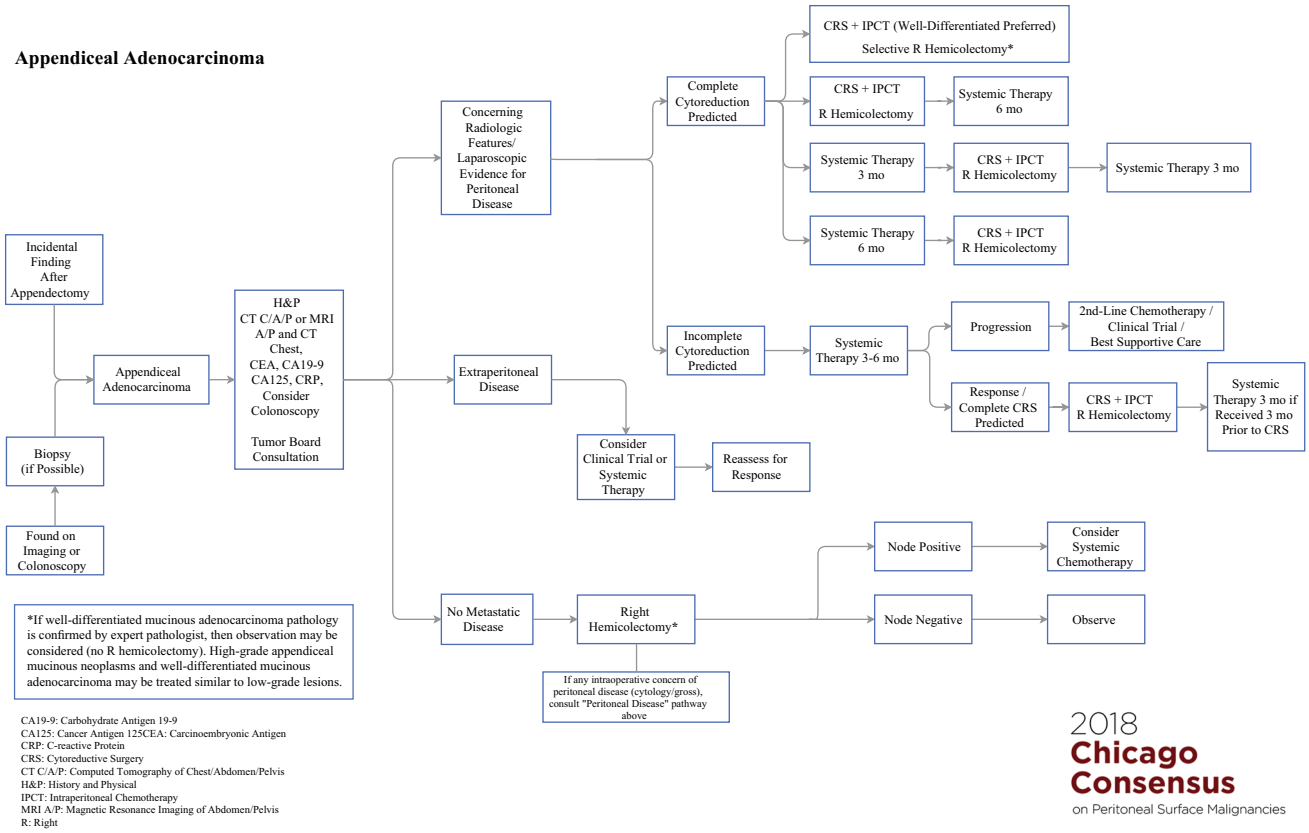

FIG. 3 Appendiceal adenocarcinoma management pathway

and its grade. Standard hematoxylin–eosin staining and immunohistochemistry methods are the basis of the pathological evaluation of appendiceal tumors. However, because of controversial and confusing nomenclature of several appendiceal neoplastic entities, the pathological assessment should be performed by a pathologist experienced in appendiceal and peritoneal tumors.[11,19]

On gross evaluation, most appendices with primary mucinous neoplasia show appendiceal dilatation as a result of abnormal accumulation of mucin within the lumen. The gross and macroscopic examination of these neoplasms should include the location of the tumor within the appendix (tip vs body vs base), the size of the tumor, the distance of tumor from the proximal resection margin (when possible), the presence or absence of mucin deposits on the serosa, the presence or absence of perforation, and the presence of any solid areas. Following formalin fixation, the entire appendix should be submitted for histologic examination, with the margin of resection separately designated.

After formalin fixation, peritoneal tissue should be measured and examined for mucin deposits and any firm nodules. If the specimen consists solely of mucin or contains a separate mucinous component, a measurement should also be given for this component and careful inspection for solid areas should be performed. For each specimen part, it is reasonable to submit 1 section per centimeter of mucinous deposit initially. If initial sections demonstrate high-grade disease, then there is no added value to additional tissue sections. However, detection of only acellular mucin or low-grade disease should prompt additional tissue sections, including submission of all mucinous material when feasible. Because of the low cellularity in many of these specimens, intraoperative assessment via frozen section is not recommended. Mucinous specimens can be processed and embedded in paraffin according to standard laboratory protocols. If molecular analysis is needed, microdissection may be required to obtain sufficient tumor DNA.

Biopsies of the peritoneal tumor deposits should be performed using image-guided core-needle technique or via a diagnostic laparoscopy. Positioning of the needle tracts and trocars should take into consideration the potential risk of seeding along the tract (midline preferred).

The presence of mucin without epithelial cells in a peritoneal biopsy specimen should not be classified as benign disease or a nondiagnostic sample; its significance and further management decisions should be determined by providers experienced in the management of appendiceal tumors. Cytologic evaluation of mucinous ascites can

identify glandular cells, although low tumor cellularity and lack of consensus guidelines limit the value of this method.

The pathological evaluation of the primary appendiceal tumor specimen should include the following features:

- Organ and site.
- Primary diagnosis according to *Digestive System Tumours*, volume 1 of *WHO Classification of Tumours*, fifth edition.[20–22] For GCA, histologic classification as typical GCA (Tang group A), signet ring cell type (Tang group B), or poorly differentiated carcinoma type (Tang group C) should be noted.[23]
- Histologic grade, specifically including the presence of signet ring cells.
- Tumor stage.
- Presence of perforation of appendix or tumor.
- Presence of mucin or neoplastic epithelial cells on the appendiceal serosa or mesoappendix.
- Presence of lymphatic vessel invasion, large vessel invasion, or perineural invasion.
- Status of margins.
- Status of lymph nodes.

The pathological evaluation of the peritoneal metastases should include the following:

- Histologic type according to the World Health Organization classification.[20–22]
- Histologic grade.
- Presence of signet ring cells, including percentage of tumor composed of signet ring cells.
- Results of ancillary studies, including immunohistochemistry to determine the potential origin of the tumor.

Principles of Systemic Chemotherapy

Limited evidence regarding the role of systemic chemotherapy in appendiceal neoplasms is available, and the existing evidence shows limited efficacy for the most common subtypes. Nonmucinous epithelial appendiceal neoplasms are generally approached and treated using colorectal cancer treatment pathways (Fig. 3).

Low-grade mucinous appendiceal neoplasms and low-grade mucinous carcinoma peritonei of appendiceal origin are generally considered indolent and show minimal to no responsiveness to systemic chemotherapy (Fig. 2).[24–26] Therefore, patients who are candidates for surgical cytoreduction are treated with surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) followed by surveillance. For patients with unresectable disease and/or recurrent disease not amenable to resection, systemic therapy can be used according to the treatment algorithms for mucinous colorectal cancer (Fig. 2).[27,28]

For patients with mucinous appendiceal adenocarcinoma, nonmucinous appendiceal adenocarcinoma, signet ring cell adenocarcinoma, high-grade mucinous carcinoma peritonei, or high-grade and/or advanced-stage GCA, systemic chemotherapy is used as part of multimodality therapy akin to the treatment of colorectal cancer.[29] There is limited evidence regarding efficacy in appendiceal cancer specifically, but several studies suggest similar response rates in these cancer subtypes.[27,29] It is worth noting that not all patients with GCA necessarily require systemic chemotherapy, especially those with Tang group A tumors (Fig. 1). However, limited evidence to help guide this decision is available.

For patients who are candidates for cytoreductive surgery and HIPEC, systemic chemotherapy can be used preoperatively, postoperatively, or both.[24,26,30] Following standards used in other colorectal cancer settings, a combined total of 6 months of chemotherapy is usually recommended.

Principles of Surgery

Surgery with a curative intent can be considered for patients with either low-grade or high-grade subtypes of appendiceal neoplasms and peritoneal metastases. However, inclusion criteria and expected outcomes are notably different.

Peritoneal metastases of appendiceal origin are often detected incidentally at the time of appendectomy or diagnostic laparoscopy. In these situations surgical resection should be limited to steps that will help establish an accurate diagnosis (most commonly peritoneal biopsy and appendectomy if feasible). More extensive resections or partial debulking should be avoided at this time.

Complete cytoreduction is the main goal of surgical management of peritoneal metastases and is the most basic principle in preoperative decision-making. It is important to note that for low-grade appendiceal mucinous neoplasms and well-differentiated mucinous adenocarcinoma, right hemicolectomy is not always necessary.[31,32]

Cross-sectional imaging with or without diagnostic laparoscopy is used to estimate the likelihood of complete cytoreduction. Multifocal bowel obstruction, extensive involvement of the small bowel, biliary obstruction, and ureteral obstruction (especially bilateral) usually preclude successful curative-intent surgery.

For patients with low-grade mucinous neoplasm (grade 1), cytoreductive surgery with HIPEC is the treatment of choice. Excellent long-term survival can be achieved even in patients with a high burden of disease if complete cytoreduction can be achieved.[33–35] Patients who develop peritoneal recurrence after initial cytoreduction may be candidates for repeat surgical procedures.[36–38]

Patients with adenocarcinoma and peritoneal metastases are less likely than those with low-grade primary neoplasms and peritoneal disease to have complete cytoreduction. These patients also have worse survival rates when a high disease burden is present.[39,40] Preoperative predictive scoring systems can be helpful in preoperative decision-making,[41] although an absolute cut-off value of peritoneal disease burden has not been established.

Surgeons performing cytoreductive surgical procedures must be expert in assessing all of the peritoneal surfaces and knowledgeable about the typical patterns of involvement with different types of peritoneal surface malignancies. They need to have expertise performing multiple visceral resections and knowledge of standard peritonectomy techniques. Palliative debulking procedures (or incomplete cytoreductions/ablations) are generally discouraged except for patients with low-grade tumors; these procedures can be considered in appropriately selected patients. The burden of disease must be documented with a standard scoring system such as the peritoneal cancer index (PCI) score, and completion of cytoreduction should be documented with a CC or R score.[42]

Principles of Intraperitoneal Chemotherapy

Intraperitoneal chemotherapy has been applied in most studies that assessed complete cytoreduction for peritoneal metastases of appendiceal origin. The only randomized controlled study on this subject was designed to assess outcomes of cytoreductive surgery (CRS) and HIPEC in patients with colorectal cancer but included some patients with appendiceal adenocarcinoma. This study showed improved survival for patients treated with CRS and HIPEC plus systemic chemotherapy as compared with systemic chemotherapy with or without palliative surgery.[43] The first and only randomized trial of patients with appendiceal cancer was recently reported. The primary aim of this trial was to evaluate the toxicity of HIPEC with mitomycin C versus HIPEC with oxaliplatin. Progression-free and overall survival did not differ between groups, but the overall results confirmed that long-term survival is possible if complete cytoreduction is achieved.[44]

Large cohort studies of complete cytoreduction using peritonectomy procedures and visceral resection without HIPEC or early postoperative intraperitoneal chemotherapy are not available.

Current regimens that may be used for intraperitoneal chemotherapy are as follows:

- Mitomycin 30 mg at time 0, and 10 mg at time 60 for 90 min.
- Mitomycin 30 mg/m^2 for 90 to 120 min.
- Mitomycin 15 mg/m^2 plus doxorubicin 15 mg/m^2 for 90 min.
- Oxaliplatin 300 mg/m^2 for 30 min.

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