



# The Institute for Cancer Care at Mercy Medical Center

25 Years of Experience Treating Peritoneal Surface Malignancies



**Expanding Access to Care.**  
**Advancing Research.**  
**Building Alliances.**  
**Saving Lives.**

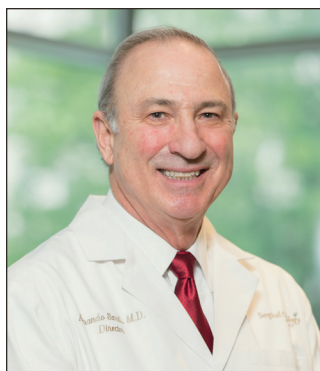
Peritoneal carcinomatosis is a common presentation in gastrointestinal and gynecologic malignancies with limited treatment options. Many patients are offered palliative therapies, but long-term survival and quality of life can be achieved with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). The Institute for Cancer Care at Mercy Medical Center in Baltimore, Maryland is a leading peritoneal surface malignancy center, specializing in the CRS/HIPEC procedure. Since 1994, Armando Sardi, M.D., FACS, Medical Director, The Institute for Cancer Care at Mercy and Chief, Division of Surgical Oncology, and his colleagues, Vadim Gushchin, M.D., FACS, and Kurtis Campbell, M.D., FACS, have performed more than 800 successful CRS/HIPEC procedures. Our multidisciplinary team is devoted to medical excellence, research, patient advocacy, and advancing the treatment of peritoneal surface malignancies.

**P**eritoneal surface malignancies present oncology clinicians with unique challenges and limited treatment options. However, long-term outcomes can be achieved with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). The peritoneal surface malignancy program at Mercy Medical Center is proud to be an internationally recognized center in the treatment of peritoneal carcinomatosis with CRS/HIPEC. This multidisciplinary team is dedicated to advancing breakthrough treatments for cancer management, while keeping hope alive through every stage of treatment, recovery and survivorship. The patient-centered approach is mastered through the combined knowledge and expertise of select surgical, gynecological, medical and radiation oncologists, radiologists, pathologists, primary care physicians, physician assistants, specialized nurses and nurse navigators, registered dietitians, geneticists and other cancer specialists.

**On the cover:** Drs. Vadim Gushchin, surgical oncologist, Teresa Diaz-Montes, gynecologic oncologist and principal investigator, Armando Sardi, surgical oncologist and principal investigator, and Hyung Ryu, gynecologic oncologist, are the first in the United States to explore the application of HIPEC in the initial management of ovarian, fallopian tube and primary peritoneal cancers.

Not pictured: Kurtis Campbell, M.D.

## Message from the Director



**Armando Sardi, M.D., FACS**  
**Director, The Institute for Cancer Care at Mercy**  
**Chief, Division of Surgical Oncology**

Peritoneal carcinomatosis, a complex condition characterized by the spread of gastrointestinal and gynecologic cancers to the peritoneum, is associated with significant mortality. It can arise from tumors of any organ, but frequently from the appendix, colon, ovary, stomach, and uterus, as well as mesothelioma and sarcoma. Once these tumors metastasize to the peritoneum, management is challenging because the disease is widespread, it also may involve multiple solid organs, and has limited response to systemic treatments. The majority of patients are offered palliative therapies; however, long-term survival and quality of life can be achieved with the combination of extensive cytoreductive surgery to remove all visible tumors immediately followed by intraoperative hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).

Today, surgery remains the primary treatment for most solid tumors. This also is true for peritoneal carcinomatosis. CRS/HIPEC is the standard of care for appendiceal cancer and peritoneal mesothelioma and is an effective option for advanced gastrointestinal and gynecological malignancies. Since our program began in 1994, there has been tremendous growth in the application and number of surgeons performing CRS/HIPEC.

The success of this approach is significant with data showing 10- and even 20-year survival. Although most patients are referred for HIPEC in a delayed fashion, typically after multiple failed treatments, the results obtained by this approach show a benefit unmatched by any other treatment

modality available today. This is especially true for patients with advanced, stage III-IV cancers. While the use of systemic chemotherapy is beneficial for many, patients with peritoneal spread of these malignancies treated with systemic chemotherapy alone have poor survival, usually only a few months.

As of August 2019, our peritoneal surface malignancy center has performed more than 800 successful CRS/HIPEC procedures of which the majority of patients are alive (63%) and disease-free (46%). This is remarkable, as most patients have stage IV disease and already failed the standard of care surgery with or without chemotherapy (Table I). In order to obtain these results, the importance of a multidisciplinary team cannot be over emphasized. These patients need tremendous support following HIPEC, as well as diligent follow-up every six months to obtain the results presented.

Despite these promising results and over 3,000 publications worldwide on CRS/HIPEC, most patients are still referred late. Unfortunately, most patients discover CRS/HIPEC from social media, such as Google and Facebook. This publication illustrates the results and challenges in treating patients with each primary tumor type and clarifies any misunderstanding on the benefit and outcomes of CRS/HIPEC. We also hope it provides patient advocacy so that early referrals are made by healthcare professionals to experienced CRS/HIPEC centers.

**Table I: HIPEC Survival by Diagnosis**

Primary	5-year OS	5-year PFS	Alive	Disease Free	Longest Survival (years)
Appendiceal	65%	56%	65%	57%	20.9
Ovarian/FT/PPC	50%	31%	59%	41%	20.7
Colorectal	23%	8%	40%	25%	7.9
Mesothelioma	57%	56%	46%	31%	12.3
Gastric	10%	13%	9%	9%	7.9
Uterine Sarcoma	45%	38%	50%	43%	14.3
Endometrial	67%	25%	60%	40%	7.1

OS: Overall Survival; PFS: Progression-Free Survival; FT: Fallopian Tube; PPC: Primary Peritoneal Carcinoma



# Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy

Peritoneal carcinomatosis is a condition characterized by the diffuse spread of cancer throughout the abdominal cavity. It includes extensive peritoneal surface involvement and may or may not involve solid organs, such as the liver, spleen and lymph nodes. This condition can be caused by tumors of the appendix, colon, rectum, small bowel, ovary, fallopian tube, endometrium and stomach, as well as from primary peritoneal tumors, sarcomas, and mesothelioma, and rarely from other tumors such as breast and prostate. Commonly thought to be incurable, advanced cancers with peritoneal spread typically have limited treatment options and result in high mortality rates. However, there are encouraging results with an aggressive therapeutic surgical technique of cytoreductive surgery (CRS) with hyperthermic

intraperitoneal chemotherapy (HIPEC).

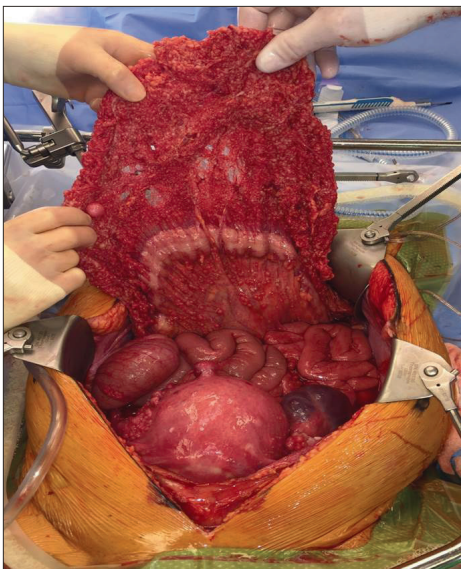
Cytoreduction refers to the removal of all visible tumors from the abdominal cavity, often including colectomy, splenectomy, liver resection(s), as well as peritonectomies from the pelvis to the diaphragm, depending on the extent of tumor involvement (Figure 1). A complete cytoreduction, defined as no visible tumor or residual tumor nodules <2.5 mm, is associated with longer survival. Cytoreductive surgery aims to remove all visible disease; however, there is likely microscopic disease left behind. In order to eradicate these microscopic cells, CRS is immediately followed by intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC). The chemotherapy agent is heated to a temperature of 43 Centigrade and perfused directly into

the abdominal cavity, circulating for 90 minutes, allowing direct contact of the chemotherapy to all peritoneal surfaces (Figure 2). The high temperatures potentiate the efficacy of the chemotherapy agents, while the intraoperative peritoneal perfusion enhances the regional effect of the chemotherapy.

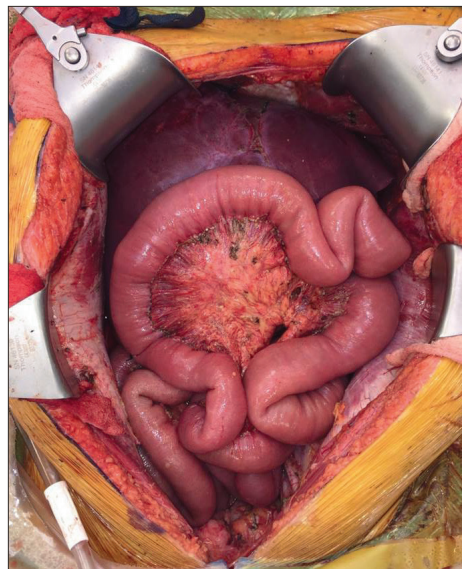
To achieve oncological success, strict selection criteria, including age, performance status, prior surgeries or other therapies, extent of disease, and quality of life, must be followed. Evidence of resectable, intraperitoneal disease should be seen on imaging and ultimately deemed resectable by the surgical team. Important tools to determine CRS/HIPEC eligibility include clinical examination, radiographic imaging, and serum tumor markers (CA-125, CEA, and CA-19-9). Since radiographic imaging does not always capture the full extent of peritoneal disease, diagnostic laparoscopy can help determine the probability of a complete cytoreduction without an extensive surgical procedure.

CRS/HIPEC requires extensive surgery and complications can occur; however, when closely monitored, these can be managed appropriately with an acceptable rate of grade III/IV complications. Pulmonary and gastrointestinal complications can be associated with disease burden and degree of surgical resection required to achieve a complete cytoreduction. Gastrointestinal complications are similar to those seen in other large surgeries involving bowel resection(s) including fistula and anastomotic leak.

**Figure 1: Cytoreductive Surgery**



Peritoneal dissemination of uterine sarcoma



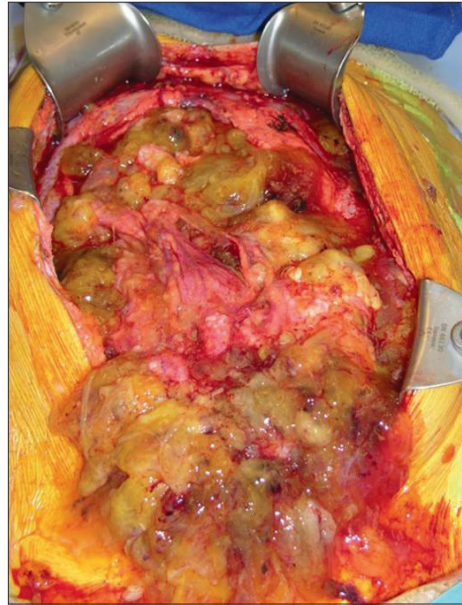
Peritoneal cavity post-cytoreductive surgery

## Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy continued

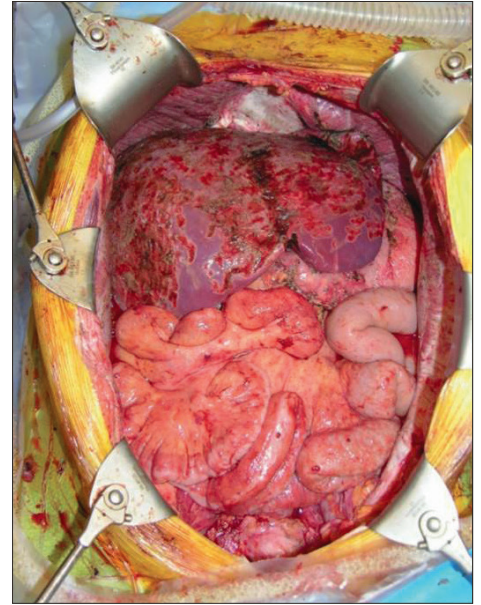
We have been able to perform CRS/ HIPEC safely with <3% anastomotic leak rate.

Overall, peritoneal carcinomatosis is often associated with disease progression and poor prognosis and has traditionally been treated with palliative intent. However, CRS/HIPEC with or without systemic chemotherapy has proven considerably more valuable than traditional surgery or systemic chemotherapy alone and could extend or improve the lives of many patients who would otherwise have no options to effectively treat their advanced cancer.

**Figure 1: Cytoreductive Surgery** continued

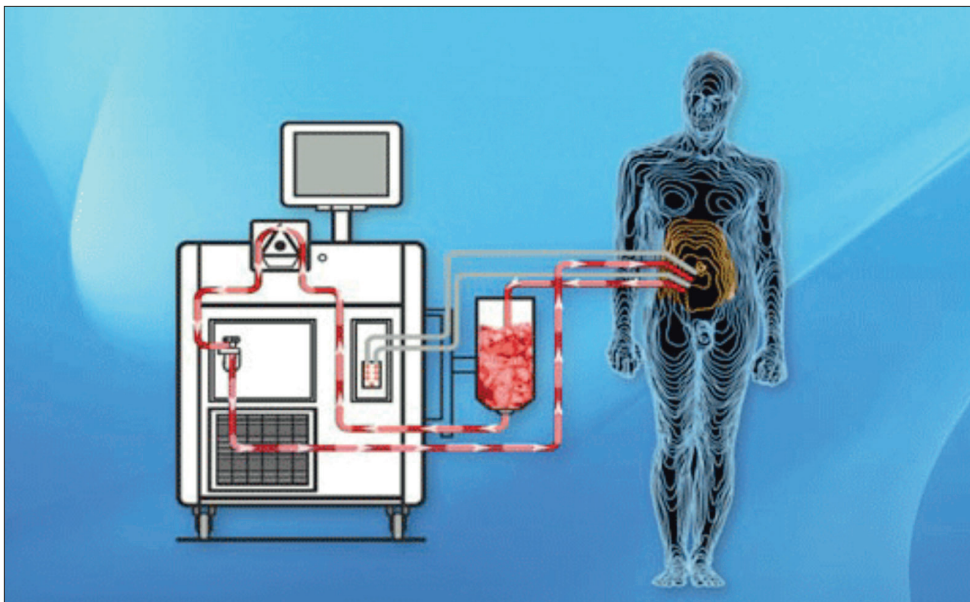


Peritoneal dissemination of mucinous appendiceal cancer



Peritoneal cavity post-cytoreductive surgery

**Figure 2: Hyperthermic Intraperitoneal Chemotherapy (HIPEC)**



HIPEC refers to the perfusion of a heated chemotherapy agent directly into the peritoneal cavity. Inflow and outflow catheters are placed and the abdomen is shaken in order to ensure contact of the chemotherapy to all peritoneal surfaces. It is performed intraoperatively after cytoreductive surgery with the intent to eradicate any residual microscopic disease.

(Diagram courtesy of ThermaSolutions, Inc.)

# Peritoneal Surface Malignancy Center of Excellence

The 2018 Chicago Consensus Guidelines for Peritoneal Surface Malignancies defines specific criteria for the management of these complex diagnoses that commonly lack strong national guidelines. Here are a few examples of how Mercy Medical Center measures up:

Criteria	Chicago Consensus Standards	Mercy Medical Center
Number of CRS/HIPEC cases per year	At least 12 per surgeon	-Average over 70 CRS/HIPEC procedures annually -93 performed in 2018
CC-0/1 Rate	>60%	89%
Ostomy Rate	<25%	-11% with end ileostomy/colostomy - 4% with anastomosis and protective ileostomy
Average Length of Stay	<14 days	10 days
Average ICU Length of Stay	<48 hours	24 hours
Major Complications Rate	<40%	13.5% Clavien-Dindo grade $\geq$ III B
Readmission Rate	<33%	27%
30-day Mortality	<5%	1% (n=8) 30-day Mortality 1.6% (n=13) 60-day Mortality 2.3% (n=21) 90-day Mortality

## WHO SHOULD I REFER?

Conditions We Treat:	Who to Refer?
<ul style="list-style-type: none"> <li>• Appendiceal Cancer</li> <li>• Colon Cancer</li> <li>• Endometrial Cancer</li> <li>• Fallopian Tube Cancer</li> <li>• Gastric Cancer</li> <li>• Mesothelial Cysts</li> <li>• Ovarian Cancer</li> <li>• Peritoneal Mesothelioma</li> <li>• Peritoneal Sarcomatosis</li> <li>• Primary Peritoneal Cancer</li> <li>• Pseudomyxoma Peritonei</li> <li>• Small Bowel</li> <li>• Uterine Sarcoma</li> <li>• Other Rare Cancers (Neuroendocrine tumors, gallbladder cancer, prostate cancer, breast cancer, cervical cancer)</li> </ul>	<ul style="list-style-type: none"> <li>• Cancers with Intraperitoneal Metastases</li> <li>• Perforated Abdominal Cancers</li> <li>• Abdominal Cancers with Positive Intraperitoneal Cytology</li> <li>• Peritoneal Seeding of Invasive Cancer</li> <li>• Large Volume of Peritoneal Carcinomatosis or Sarcomatosis</li> <li>• No Known Distant Extra-peritoneal Metastases (i.e. Bone, Pulmonary)</li> <li>• Advanced Staged Gynecologic Cancers</li> <li>• Gynecologic cancers with/without pleural effusions who responded to neoadjuvant chemotherapy</li> </ul>

At Mercy, we pride ourselves on coordinating care with multiple physicians from around the country so our patients can continue to follow up with their local primary care physician and medical oncologist.



## Appendix Cancer

Appendiceal cancer is a rare malignancy usually diagnosed incidentally in 1% of appendectomies for acute appendicitis, especially in middle adulthood patients.<sup>1</sup> This rare tumor frequently presents with peritoneal dissemination due to vague symptoms. Healthcare professionals' lack of awareness of successful treatment options for intraperitoneal disease adds to the delay in referral for CRS/HIPEC for these patients. At this advanced stage, peritoneal dissemination of appendiceal cancer is associated with rapid progression and poor prognosis, with 10-year overall survival of approximately 35%.<sup>2</sup>

It is a common source of confusion when an incidental finding of an appendiceal malignancy presents on a pathology report, which could show a wide range of neoplasms, including mucinous adenocarcinomas, non-mucinous adenocarcinomas, goblet cell carcinomas and neuroendocrine carcinomas. Mucinous adenocarcinomas represent more than half of cases and include three subtypes: low-grade mucinous carcinoma peritonei (LGMCP), high-grade mucinous carcinoma peritonei (HGMCP), and high-grade mucinous carcinoma peritonei with signet ring cells (HGMCP-S), which has the worst prognosis.<sup>3</sup> These neoplasms are molecularly, histopathologically, and clinically distinct from colorectal cancer. Although outcomes depend on the histopathology and quality of cytoreduction, CRS/HIPEC has proven to be the most effective treatment and is the current standard of care for all subtypes.

When CRS/HIPEC fails, there are few treatment options. Although there are no set recommendations or prospective data, oncologists commonly offer 5FU-based systemic chemotherapy in settings of high-grade, lymph node positive, residual, or un-resectable disease according to colorectal cancer regimens, despite their clear molecular and histopathologic differences.<sup>4</sup> Our recent retrospective study confirmed that the use of preoperative systemic chemotherapy did not decrease disease burden, improve the complete cytoreduction rate, or improve progression-free or overall survival in patients with peritoneal dissemination from high-grade appendiceal cancer.<sup>5</sup> Therefore, additional therapies are needed and CRS/HIPEC should be the treatment of choice for resectable patients.

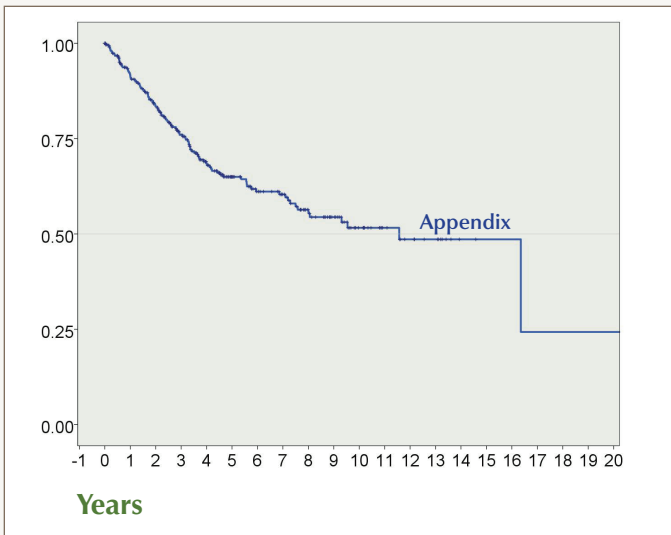
For more than two decades, we have treated more than 400 patients with appendiceal peritoneal carcinomatosis and are committed to achieving complete cytoreduction (residual tumor <0.25cm), which is the paramount factor associated with superior clinical outcomes and survival.<sup>6</sup> We have an 88% complete cytoreduction rate (CC-0/1), even with extensive gross peritoneal disease or poor histology. Long-term outcomes demonstrate an overall survival at 3-, 5-, 10- and 20-years of 76%, 65%, 52%, and 24%, respectively, and a median overall survival of 12 years (*Figure 3*). Even in the most aggressive histopathologic subtype, HGMCP-S, a 5-year survival of 25% can be achieved with CRS/HIPEC at our center.<sup>7</sup>

Summary:

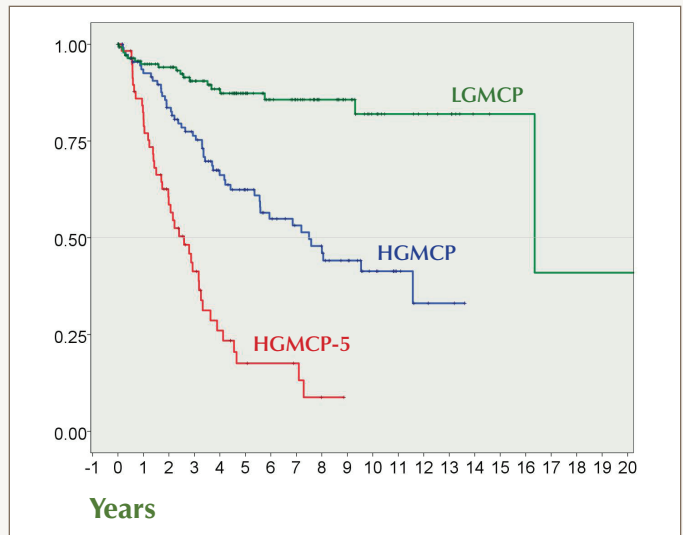
1. Incidental appendix tumors are a common source of confusion and uncertainty. Referral to peritoneal surface malignancy center is key for proper treatment.
2. CRS/HIPEC is the treatment of choice for peritoneal dissemination appendiceal neoplasms. Achieving a complete cytoreduction is paramount for good outcomes.
3. Patient outcomes are most significantly impacted by histopathologic subtype, with the best outcomes achieved with LGMCP and the worst outcomes in HGMCP with signet ring cells.
4. Appendiceal cancers do not seem to have a significant response to colorectal-type systemic chemotherapies. Thus, there is a need for additional targeted therapies when CRS/HIPEC fails.
5. At an experienced center, a median overall survival of 12 years can be achieved even with extensive peritoneal disease or poor histology.

**Figure 3: Overall survival in patients with appendiceal peritoneal carcinomatosis and by histopathic subtype treated with CRS/HIPEC at Mercy**

**Overall Survival**



**Overall Survival by Histopathology**



	3-y	5-y	10-y	20-y	mOS (y)
Appendix cancer	76%	65%	52%	24%	11.5

	3-y	5-y	10-y	20-y	mOS (y)
LGMCP (146)	91%	87%	82%	41%	16
LGMCP (146)	91%	87%	82%	41%	16
HGMCP-5 (39)	41%	18%	-	-	2.6

HGMCP: high-grade mucinous carcinoma peritonei. HGMCP-S: high-grade mucinous carcinoma peritonei with signet ring cells.

LGMCP: low-grade mucinous carcinoma peritonei. mOS: median overall survival, y: years



## Colorectal Cancer

Colorectal cancer (CRC) is the 3rd most common cancer in men and women worldwide accounting for 9.7% of all cancers with 135,430 projected new cases in the United States.<sup>8</sup> The peritoneum is the second most common metastatic site, after the liver, occurring in 13-17% of patients.<sup>9,10</sup> It can occur at the time of initial presentation (synchronous, 35-57%) or as recurrent disease (metachronous, 43-56%).<sup>11-13</sup> With an increase in diagnostic laparoscopies, physicians may encounter peritoneal spread that did not appear on imaging and determining the best course of treatment is challenging. Patients with CRC peritoneal carcinomatosis have poor prognosis and are often considered to have terminal disease with median survival of 6 months if untreated and 5-year survival <5% with systemic chemotherapy alone.<sup>13-15</sup> The majority of these patients are recommended systemic chemotherapy, palliative surgery for symptom relief, and/or bowel stenting;<sup>16</sup> however, CRS/HIPEC can improve survival in select patients.

Currently, there is conflicting evidence on the efficacy of HIPEC. Some studies have found improved survival outcomes with CRS/HIPEC compared to CRS and/or systemic chemotherapy alone. A Dutch randomized trial reported a median survival of 12.6 months in the standard therapy arm (fluorouracil-leucovorin +/- palliative surgery) vs 22.3 months in the experimental therapy arm (CRS/HIPEC followed by fluorouracil-leucovorin systemic chemotherapy).<sup>17</sup> Other studies reported a median overall survival of over 30 months and up to 48 months when a complete

cytoreduction is achieved.<sup>18-23</sup> On the other hand, initial results from the recent PRODIGE 7 trial showed no significant differences in survival (median OS: 41.2 months in non-HIPEC vs 41.7 months in HIPEC group). However, both arms achieved long-term survival, which underscores the benefit of cytoreduction in metastatic CRC. In addition, patients with intermediate disease burden (PCI 11-15) showed significant improvement in OS with CRS/HIPEC (median OS: 32.7 months in non-HIPEC vs 41.6 months in HIPEC group,  $p=0.02$ ). While these preliminary results and protocol are highly debated and the full results have not been released or subject to peer review, it is clear that quality surgery and strict patient selection are vital to achieve the biggest survival benefit.

NCCN guidelines only recommend CRS/HIPEC at experienced centers for cases in which a complete resection can be achieved. Additionally, in 2014, the *American Society of Peritoneal Surface Malignancies* published guidelines to standardize the delivery of HIPEC in CRC.<sup>24</sup> When these recommendations are followed, improved survival of over 3 years can be achieved in patients with metastatic CRC.

We have performed more than 90 successful CRS/HIPEC procedures for CRC peritoneal carcinomatosis since 1999. Achieving a complete cytoreduction is the most important prognostic factor, with the best results seen with no residual disease (CC-0). We have a 91% complete cytoreduction rate (CC-0/1) and median overall survival of 3 years. Patients with CC-0

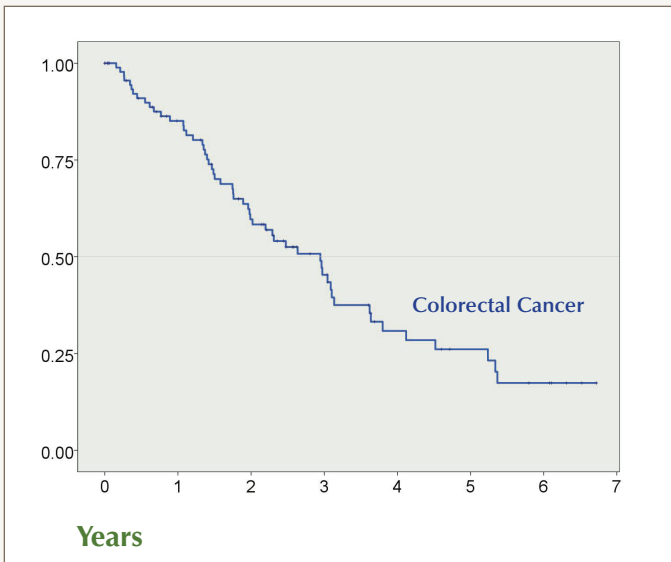
cytoreductions have significantly improved overall survival compared to patients with macroscopic residual disease with median overall survival of 3.1 vs 1.5 years, respectively ( $p=0.043$ ) (Figure 4). In addition, despite an average surgery length of over 9 hours, the median hospital stay is 10 days with no 30-day postoperative mortality and few ( $n=3$ ) grade IV complications that required reoperation.

### Summary:

1. CRS/HIPEC may be a treatment option for peritoneal spread of colorectal cancer.
2. However, patient selection is key and CRS/HIPEC should only be performed when a complete cytoreduction is feasible. Patient evaluation should include imaging studies, colonoscopy, diagnostic laparoscopy, and serum and molecular markers to determine whether chemotherapy is necessary prior to CRS/HIPEC.
3. CRS/HIPEC should only be performed at a specialized center by an experienced surgeon.
4. CRS/HIPEC can achieve a median overall survival of over 30 months in select patients.

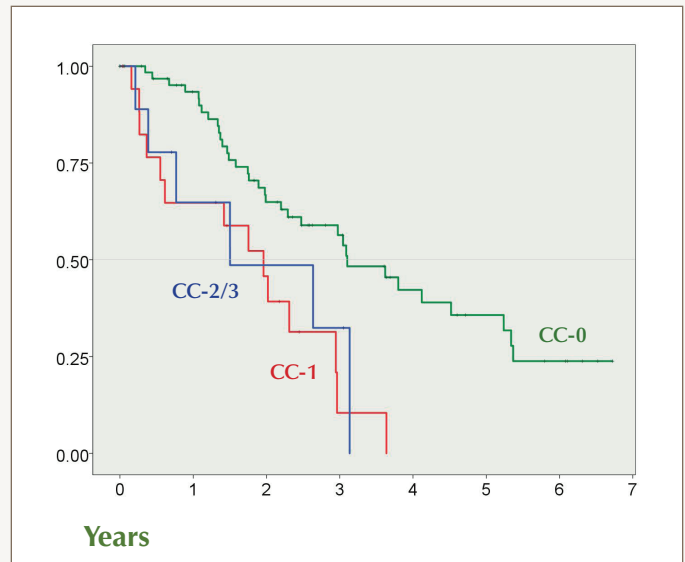
**Figure 4: Overall survival after CRS/HIPEC at Mercy for colorectal and by quality of cytoreduction**

**Overall Survival**



	1-y	3-y	5-y	mOS (y)
Colorectal cancer	85%	45%	26%	3

**Overall Survival by Cytoreduction**



	1-y	3-y	5-y	mOS (y)
CC 0 (n=67)	93%	56%	36%	3.1
CC 1 (n=18)	65%	11%	-	2
CC 2-3 (n=9)	65%	32%	-	1.5

CC: completeness of cytoreductive score; CRS/HIPEC: cytoreductive surgery and hyperthermic intraperitoneal chemotherapy;

mOS: median overall survival; y: years

# Ovarian Cancer

Epithelial ovarian cancer (EOC), a common worldwide malignancy, has estimated 22,530 new cases in the United States resulting in 13,980 deaths annually.<sup>25</sup> Epithelial malignancies arising from the ovary(-ies), fallopian tube(s), or peritoneum are grouped as one entity, known as epithelial ovarian cancer, due to the similarity of symptoms, prognosis, and treatments. Since there are no screening tests, the majority of women are diagnosed at advanced stages (FIGO III/IV) with symptoms related to pleural effusion, bowel obstruction, and venous thromboembolism. In these advanced stages, survival remains bleak with a 5-year survival of 29% according to NIH SEER data.<sup>26</sup>

Initial management includes optimal surgical cytoreduction and platinum-taxane combination systemic chemotherapy. With high recurrence rates, most patients will require additional surgery and multiple chemotherapy regimens.<sup>27</sup> In recent decades, new treatment approaches have been studied with CRS/HIPEC emerging as a promising loco-regional treatment that can benefit patients with longer recurrence-free and overall survival without increased toxicity compared to surgery alone. *The New England Journal of Medicine* recently published results from a randomized clinical trial comparing patients with newly diagnosed stage III EOC treated with neoadjuvant chemotherapy, interval debulking surgery with or without HIPEC, followed by adjuvant chemotherapy and found improved

survival in the HIPEC group (median overall survival: 33.9 vs 45.7 months).<sup>28</sup> These positive results served as the basis for adding HIPEC to interval debulking surgery in the NCCN guidelines.

We have performed over 150 CRS/HIPECs for advanced primary and recurrent EOC and have seen encouraging results. In newly diagnosed patients treated with upfront CRS/HIPEC, overall survival at 3 and 5 years is 68% and 55% with a median survival of 5.7 years. Similar overall survival outcomes are seen in patients with recurrent disease at 57% and 54% when CRS/HIPEC was used as a salvage procedure, yielding a median survival of 5.8 years. Additionally, patients who initially present with unresectable disease or poor performance status are offered neoadjuvant systemic chemotherapy (3 cycles) followed by CRS/HIPEC. These patients have an overall survival at 1 and 3 years of 97% and 38% with a median survival of 2.2 years. (Figure 5)

While the role HIPEC in EOC treatment is still being investigated, it is well established that survival is inversely related to the extent of residual disease after initial surgery. Complete cytoreduction status is the most important predictor of long-term outcomes in advanced EOC and should be considered the paramount goal when treating advanced EOC. However, multiple results from the United States and abroad showed that only 25-50% of patients receive adequate cytoreductions. Surgery by both a surgical oncologist,

who adheres to stricter cytoreduction standards and is experienced in the upper abdomen, and a gynecologic oncologist, who is experienced in the pelvis, may offer the best chance at achieving a complete cytoreduction.<sup>29,30</sup>

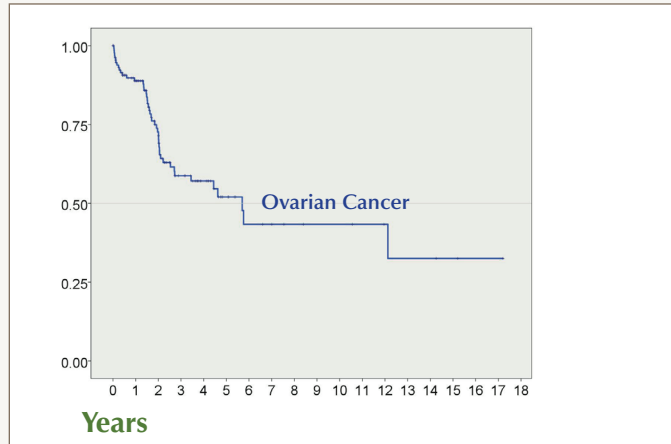
To continue advancing treatment for this deadly disease, in 2014, principal investigators, Armando Sardi, M.D. and Teresa Diaz-Montes, M.D., MPH, opened the study entitled, “*A phase II randomized study: Outcomes after cytoreductive surgery (CRS) with or without carboplatin hyperthermic intraperitoneal chemotherapy (HIPEC) followed by systemic chemotherapy with carboplatin and paclitaxel as initial treatment of ovarian, fallopian tube, and primary peritoneal cancer*” (NCT02124421), which is the only randomized clinical trial to evaluate the role of HIPEC as upfront treatment in the United States. Through our gynecologic and surgical oncology collaborative, we aim to offer women the best surgical treatment according to stricter surgical oncology standards in order to enhance disease free intervals and improve survival. Furthermore, at our center, the use of neoadjuvant systemic chemotherapy before CRS/HIPEC is considered exclusively when a complete cytoreduction is not feasible or patients are not candidates for lengthy surgeries due to comorbidities or performance status.

**Figure 5: Overall Survival of Patients with Epithelial Cancer after CRS/HIPEC**

Summary:

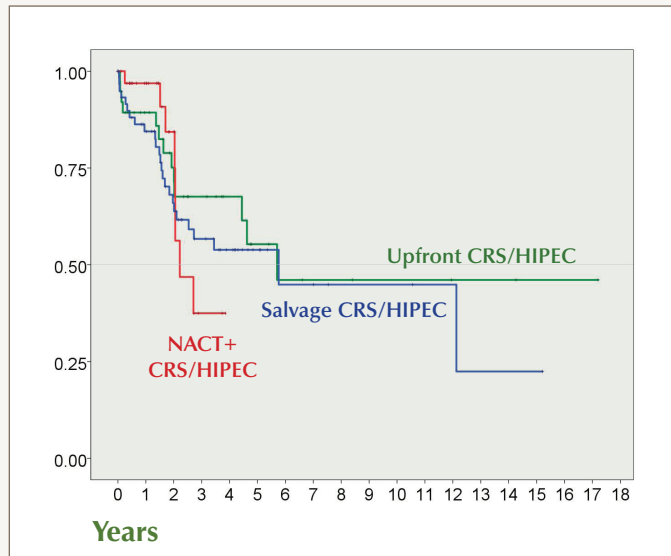
1. Quality of cytoreduction is an important prognostic factor for overall and progression-free survival. CRS performed at an experienced center and by both a gynecologic oncologist and surgical oncologist may offer the best surgical treatment based on the highest standards and improve patient outcomes.
2. CRS/HIPEC was recently investigated after neoadjuvant chemotherapy (NACT) for EOC and is currently being studied as upfront therapy and for recurrence.
3. HIPEC was recently added to the NCCN guidelines as an option at the time of interval debulking surgery after NACT because of emerging prospective data showing improved progression-free and overall survival.
4. In our clinical trial of CRS/HIPEC as upfront therapy, the overall survival at 3- and 5-years is 68% and 55%, respectively. Similarly, in recurrent disease, the 3- and 5-year overall survival is 57% and 54%, respectively.
5. Patients who receive NACT have shorter OS and PFS, which could be due to the nature of the disease, creation of resistant cells, or residual microscopic cells at surgery. Thus, NACT should be reserved only for patients who are not surgical candidates at the time of diagnosis.

**Overall Survival**



	1-y	3-y	5-y	10-y	mOS (y)
Ovarian cancer (N=136)	89%	59%	52%	43%	5.7

**Overall Survival Type of Treatment**



CRS/HIPEC	1-y	3-y	5-y	10-y	mOS (y)
Upfront (38)	89%	68%	55%	46%	5.7
Salvage (62)	84%	57%	54%	45%	5.8
After NACT (36%)	97%	38%	-	-	2.2

CRS/HIPEC: cytoreductive surgery/hyperthermic intraperitoneal chemotherapy; mOS: median overall survival; NACT: neoadjuvant chemotherapy; y: years

## Peritoneal Mesothelioma

Malignant mesothelioma is a rare and aggressive tumor of the mesothelial lining including the pleura, peritoneum, and pericardium.<sup>31</sup> While pleural mesothelioma is more common and better studied, approximately 10% of all mesotheliomas are peritoneal.<sup>32</sup> Both forms of the disease are linked to asbestos exposure, although the association is less clear for peritoneal mesothelioma.<sup>32</sup> With a projected increase in incidence over the next several decades, more patients will require care and recommending the optimal treatment plan is essential.<sup>31,33</sup>

Treatment options for peritoneal mesothelioma remain limited and include surgical resection for select patients, palliative chemotherapy, and/or radiation. Previously, peritoneal mesothelioma was largely treated with systemic chemotherapy, surgical debulking, and whole-abdomen radiation. However, this was associated with significant morbidity and median overall survival between 6-12 months, similar to no treatment at all. CRS/HIPEC has been increasingly used as a surgical treatment modality and is the standard of care for peritoneal mesothelioma, producing a median survival of over 60 months.<sup>31,33</sup>

At Mercy, the 1-, 3-, 5-, and 10-year overall survival for peritoneal mesothelioma patients is 87%, 66%, 58%, and 44%, respectively. The median overall survival is 69 months (5.7 years), which improves to 124.3 (10.3 years) with a complete cytoreduction (CC-0/1). We are dedicated to achieving the best

outcomes for our patients and have a complete cytoreduction rate of 77% in peritoneal mesothelioma.

Despite this improvement in modern management, much is still not understood about this rare condition, including its link to environmental exposures and mutational landscape. In collaboration with INOVA, we recently analyzed the genome of peritoneal mesothelioma samples using next-generation sequencing. The most frequent mutations were in BAP1 and other genes involved in DNA repair. This is an important, necessary first step to better understand the disease biology and to develop novel targeted treatments.

Summary:

1. CRS/HIPEC is the treatment of choice for peritoneal mesothelioma.
2. Patients with or with suspected peritoneal mesothelioma should be referred to an experienced peritoneal surface malignancy center for CRS/HIPEC evaluation.
3. With CRS/HIPEC, a median survival of up to 60 months can be achieved.

## Gastric Cancer

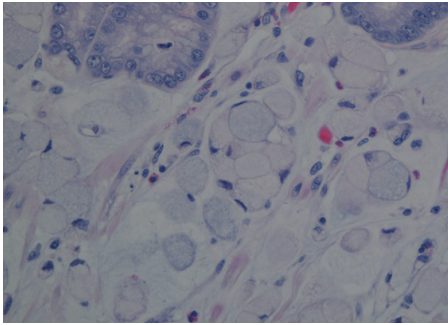
Although the incidence of gastric cancer is declining in the United States, the mortality rate remains high. According to the NCI, only 10-20% of patients are diagnosed at an early stage, leaving the majority with either regional or peritoneal metastases.<sup>34,35</sup> This is largely because early staged gastric cancers are usually asymptomatic and over 40% present with peritoneal spread.<sup>36</sup> Once gastric cancer has metastasized to the peritoneum, median overall survival drops to 3 months.<sup>37</sup> Treatment options are typically palliative, relying on systemic chemotherapy with limited efficacy. However, in the search for better treatment options, the role of surgery is expanding. In select patients with limited or localized peritoneal disease, recent data supports CRS/HIPEC as an option in combination with other therapies.

At the 2018 Gastrointestinal Cancers Symposium, a French study explored the potential role of CRS alone vs CRS/HIPEC in gastric cancer with peritoneal carcinomatosis and presented results on 277 patients. CRS/HIPEC was associated with improved overall survival and progression free survival compared to CRS alone (median OS: 18.8 vs 12.1 months).<sup>38</sup> This is a significant improvement from palliative systemic chemotherapy alone where median survival is approximately 6 months.<sup>39,40</sup>

We have performed 11 successful CRS/HIPEC procedures for gastric cancer since 2003 with an 82% complete cytoreduction (CC-0/1) rate. The 1-year progression-free survival is 50%. Median overall survival is 14 months, which



## Rare Cases of Peritoneal Carcinomatosis



Gastric Cancer Cells

improves to 18 months with a complete cytoreduction. These results are similar to that of the best available trials.

However, it is clear that patient selection is key, especially with regard to disease burden. Diagnostic laparoscopies to evaluate the spread of disease are essential and an experienced, multidisciplinary approach remains vital in the management of this aggressive malignancy. Working concomitantly with medical oncology is important as neoadjuvant chemotherapy is usually recommended.

### Summary:

1. CRS/HIPEC is an option for patients with gastric cancer.
2. Complete cytoreduction and low disease burden are essential to obtain good outcomes.
3. Patients with extensive peritoneal disease will have a poor survival even with HIPEC.

While peritoneal carcinomatosis most commonly arises from the appendix, colon, stomach, ovary, fallopian tube, and peritoneum, it can also occur in other cancers, including endometrial, breast, and prostate cancers, as well as neuroendocrine tumors. While it is rare for these tumors to present with peritoneal metastases, CRS/HIPEC may be a treatment option if the biology of the peritoneal spread mirrors that of appendiceal cancers.

Once peritoneal carcinomatosis occurs in these rare cases, it is associated with significant mortality and treatment options are limited, focusing on mainly palliative intent with no strong recommendations on how to treat these patients. Most patients are typically offered systemic therapy with/without palliative surgery. However, some case series and retrospective studies suggest that CRS/HIPEC may be a promising approach for highly selected patients with peritoneal spread and no extra-peritoneal disease. For example, a 2018 retrospective Italian study of 33 patients with peritoneal dissemination of endometrial cancer treated with CRS/HIPEC reported a median overall survival of 33.1 months and a median progression free survival of 18 months.<sup>54</sup> While the data is retrospective and includes a relatively small number of patients, this is significantly improved compared to standard therapy (5-year OS of 20%).<sup>55,56</sup> Generally, for these rare tumors, prognosis appears to be directly correlated to disease burden and strict patient selection is essential.

We have vast experience in treating cancers with peritoneal spread, including tumors that rarely have intraperitoneal metastasis and uncommon histopathologic subtypes, such as breast, prostate, endometrial, gallbladder, neuroendocrine, peritoneal sarcoma, clear cell carcinomas, granulosa cell tumors, mucinous cystadenomas, and carcinosarcomas. We have achieved an 88% complete cytoreduction rate in these patients. In advanced endometrial cancer, including both newly diagnosed and recurrent disease, our median overall survival is 6.6 years.

Although the number of patients treated is low, these outcomes show response while other therapies are unable to produce similar outcomes. However, additional studies using prospective data and multi-center collaborations are necessary.

### Summary:

1. When peritoneal metastasis from uncommon primary sites occurs, treatment options are limited and there are no strong guidelines on the optimal treatment plan.
2. Although data is limited, CRS/HIPEC may be a treatment option and has shown promising outcomes for these patients with intraperitoneal metastases when a complete cytoreduction is feasible.
3. Additional multi-center studies are necessary to evaluate the true benefit of CRS/HIPEC in these rare cases.

# Uterine Sarcoma

Uterine sarcomas are rare mesenchymal tumors accounting for approximately 7% of all uterine cancers.<sup>41</sup> Although rare, the incidence is rising.<sup>42</sup> Uterine sarcomas encompass a variety of neoplasms, including leiomyosarcoma, endometrial stromal sarcoma and adenosarcoma.<sup>43</sup> Leiomyosarcoma is the most common type, accounting for 63% of cases.<sup>44</sup> Uterine sarcomas are characterized by their poor response to systemic chemotherapy and high recurrence rates.

Uterine sarcomas are challenging to diagnose and treat. Symptoms are non-specific, typically including pelvic pain, abdominal distention and

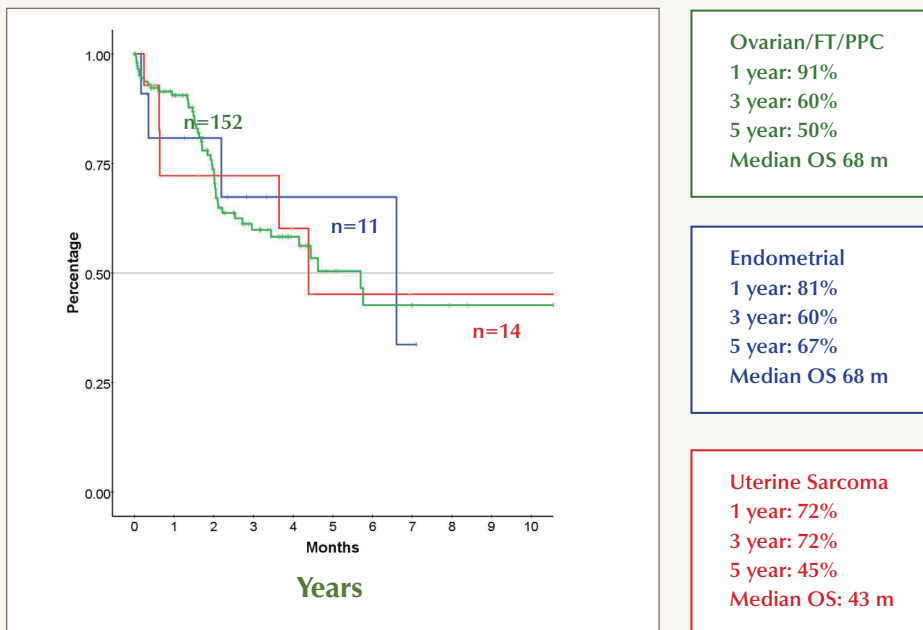
abnormal vaginal bleeding. In addition, their aggressive biology makes late or metastatic disease common. However, even when resected at an early stage, the risk for metastatic relapse remains high. An estimated 50-70% of women will have recurrent disease regardless of the diagnosis stage.<sup>45</sup> In addition, once disease is advanced, 5-year overall survival is less than 30% compared to 50-55% in early staged disease.<sup>46,47</sup>

Surgery is the standard treatment for uterine sarcomas, but optimal management of these patients, especially with recurrence, is uncertain. In the recurrent setting or when patients are not surgical candidates, systemic

chemotherapy and radiation therapy can be considered. However, median disease free survival in patients with recurrent uterine sarcoma treated with chemotherapy only ranges from 2-6 months.<sup>48</sup> Although treating peritoneal sarcomatosis with CRS/HIPEC is controversial, several studies have described favorable results with this therapy.<sup>49-52</sup> In a recent review of seven international HIPEC centers, the median overall survival was 37 months with a 1, 3, and 5-year survival of 76%, 54%, and 32%, respectively.<sup>53</sup> Thus, CRS/HIPEC may offer survival benefit for patients facing this rare, deadly disease with limited treatment options. However, further studies are necessary.

We have a 5-year survival of 45% with a median survival of 43 months in patients with recurrent peritoneal dissemination of uterine sarcoma (Figure 6). Although the number of patients treated is low, these outcomes show response while other therapies are unable to produce similar outcomes.

**Figure 6: Overall Survival for Gynecological Malignancies after CRS/HIPEC**

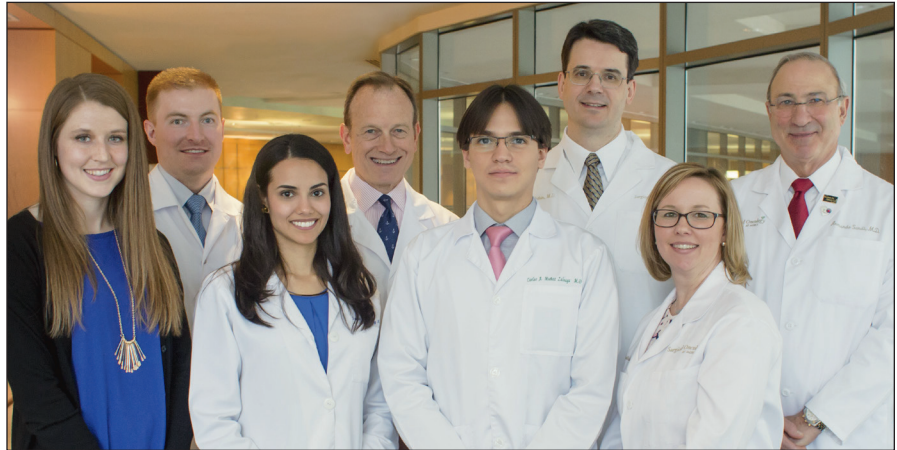


**Summary:**

1. Uterine sarcomas have poor response to systemic chemotherapy and high recurrence rates.
2. Optimal management of patients with recurrence or metastatic disease is uncertain and may include surgery, chemotherapy, and/or radiation.
3. Although current data is limited, several studies have shown favorable results with CRS/HIPEC with median survival of 37 months.

# Institute for Cancer Care at Mercy Medical Center Comprehensive HIPEC Program

Peritoneal carcinomatosis is a complex diagnosis that is challenging to treat. Our multidisciplinary, comprehensive cancer care program excels in patient outcomes and research for the treatment of rare and advanced peritoneal surface malignancies. Our commitment to providing excellent personalized care is evident in every aspect of our treatment program – from compassionate, individualized care, from initial consultation through survivorship to cultivating cross-specialty collaborations and cutting-edge clinical research.



The Research Team is comprised of surgical oncologists, medical oncologists, pathologists, a research advisor, fellows from Colombia and Russia, a research nurse, and a research coordinator. (Pictured left to right) Victoria Eskay, Drs. Arkaddi Sipok, Kurtis Campbell, Vadim Gushchin, Armando Sardi, Michelle Sittig, RN, and Drs. Carlos Munoz-Zuluaga and Farah El-Sharkawy. Not pictured: Drs. Kimberly Studeman, Peter Ledakis, Ekaterina Baron, Andrei Nikiforchin, Carol Nieroda, and research coordinator, Mary Caitlin King.

## Commitment to Our Patients

Personalized care from initial consultation through treatment and survivorship  
Understanding unique patient circumstances, needs, and goals

## Clinical Research

Committed to advancing medicine through research  
10 open studies and clinical trials



## Team-Based Treatment

Multidisciplinary approach involving surgical, gynecologic and medical oncology, nutrition, pastoral care, and physical therapy among other specialties

Unique cross-specialty collaborations to achieve better outcomes

High-quality physicians and staff who are passionate about our patients and mission

## Outstanding Results

85% surgical completion rate  
Average hospital stay of 10 days  
Average survival of 18.5 years in appendiceal cancer

## Patient Advocacy

Led by the Board of Influencers  
Cultivate a network of patients and physicians across the U.S.  
Promote awareness and funding for HIPEC treatment and research through regional events

## Research Program

The Surgical Oncology Research Department consists of research scholars, a research advisor, a research nurse, and study coordinators. The team manages clinical trials and research studies, performs medical literature reviews, and conducts data collection and analysis. In addition, prospective data collection since 1994 has allowed extensive, comprehensive research.

We aim to increase HIPEC education and awareness as a life-saving treatment option in cancers with peritoneal spread among medical providers through:

- Clinical research trials/studies
- 10 open studies with 4 clinical trials open to enrollment
- Presentations at national and international symposia
- Publication of more than 50 manuscripts in major medical journals since 2009

This work will ultimately lead to timely referrals and the appropriate care with improved patient outcomes.



(L to R) Research fellows Drs. Andrei Nikiforchin (Russia), Ekaterina Baron (Russia), and Carlos Munoz-Zuluaga (Colombia) presented on peritoneal surface malignancies and CRS/HIPEC at the 2020 Advanced Cancer Therapies conference led by the Society of Surgical Oncology in Orlando, FL.

## Research Scholar Program

The Surgical Oncology Research Scholar Program at Mercy Medical Center aims to train future researchers in order to expand the knowledge available to both the scientific and medical community and improve outcomes for patients diagnosed with cancer.

The program consists of modules including basic research orientation, medical literature review, study design, data collection and analysis, and elements of publication and presentation. The scholar engages in various research methodologies, working independently with colleagues at Mercy Medical Center and in collaboration with other institutions worldwide. The scholar participates in weekly oncology conferences and works directly with physicians and other clinical staff to engage in every aspect of research.



## Affiliations & Collaborations

### Appendiceal Cancer

#### COLLABORATORS:

- University of California, San Diego (Dr. Jessica Metcalf, PhD)
- University of South Carolina (Dr. Traci Testerman, PhD)
- Uniformed Services University of Health Sciences (Dr. D. Scott Merrell, PhD)

#### AIMS:

- To investigate the microbial and immunological microenvironment of appendiceal tumors through animal and microbiome research and correlate with patient outcomes
- To develop and advance an animal model of this rare disease in order to improve our understanding of the biological behavior and investigate additional treatment options

### Peritoneal Mesothelioma

#### COLLABORATORS:

- INOVA Fairfax Department of Surgical Oncology
- INOVA Fairfax Translational Medicine Institute

#### AIMS:

- To evaluate the molecular landscape of peritoneal mesothelioma tumors through DNA and RNA sequencing in order to understand the molecular and biological behavior of these tumors and aid in the development of targeted therapies

- To create a multi-center database of this rare malignancy in order to increase sample size and improve statistical power of important research

### Ovarian Cancer

#### COLLABORATORS:

- The Lya Segall Ovarian Cancer Institute at Mercy Medical Center (Dr. Teresa Diaz-Montes and Dr. Hyung Ryu)

#### AIMS:

- To provide the highest quality surgery and improved clinical outcomes through cross-specialty clinical collaborations
- To investigate the role of upfront and interval CRS/HIPEC in patients with newly diagnosed EOC in order to improve patient outcomes
- To evaluate the role of CRS/HIPEC in recurrent EOC, as well as endometrial cancers and uterine sarcomas, to provide additional treatment options

## Clinical Trials

We offer clinical trials and protocols for common malignancies, such as ovarian cancer, as well as rare tumors, such as appendix cancers. Below is a list of our current open studies:

**A phase II randomized study: Outcomes after cytoreductive surgery (CRS) with or without carboplatin hyperthermic intraperitoneal chemotherapy (HIPEC) followed by systemic chemotherapy with carboplatin and paclitaxel as initial treatment of ovarian, fallopian tube, and primary peritoneal cancer (NCT02124421)**

- Mercy Medical Center is the first institution in the United States to study the role of CRS/HIPEC for newly diagnosed with ovarian, fallopian tube, or primary peritoneal cancers. Literature exists involving CRS/HIPEC in the role of recurrent disease and in the neoadjuvant setting; however, there is no published data on the role as a primary treatment option in the United States.
- This phase II randomized clinical trial aims to determine the toxicity and postoperative complications related to CRS/HIPEC as an initial treatment option for patients with ovarian, fallopian tube, or primary peritoneal cancers and its impact on quality of life.

*continued*



## Clinical Trials continued

### **Clinical Trial to Define the Effect of Perioperative H. Pylori Eradication with Antibiotic Treatment on the Long Term Outcomes of Patients with Pseudomyxoma Peritonei of appendiceal origin undergoing Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) (NCT02387203)**

- Based on our previous research we found bacteria, including H. pylori, present in appendiceal tumors within the peritoneal cavity.
- This phase II, open label, historical controlled study examines the use of the FDA approved H. pylori triple antibiotic therapy in patients undergoing CRS/HIPEC for appendiceal neoplasms with peritoneal dissemination and its effect on patient outcomes and survival, as well as the tumor microenvironment.

A cohort study of the gastrointestinal microbiome in appendiceal cancer with peritoneal spread (NCT02599116)

- The primary study aim is to determine whether the gastrointestinal microbiome of appendiceal cancer patients with peritoneal spread differs from a healthy, age-matched cohort of the American population.
- Patients scheduled to undergo CRS/HIPEC provide pre- and post-operative fecal samples. This is a collaborative study with the University of California, San Diego and Rob Knight, PhD who performs the microbial genetic testing and analysis of samples provided.

### **Injection of Bromelain and Acetylcysteine in Combination into Recurrent Mucinous Tumour or Pseudomyxoma Peritonei (NCT03976973)**

- A multi-center, international phase II trial for patients with mucinous peritoneal tumors, including pseudomyxoma peritonei (PMP), that are not suitable for CRS/HIPEC or other potentially beneficial surgery
- Combination drug treatment of bromelain and acetylcysteine is injected directly into the tumor or peritoneal cavity with a 24 hour dwell time. The expectation is that the drug combination of bromelain and acetylcysteine, via direct injection into the tumor, will dissolve the tumor/mucin, allowing drainage and symptomatic relief.

### **Intraoperative Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Intra-abdominally Advanced Colorectal, Appendix, Gastric, Small Bowel, Primary Peritoneal, Ovarian Cancers, Peritoneal Mesothelioma and Sarcomas**

- This prospective observational study of CRS/HIPEC patients provides significant analytical data to refine future treatment protocols and enhance patient care.
- Biospecimens harvested during and stored after CRS/HIPEC can be used to determine assays of tumor gene expression analysis and the correlation with disease outcomes and prognosis. The availability of these samples is essential to ongoing cancer research which allows researchers to frame questions that can be answered only by examining hundreds of patient specimens.

- Biospecimens are also essential for research aimed at the development of personalized medicine, in which treatments and other interventions will be tailored to patients based on their individual genetic characteristics and the unique molecular features of their disease.

### **Microbiologic and Immune Characteristics of Peritoneal Tissues in Patients with Appendix Cancer with Peritoneal Spread**

- This prospective observational study aims to determine the microbiological environment, systemic and local immune responses, and specific genetic mutations of appendiceal tumors harvested during CRS/HIPEC.
- This is a collaborative study with microbiologists and immunologists at the Uniformed Services University of Health Sciences in Bethesda, MD and the University of South Carolina.

### **Identification of genomic alterations in diffuse malignant peritoneal mesothelioma**

- The objective of the study is to characterize and describe the genomic profile of malignant peritoneal mesothelioma utilizing next-generation sequencing technology with an emphasis on describing the presence or absence of defined cancer related genes. It is an initial step towards understanding the biological behavior of the disease and identifying potential therapeutic targets for personalized treatments.
- This is a collaborative study with INOVA Fairfax Department of Surgical Oncology and the Institute for Translational Medicine.



# HEAT IT TO BEAT IT



Founded by a group of grateful patients over 10 years ago, Heat it To Beat It is an annual walk that raises awareness and funding for peritoneal carcinomatosis research at Mercy Medical Center. The walk offers patients, families, and clinicians an opportunity to come together to share stories of healing, foster hope and community, and celebrate survival. The above photo is of our peritoneal carcinomatosis survivors, caregivers, and providers at the 10th anniversary Heat it To Beat It walk in September 2019.

**To refer a patient, please contact 410.332.9294 (Department of Surgical Oncology) or 412.682.7426 (The Lya Segall Ovarian Cancer Institute).**



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