Ann Surg Oncol (2020) 27:1774–1779
https://doi.org/10.1245/s10434-020-08324-w

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

The Chicago Consensus on Peritoneal Surface Malignancies: Management of Peritoneal Mesothelioma

Chicago Consensus Working Group

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ABSTRACT The Chicago Consensus Working Group provides multidisciplinary recommendations for the management of peritoneal mesothelioma. 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 of the appropriate management of peritoneal surface disease. They are not intended to replace the quest for higher levels of evidence.

PERITONEAL MESOTHELIOMA

This article provides multidisciplinary recommendations for the management of malignant peritoneal mesothelioma 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 elsewhere.[1,2]

Malignant peritoneal mesothelioma (MPM) is a neoplasm that typically presents with abdominal pain, abdominal distension, and ascites. The incidence of MPM is higher in men than in women, although among women with mesothelioma, the peritoneum is a more common site of origin.[11] Asbestos exposure has been documented in many cases of MPM. However, unlike pleural mesothelioma, many cases of MPM are idiopathic. Germline (*BAP1*) mutations are observed more frequently in MPM than in pleural mesothelioma, although these mutations are identified in a minority of patients with MPM.[12] Prognostic factors include histologic differentiation, thrombocytosis, high Ki-67 level, burden of disease [according to the peritoneal cancer index (PCI)], and the presence of lymph node metastases or extra-abdominal disease. Predictive factors include PCI score and the ability to perform complete cytoreduction. Benign multicystic mesothelioma and well-differentiated papillary peritoneal mesothelioma are indolent in their course and are not clearly neoplastic in nature. The roles of surgery and chemoperfusion are inadequately defined except for symptomatic or progressive disease. Mesothelioma arising from the tunica vaginalis is similar in morphology to mesothelioma arising from the peritoneum and may be distinguished from peritoneal mesothelioma that tracks along a patent processus vaginalis.

After adequate cross-sectional imaging (computed tomography or diffusion-weighted magnetic resonance imaging of the abdomen and pelvis), patients with epithelioid mesothelioma (or extremely well-selected biphasic or sarcomatoid mesothelioma) who are fit for operation offered cytoreductive surgery (CRS) and intraperitoneal or systemic chemotherapy when complete surgical cytoreduction can be achieved. (See *Peritoneal Mesothelioma Management Pathway*, Fig. 1).

Principles of Pathology

The diagnosis of mesothelioma requires examination of tissue architecture and can rarely be made with fine-needle aspiration or cytology specimens. Biopsies for peritoneal mesothelioma should preferably be made through the

The collaborators for the Chicago Consensus Working Group are listed in the acknowledgments.

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First Received: 4 July 2019;
Published Online: 13 April 2020

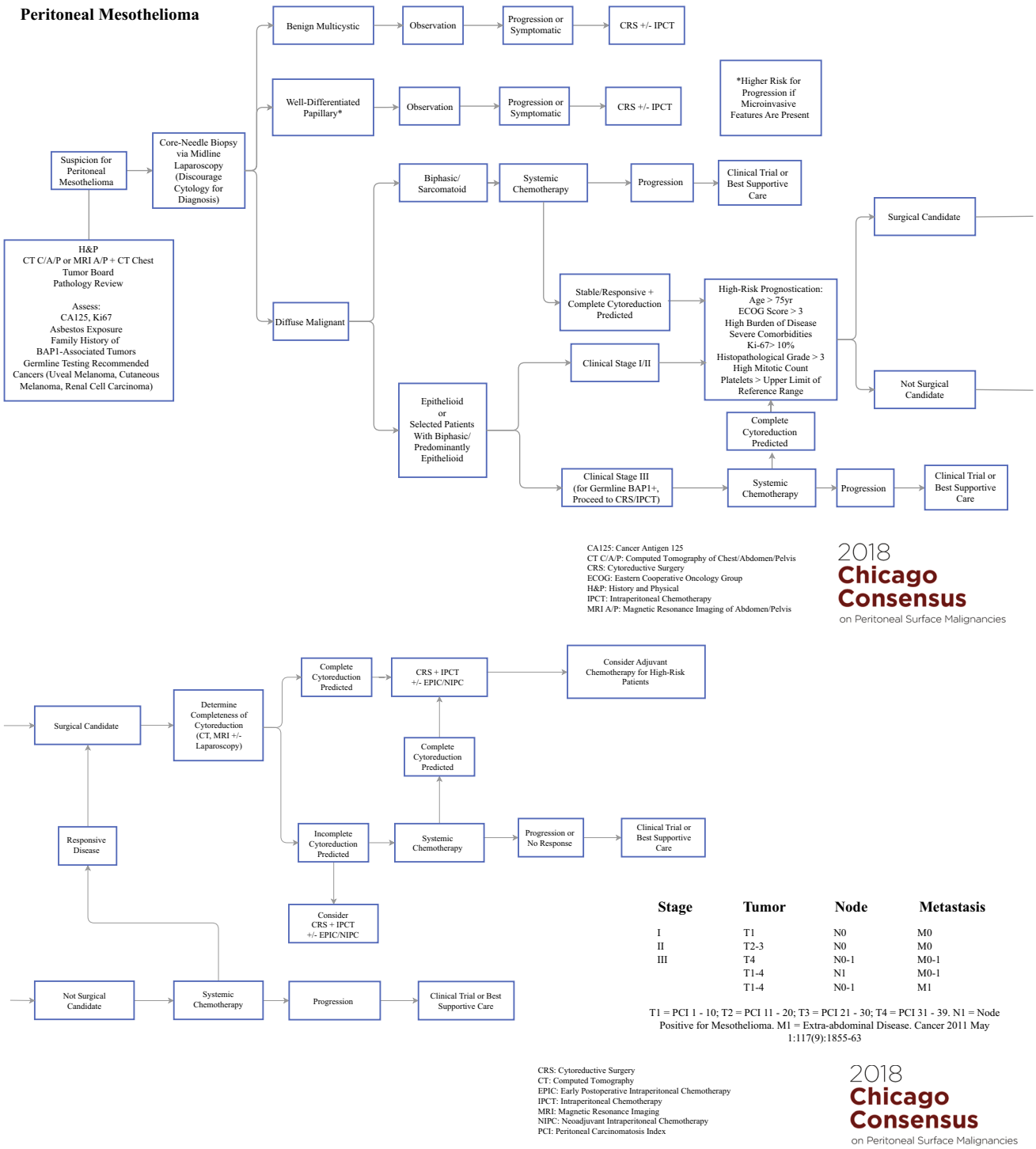

FIG. 1 Peritoneal mesothelioma management pathway

midline (to allow for resection of the biopsy tract during CRS) via image guidance or under direct visualization with laparoscopy or laparotomy. Pathological analysis of the biopsy sections is essential to distinguish the histologic variants and the architecture. Stromal invasion, dense cellularity, complex papillae, necrosis, and inflammation can distinguish mesothelioma from hyperplasia. Immunohistochemistry is essential to the diagnosis of this disease, and presence of calretinin, cytokeratin 5/6, WT1, and podoplanin are useful for diagnosis.[13,14] *BAP1* deletion is frequent in tissues but does not always indicate germline mutations.[12,15]

Principles of Surgery

In a multi-institutional series of 401 patients, patients undergoing complete cytoreduction (less than 2.5-mm visible residual disease) and those receiving hyperthermic intraperitoneal chemotherapy (HIPEC) had the most favorable survival. The burden of peritoneal disease as measured by the PCI was prognostic but was not an independent predictor of outcome. The median survival for the entire cohort was 53 months (range 1–235 months).[16] Complete cytoreduction frequently requires parietal peritonectomy, including visceral resections as necessary to achieve complete cytoreduction. Results of a small series suggested that total rather than selective parietal peritonectomy was associated with better survival, but this finding has not been validated.[17] The presence of bicavitary mesothelioma is a relative contraindication to surgery. In selected situations, bicavitary surgery with resection of the diaphragm and bicavitary chemoperfusion or staged approaches may be used.

Principles of Chemotherapy

Limited data on the activity of systemic chemotherapy in MPM are available. Most mesothelioma trials exclude these patients because of the rarity of MPM, the different natural histories of disease in the pleura and peritoneum, and the challenges of reproducibly measuring peritoneal disease and applying radiology criteria for response to treatment. Therefore, assumptions about the activity of specific agents for MPM are extrapolated from trials performed exclusively in patients with malignant pleural mesothelioma and from pharmaceutical expanded access programs. In the recently published American Society of Clinical Oncology practice guideline for pleural mesothelioma, the recommended first-line chemotherapy is pemetrexed plus a platinum (cisplatin or carboplatin); bevacizumab may be also offered to patients with no contraindication to its use. Because it is generally assumed that the efficacy of most systemic chemotherapy regimens is similar in both disease sites, these are also the recommended regimens for MPM.

The role of systemic chemotherapy in the neoadjuvant and adjuvant settings has not been fully examined. A retrospective multicenter study of 126 patients treated from 1991 to 2014 found an inferior 5-year survival for neoadjuvant compared with adjuvant chemotherapy (40% vs. 67%).[18] Selection bias is a confounder because patients with more aggressive or bulkier disease are more likely to receive systemic therapy before surgery. Treatment with contemporary pemetrexed-based adjuvant regimens also resulted in superior progression-free survival. In 2 small series, selected patients whose disease recurred after an original cytoreduction were able to undergo iterative cytoreduction, with similar morbidity and oncological outcomes.[19,20]

Principles of Intraperitoneal Chemotherapy

A systematic review including data on 1047 patients found that survival with intraperitoneal cisplatin administered during HIPEC (alone or in combination) was better than with mitomycin (49% vs. 30% expected 5-year survival).[21] In a small single-institution study, long-term intraperitoneal chemotherapy with normothermic intraperitoneal paclitaxel or pemetrexed with intravenous cisplatin in the adjuvant setting was associated with prolonged survival (75% 5-year survival, $P = .03$).[22] This treatment has been combined with a second look or cytoreduction with favorable results. Because these studies are all retrospective, firm conclusions regarding selection of chemotherapy agents for intraperitoneal administration cannot be made.

Intraperitoneal Dosing Regimens

- Cisplatin 50 mg/L + doxorubicin 15 mg/L of perfusate for 90 min (HIPEC)
- Cisplatin 50 mg/m^2 + doxorubicin 15 mg/m^2 for 90 min (HIPEC)
- Cisplatin 100–400 mg/m^2 for 90–110 min (HIPEC)
- Ifosfamide 1300 mg/m^2 intravenously + mesna 15 min prior to HIPEC, followed by paclitaxel 20 mg/m^2 (EPIC POD 1)
- Mitomycin 30 mg/m^2 for 90–110 min
- Mitomycin 30 mg at time 0, followed by mitomycin 10 mg beginning at 60 min and continuing for 90–110 min
- HIPEC with mitomycin 10 mg/m^2 or cisplatin 100 mg/m^2 for 60 min, followed by weekly infusions of cisplatin 100 mg/m^2 or cisplatin 50 mg/m^2 + gemcitabine 250 mg/m^2, alternating with fixed-dose doxorubicin 25 mg for 8 cycles
- Intraperitoneal port placement at the time of CRS and HIPEC, followed by intraperitoneal paclitaxel 20 mg/m^2 or intraperitoneal pemetrexed 1000 mg/m^2 at 6 weeks, repeated every 3 weeks for 6 cycles

Synoptic Pathology Report

Malignant mesothelioma: epithelioid, biphasic, or sarcomatoid; see parameters below

Mesothelioma-Specific Pathologic Parameters

Macroscopic:

- Specimen type:
  - Biopsy
  - Small excision
  - Major resection
- Tumor site: peritoneum, omentum
  - Peritoneum
  - Omentum
  - Organ site

Microscopic:

- Histologic type: __% solid, __% acinar, __% micropapillary (for epithelioid only), __% other (specify pattern)
- Nuclear grade (for epithelioid only): __ of III
- Nuclear atypia score: __ (1 for mild, 2 for moderate, 3 for severe)
- Mitotic count: __ [1 for low (1/10), 2 for intermediate (2–4/10), 3 for high (≥ 5/10)]
- Sum of atypia score and mitotic count: __ (2 or 3 = grade I, 4 or 5 = grade II, 6 = grade III)
- Necrosis (for epithelioid only):
  - Present
  - Absent
- Percent epithelioid: _____ (for biphasic only)
- Extent of invasion:
- Other findings: _____ (BAP1, PD-L1, etc.)
- Block(s) for molecular markers:

ACKNOWLEDGMENT **Collaborators**: **Darryl Schuitevoerder, MBBS**, University of Chicago, Department of Surgery, Chicago, IL; **Francisco J. Izquierdo, MD**, Clínica Santa María, Department of Surgery, Providencia, Chile; **Alejandro Plana, BA**, University of Chicago, Department of Surgery, Chicago, IL; **Garrett M. Nash, MD, MPH**, Memorial Sloan Kettering, Surgery, New York, NY; **Leopoldo J. Fernandez, MD**, Virginia Commonwealth University Massey Cancer Center, Hunter Holmes McGuire VAMC, Surgical Oncology, Richmond, VA; **Michael D. Kluger, MD, MPH**, Columbia University College of Physicians and Surgeons, Division of GI & Endocrine Surgery, New York, NY; **Lloyd A. Mack, MD, MSc**, University of Calgary, Departments of Surgery and Oncology, Calgary, AB, Canada; **Joshua M. V. Mammen, MD, PhD**, University of Kansas, Department of Surgery, Kansas City, KS; **Colette R. Pameijer, MD**, Penn State College of Medicine, Department of Surgery, Hershey, PA; **Patricio M. 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FUNDING The Irving Harris Foundation and the University of Chicago.

DISCLOSURES Garrett M. Nash reports non-financial support from Intuitive outside the submitted work. James C. Cusack reports grants from Lumicell Inc. outside the submitted work. Carla Harmath serves on the medical advisory council of Accumen. Hedy Kindler reports personal fees and non-financial support from Inventiva, AstraZeneca, Boehringer Ingelheim, Merck, and Paredox; personal fees from Aldeyra Therapeutics, Bayer, BMS, Erytech, Five Prime Therapeutics, Ipsen Pharmaceuticals, Kyowa, and MedImmune; and funds to support clinical trials at her institution from Aduro, AstraZeneca, Bayer, BMS, Deciphera, GSK, Lilly, Merck, MedImmune, Polaris, Verastem, and Blueprint, all outside the submitted work. Aytekin Oto reports grants from Philips Healthcare, Guerbet, and Profound Healthcare, and serves as a medical advisory board member for Profound Healthcare, all outside the submitted work. Nita Ahuja reports grant funding from Cepheid and Astex, has served as a consultant to Ethicon, and has licensed methylation biomarkers to Cepheid. Jesus Esquivel reports personal fees from Eight Medical. The remaining authors disclosed no conflicts of interest.

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