Genomics of Peritoneal Malignancies

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KEYWORDS

• Colorectal • Ovarian • Pancreatic • Microarray • Sequencing • Mutations
• Epigenetics • Genomics

KEY POINTS

- Inherited and somatic genetic mutations, epigenetic alterations, and other genomic aberrations contribute to peritoneal metastasis in select gastrointestinal, gynecologic, and orphan cancers.
- Classifications systems for disease subtypes based on genomic variants for colorectal, pancreatic, and epithelial ovarian cancers linked to peritoneal metastasis are highlighted.
- Genomic markers with associations to immunologic and cellular pathways important to cancer metastasis, and future significance to precision medicine, are emphasized.

GENOMICS OF GASTROINTESTINAL CANCERS AND PERITONEAL METASTASIS

Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer mortality in the United States and third globally.[1] Patient morbidity is due to metastases, which develop in up to 50% of patients.[1] The majority of metastatic CRC are initially responsive to chemotherapy; however, resistance develops rapidly, such that the median survival for metastatic CRC has plateaued at 23 to 27 months despite the development of multiple targeted therapies.[1] Prognosis for early stage disease with localized tumor have improved with 5-year survival reaching upwards of 70% and up to 90%.[1] However, approximately 10% metastasize only into peritoneal tissues, although peritoneal

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metastases can often be a late stage finding of disease along with multifocal metastases at other sites. Moreover, synchronous peritoneal carcinomatosis occur in 5% to 6% of colon cancers and 1% to 2% of rectal cancers.[2] These patients with isolated peritoneal metastases are treated with systemic chemotherapy but increasingly with extensive surgery termed cytoreductive surgery, along with intraoperative delivery of chemotherapy or hyperthermic intraperitoneal chemotherapy, a combined approach to chemotherapy administration applied at the site of tumor resection; the median survival with this procedure is 30 months with a 5-year survival of 26%.[2,3] (See Paul H. Sugarbakers' article, "Peritoneal Metastases, A Frontier for Progress," and Travis E. Grotz colleagues' article, "Patient Selection for Cytoreductive Surgery," in this issue.)

Somatic mutations in genes known as driver mutations are associated with peritoneal metastases and are also predicative markers for treatment and survival prognostics. With peritoneal dissemination, TP53 gene mutations are observed in 35% to 75% of cases as compared with primary adenocarcinomas, and are the most common mutations observed with peritoneal metastasis.[4,5] Mutations occurring in KRAS occur in approximately 40% to 50% of patients with CRC, and are also associated with metastases. Reports of KRAS mutations in primary tumors resulting in metastases has a correlation of 95%.[6,7] A third common driver mutation is BRAF, occurring in approximately 10% of patients as a missense mutation resulting in V600E and is associated with peritoneal disease and poor overall survival, in addition to propagation via the lymphatic system.[2] Detection of PIK3CA mutations occur in 15% of metastatic diseases, and within peritoneal carcinomatosis anti-epidermal growth factor receptor therapy combined with an oxaliplatin regimen (ie, FOLFOX) has resulted in some benefit, although PIK3CA status and therapy benefits from antiangiogenic and MAPK pathway inhibitors remain uncertain.[2,8]

Additional new biomarkers arising from next-generation sequencing technologies include epigenetic markers. Tumor suppressor genes are notably silenced through hypermethylation and hypomethylation at tandem repeat loci known as CpG islands, and modification at promoter regions typically results in gene silencing; several of these genes are correlated with metastasis, including peritoneal disease. Better screening for familial CRCs, through mutation or epigenetic silencing, of mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *STK11*, and *SMAD/DPC4*) and mutation of adenomatous polyposis coli[9–12] provide earlier disease detection capabilities and insight in metastatic potential. Typically, microsatellite instable cancers are more responsive to immune-therapies owing to mutational burden resulting in better antigenicity.[13] Other epigenetic marks are discussed in **Table 1**. Although microsatellite instable cancers account for less than 15% of CRCs, the prognostics for metastatic peritoneal disease remain better than microsatellite stable phenotypes.[1] Downstream transcriptional elements, including RNAs resulting from epigenetic modifications and driver gene mutations, has produced a new cohort of metastatic and recurrence-associated markers. Within these, changes in microRNA expression are associated specifically with peritoneal metastasis, such as miR-139-5p, others are linked to metastasis in additional sites, including miR-121.[25–27] The role of these and other macromolecular and micromolecular genetic elements are nascent, and our knowledge of their role in cancer is developing with several promising studies revealing prognostic markers and targets for future therapy.

Appendiceal Cancer

Distinct from CRC, appendiceal malignancies are rare, accounting for approximately 0.4% of gastrointestinal tumors.[28] Patients most commonly present with right lower quadrant pain and acute appendicitis, with tumors found incidentally on pathologic