



**Kaiser Foundation Health Plan
of Washington**

Clinical Review Criteria

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

- Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
- Intraoperative Chemo Hyperthermic Peritoneal Perfusion (CHPP)
- Intraperitoneal Hyperthermic Chemoperfusion (IHCP)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Hyperthermia for Treatment of Cancer (110.1) <i>*Per NCD: Covered in connection with radiation therapy for certain types of malignancies, <u>not covered</u> in connection with chemotherapy</i>
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

Service	Criteria Used
Cytoreductive Surgery Perioperative Hyperthermic Intraperitoneal Chemotherapy	Cytoreductive surgery and perioperative hyperthermic intraperitoneal chemotherapy may be considered medically necessary for the treatment of: <ul style="list-style-type: none"> • pseudomyxoma peritonei • diffuse malignant peritoneal mesothelioma • ovarian cancer Cytoreductive surgery and perioperative hyperthermic intraperitoneal chemotherapy is considered investigational for: <ul style="list-style-type: none"> • peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer; • all other indications, including goblet cell tumors of the appendix.
Intraperitoneal chemotherapy without hyperthermic methodology	Intraperitoneal chemotherapy without hyperthermic methodology is considered standard therapy and is not subject for review and is covered.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Colon Cancer

In the United States, approximately 108,070 patients are diagnosed with colon cancer (CRC) per year, and between 10-30% of these patients will develop peritoneal carcinomatosis (PC) at some point after their initial diagnosis. PC is characterized by intraperitoneal spread of tumor nodules in the peritoneum which may occur as a result of growth of the tumor and its invasion through the serosal lining of the bowel lumen, or as result of iatrogenic manipulation during surgical procedures. PC of colorectal origin has poor survival and is the second most frequent cause of death in patients with colorectal cancer (CRC), after metastatic liver disease. It has always been regarded as a terminal condition and was commonly treated only with palliative therapies (Franko 2012, Macri 2010, Ripley 2010, Chua 2012).

Over the last two decades, significant advances made in the field of cytotoxic chemotherapy and biological agents have changed the treatment of PC from a palliative to a potentially curative approach. Modern chemotherapeutic regimens have increased the response rate and median survival of patients with PC. However, few patients experience long-term survival with chemotherapy alone. In the 1980s a multimodal technique was developed to manage PC based on cytoreduction of the primary tumor, peritonectomy, and hyperthermic antineoplastic peritoneal perfusion (HIPEC). Theoretically cytoreductive surgery (CRS) treats the macroscopic residual disease and intraperitoneal (IP) chemotherapy treats the microscopic residual disease. IP chemotherapy is based on the principle that a high concentration of chemotherapy within the abdominal cavity will kill the tumor cells on the surface with less diffusion into the tissues and thus are less toxicity. Hyperthermia with IP chemotherapy optimizes the process as heat has direct cytotoxic effects on cancer cells and increases the cytoactivity and penetration of certain cytotoxic drugs (Verwaal 2008, Macri 2010, Ripley 2010, Vaira 2010, Glehen 2010, Mizumato 2012, Chua 2012, Miceli 2012).

HIPEC is achieved by the intraperitoneal administration of a large volume of chemotherapeutic agents in a carrier solution through an open or closed technique. It involves the placement of one inflow and three outflow catheters in the abdominal cavity after the cytoreduction surgery. The cytotoxic agent is applied through the inflow drainage using a roller pump and heat exchanger in a closed system that allows perfusion circulation. The intraperitoneal temperature should reach 41-42°C and is monitored by two sensors placed in the inflow catheter and in the Douglas pouch. At the end of the procedure the solution is drained, and the abdominal wall is closed. There is no standardized procedure for HIPEC and there are variations between the centers in the combinations and/or concentrations for the cytotoxic agents used, as well as the intraabdominal temperature and duration of the treatment which ranges from 30 minutes to 2 hours depending on the protocol of the drug used. The combination therapy of cytoreductive surgery and HIPEC is complex, has a steep learning curve, and is associated with significant morbidity and mortality. Preoperative selection of patients to achieve complete cytoreduction plays a crucial role for the success of therapy regarding the clinical and ontological outcomes as well as the patient quality of life (Glockzin 2009, Mizumato 2012).

There is controversy around the use of cytoreduction therapy and HIPEC for peritoneal surface disease from CRC, and the procedure is not widely accepted despite the Consensus Statement (issued by representatives from the major Peritoneal Surface Malignancy Centers from around the world) on the role of cytoreductive surgery and HIPEC in the management of peritoneal surface malignancies of colonic origin (Esquivel 2007).

Ovarian Cancer

Ovarian cancer is the fifth leading cause of death in women in the US and the most common cause of death from gynecological cancer in the Western World. It was estimated that around 22,280 women will be diagnosed with ovarian cancer and that 15,500 women will die of the disease in the US in 2012. Approximately two thirds of the women are diagnosed at an advanced stage due to the nonspecific nature of the presenting symptoms of ovarian cancer and its high tendency for early peritoneal spread. Peritoneal carcinomatosis occurs through exfoliation of malignant cells into the peritoneal fluid and their dissemination along the abdominal and pelvic peritoneum. Traditionally these patients with extensive peritoneal carcinomatosis were often labeled as having terminal disease and were only given palliative therapy with no curative intent (Chua 2009, Spiliotis 2011, Chan 2012, de Bree E 2012, Mulier 2012, Siegal 2012, Tentes 2012).

The standard therapy for patients with ovarian cancer is maximal cytoreductive surgery (CRS) followed by systemic chemotherapy with a platinum-based agent and a taxane combination. Ovarian cancer is one of the most chemosensitive tumors, and its response to this initial therapy is high, but the disease often recurs, mostly locoregionally, involving the peritoneum and adjacent intra-abdominal organs. The sensitivity of epithelial ovarian

cancer to chemotherapy and its tendency to remain confined to the peritoneal cavity through much of its natural history, have led the researchers to investigate regional treatment such as intraperitoneal (IP) administration of chemotherapy (IPC). The theoretical benefits include the achievement of a high drug concentration in the peritoneal cavity without the toxic effects of the systemic chemotherapy. IP chemotherapy has been investigated in clinical trials including the Gynecologic Oncology Group (GOG-172) phase III trial that showed approximately 16 months improvement in the median survival of women treated with a combination intravenous (IV) and IP chemotherapy compared to those treated with IV chemotherapy alone, but on the expense of the increased risk of toxicity and catheter-related complications. Based on the results of this as well as other trials, the National Cancer Institute (NCI) issued a clinical announcement in 2006 recommending that women with optimally debulked stage III ovarian cancer and their physicians consider a combination of intravenous (IV) and intraperitoneal chemotherapy (IPC). IPC has limited tissue penetration and may be indicated only following optimal resection of peritoneal disease when there is either no or very small macroscopic disease remaining (<1.0 cm). The use of IPC however, is controversial and is not widely accepted by the medical community as a standard treatment in the management of advanced epithelial ovarian cancer, due to its high toxicity, catheter-related complications, and negative impact on the patients' quality of life (Almadrones 2007, Trimble 2008, Runowicz 2008, Lim 2009, Spiliotis 2011, Tentes 2012, Chan 2012, de Bree 2012).

In the last two decades researchers investigated the synergistic effect of combining regional hyperthermia and intraperitoneal chemotherapy (hyperthermic IPC, or HIPEC) together with the CRS. Theoretically, in addition its tumoricidal effect, hyperthermia increases the permeability of the drug to the tumor cells (up to 5-6 mm compared to 2-3 mm of the conventional IPC). Hyperthermia may also alter the cellular metabolism, and cellular drug pharmacogenetics. A potential advantage of administering HIPEC intraoperatively is providing superior and homogenous exposure of the seroperitoneal surface to the drug and heat before the development of adhesions. The disadvantage of HIPEC compared to IPC is the shorter tumor exposure time and its administration only once during the surgery or at the most twice when a secondary surgery is performed (de Bree 2012).

Other primary peritoneal malignancies or secondary dissemination from gastrointestinal tract or other pelvic organs.

Primary peritoneal malignancies such as peritoneal mesothelioma or papillary serous carcinoma are rare, but peritoneal dissemination from gastrointestinal tract and ovarian carcinomas are common. In the past these carcinomas were regarded as terminal and the patients were only treated with palliative measures. Over the last 30 years however, novel more aggressive treatment strategies that combine cytoreductive surgery with intraperitoneal (IP) chemotherapy were explored. Hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative IP chemotherapy emerged as the most commonly used IP adjuvant therapies. Theoretically cytoreductive therapy treats the macroscopic disease, and intraperitoneal chemotherapy (IP) treats the microscopic disease and the residual or free tumor cells left in the peritoneal cavity after surgery, in order to prevent and control peritoneal dissemination. IP chemotherapy is based on the principle that a high concentration of chemotherapy within the abdominal cavity will kill the tumor cells on the surface with less diffusion into the tissues and less toxicity. Hyperthermia with IP chemotherapy optimizes the process as heat has direct cytotoxic effects on cancer cells and increases the cytotoxicity and penetration of certain cytotoxic drugs. Hyperthermia is also believed to modulate the cells of the innate and adaptive immune system, thereby improving effectiveness (Shen 2009, Glehen 2010, Mizumoto 2012, Sun 2012, MI 2013).

Medical Technology Assessment Committee (MTAC)

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

04/02/2007: MTAC REVIEW

Evidence Conclusion: *Prevention of peritoneal carcinomatosis* Two randomized controlled trials from Japan, conducted among patients who underwent surgery for T2-T4 gastric carcinoma with serosal involvement, found a significant benefit from including HIPEC treatment. The study with the stronger methodology (Yonemura et al., 2001) found a higher estimated 5-year survival in the group receiving cytoreduction and HIPEC (61%), compared to two other groups (cytoreduction and normothermic intraperitoneal chemotherapy, 44%; and surgery alone 42%). The other RCT (Fujimoto et al., 1999) had poorly described methodology, and also found a significantly higher estimated survival rate in a group receiving cytoreduction plus HIPEC compared to surgery alone. The first study had a minimum of 2.4 years of follow-up; length of follow-up was not reported in the Fujimoto study. Findings from studies on Japanese gastric cancer may not be generalizable to the United States. *Treatment of peritoneal carcinomatosis* There is evidence from one reasonably valid randomized controlled trial that HIPEC is beneficial as a treatment for peritoneal carcinomatosis (Verwaal et al., 2003). The study, which included 105 patients with histologically proven peritoneal metastases of colorectal adenocarcinoma, compared an experimental treatment (cytoreduction and HIPEC, plus adjuvant chemotherapy) to standard treatment (outpatient chemotherapy, surgery only if necessary). After a median follow-up of 22 months, the survival rate was

significantly higher in the experimental treatment group (56% vs. 39%). Sub-group analyses suggest that survival was lower in patients with extensive residual disease or involvement of more than 5 regions of the abdominal cavity. A case series by the same research group found an estimated one-year survival of 75% and three-year survival of 28% with the experimental treatment. There were no long-term survival data for the standard treatment group. The evidence base would be strengthened with additional comparative studies.

Articles: *Prevention of peritoneal carcinomatosis*. Three RCTs were identified: all were conducted by Japanese investigators. The two trials with the larger sample sizes (n=139 and n=141) were critically appraised. The third study was smaller (n=82) and had limitations including a non-significant finding with no discussion of statistical power. *Citations for the reviewed studies are as follows:* Yonemura Y, deAretxabala X, Fukimura T et al. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: Final results of a randomized controlled study. *Hepato-Gastroenterology* 2001; 48: 1776-1782. See [Evidence Table](#). Fujimoto S, Takahashi M, Mutou T et al. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 1999; 85: 529-534. See [Evidence Table](#). *Treatment of peritoneal carcinomatosis:*

One RCT from the Netherlands was identified and critically appraised (Verwaal et al., 2003). There have also been a number of case series, most had sample sizes under 100. The largest case series was a multicenter study by Glehen et al., 2004 and included 506 patients. This study was limited in that it combined data from different centers that had different protocols and patient populations. All of the centers used perioperative intraperitoneal chemotherapy, but it appears that not all used hyperthermic treatment. As a result, the Glehen article was excluded from further review. The next largest case series available in English was by Verwaal et al., 2005. This article reported long-term follow-up on 117 patients, 48 of whom were included in the 2003 RCT, and was critically appraised. *The two studies reviewed were as follows:* Verwaal VJ, van Ruth S, de Bree E et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21: 3737-3743. See [Evidence Table](#). Verwaal VJ, van Ruth S, Witkamp A et al. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12: 65-71. See [Evidence Table](#)

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of peritoneal carcinomatosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

10/16/2012: MTAC REVIEW

Evidence Conclusion: Verwaal and colleagues (2003, 2008) conducted a randomized controlled trial in one center in the Netherlands to compare the efficacy of cytoreductive surgery (CRS) and HIPEC versus systemic chemotherapy and surgery in the management of peritoneal carcinomatosis of colorectal origin. The study randomized 105 patients younger than 71 years of age, with peritoneal metastases of CRC to undergo CRS in combination with hyperthermic intraperitoneal therapy (HIPEC) or systemic chemotherapy and surgery. The authors published the results after a median of 21.6 months, and later after an extended follow-up of 91 month. The initial results of the trial showed a significantly higher median survival of the patients treated with CRS and HIPEC vs. standard therapy (22.3 months and 12.6 months respectively). After 8-years of follow-up, 9 patients were still alive. This long-term follow-up showed a median progression-free survival of 12.6 months in the CRS and HIPEC group and 7.7 months in the standard therapy group. Subgroup analyses of the results showed that patients with 6-7 regions had a very poor survival (median 5.4 months) compared to those with 0-5 regions (median >29 months), and that survival was significantly higher with success of surgical procedure i.e. complete cytoreduction. The trial had generally valid methodology; it was randomized and controlled. However, it was conducted over a decade ago and significant progress in chemotherapy has been accomplished since then. The systemic therapy with 5-FU and leucovorin used in the control group is outdated, and mitomycin-C, the HIPEC drug used in the experimental group is not the most effective drug for used for CRC. In addition, the experimental group underwent both cytoreduction and HIPEC and it is difficult to determine whether the survival benefit was due to one of the two treatment modalities or their combination, and whether heating of the chemotherapy had an additive effect to the IP therapy.

Articles: The search revealed one meta-analysis, one randomized controlled trial with long-term follow-up, and a number of observational studies with or without comparison groups. The randomized trial was selected for critical appraisal. The meta-analysis pooled the results of that RCT together with a retrospective study and was not critically reviewed. Verwaal VJ, van Ruth S, de Bree E, et al Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;21:3737-3743 See [Evidence Table](#). Verwaal VJ, Bruin S, Boot H, et al 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*.2008; 15:2426-2432 See [Evidence Table](#).

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of peritoneal carcinomatosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

02/11/2013: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine the efficacy and safety of hyperthermic intraperitoneal chemotherapy for the treatment of patients with ovarian cancer whether as an initial therapy, consolidation therapy, or for the treatment of a persistent or recurrent disease. The published studies on HIPEC for ovarian cancer are all prospective or retrospective case series. The studies included heterogeneous groups of women of different ages, different disease characteristics, stages, and tumor load, previous use of systemic chemotherapy regimens, chemo resistance, and with different indications for HIPEC therapy (primary, consolidation, persistent, or recurrent disease after initial therapy). In addition, the published studies recruited patients over long periods of time and used different HIPEC protocols and chemotherapeutic regimens some of which were outdated by the time the studies were completed and their results published. In a small observational study, Spiliotis and colleagues (2011, evidence table 1) compared survival benefit of HIPEC for ovarian cancer among two case series: one with 24 patients treated with CRS followed by HIPEC and systemic chemotherapy, and the other with 24 were treated with CRS and systemic chemotherapy alone without HIPEC for various reasons not explained by the authors. The results of the study show that the median survival was significantly higher for those who received HIPEC vs. those who did not (19.4 months vs. 11.2 months). The 1-year and 3-year survival rates were also significantly higher among patients treated with HIPEC. Within each of the two groups survival outcomes were better among patients with less extensive peritoneal disease and more complete cytoreduction. Due to the study design, the potential selection bias and confounding, it is difficult to determine whether improved survival was due to HIPEC, successful cytoreduction, or other confounding factors. An earlier observational study (Gori et al, 2005) compared the outcomes of a second look surgery and HIPEC (4-8 weeks after standard CRS and systemic chemotherapy) in 29 patients, to the outcomes for 19 patients who refused the second look and HIPEC. All patients had stage III ovarian cancer and had undergone a primary complete or optimal cytoreductive surgery (residual lesion <2cm) and 6 cycles of systemic chemotherapy. After a median follow-up of 73 months (range 24-134 months) the results showed a higher but statistically insignificant median survival patients treated with HIPEC vs. those who refused to undergo the treatment. The results of a larger retrospective case series with a historical comparison group (Ryu et al 2004, evidence table 2) show that HIPEC may be associated with better disease response and survival in patients with ovarian cancer. However, these results must be interpreted cautiously due to the limitations of the study including but not limited to potential selection bias, confounding, and other inherent limitations of case series and the use of retrospective data. Conclusion: Overall the results of the published observational studies suggest, but do not provide sufficient evidence to conclude, that HIPEC is feasible and may improve survival in women with advanced ovarian cancer. Due to the inherent limitations of the observational studies, it is hard to ascertain the extent at which the reported survival benefit resulted from selection bias, and whether it was due to the intraoperative intraperitoneal therapy, the hyperthermia, the aggressive cytoreduction therapy, the systemic chemotherapy regimens used, or other confounding factors. It is also difficult to determine whether complications occurring after major cytoreduction surgery and HIPEC were due to the surgery itself or the HIPEC. Only well conducted, adequately powered, randomized controlled trials with long-term follow-up may determine the net clinical benefit of incorporating HIPEC in the management of patients with ovarian cancer. Currently, at least three randomized controlled trials are ongoing to investigate the efficacy and safety of adding HIPEC to primary or secondary cytoreductive surgery in women with stage III or relapsing ovarian cancer. Among these trials are the OVIHIPEC trial in the Netherlands, the CHIPOR trial in France, and the HORSE trial in Italy. Their results may answer many questions about the role of HIPEC in treating ovarian cancers, its indications, efficacy, morbidity, and net clinical benefits.

Articles: The literature search did not reveal any randomized controlled trial that compared the efficacy of HIPEC to standard therapy for treatment of women with ovarian cancer. The published studies were mainly prospective or retrospective observational studies. The search identified one retrospective review and three case series that compared the outcomes of patients undergoing HIPEC to those who refused to undergo the procedure or did not receive the HIPEC therapy for various other reasons.

Two case series that compared the outcomes of patients who received HIPEC to those of patients who did not were selected for critical appraisal. Spiliotis J, Vaxevanidou A, Sergouniotis F et al. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent advanced ovarian cancer: a prospective study. *J Buon* 2011; 16:74-75. See [Evidence Table](#). Ryu KS, Kim JH, et al. Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. *Gynecol Oncol*. 2004; 94:325–332. See [Evidence Table](#).

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of ovarian cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

08/19/2013: MTAC REVIEW

Evidence Conclusion: The current review focuses on the safety and efficacy of HIPEC therapy for non-ovarian, non-colorectal cancers with serosal invasion or peritoneal carcinomatosis. Perioperative HIPEC in combination with cytoreductive surgery was evaluated in small, randomized controlled trials and a number of meta-analyses for patients with gastric cancer. The search did not identify any RCTs or large prospective studies that evaluated HIPEC for the treatment of peritoneal mesothelioma, pseudomyxoma peritonei, or for peritoneal carcinomatosis secondary to urinary bladder cancer, or uterine leiomyosarcoma. *HIPEC for Gastric cancer:* Mi DH and colleagues' meta-analysis (2013) pooled the results of 16 trials that examined the effectiveness and safety of radical surgery (RS) combined with HIPEC vs. RS without HIPEC in 1,906 patients with histologically diagnosed, primary, locally advanced gastric cancer with macroscopic serosal invasion, but with no peritoneal or distant metastases. The primary outcome of the analysis was overall survival. The pooled results indicate that compared with surgery alone, the combination of surgery with HIPEC was associated with a significant improvement in survival rate at 1,2,3,5 and 9 years. It was also associated with a significant reduction in recurrence rates at 2, 3, and 5 years. There was however, a significantly higher incidence of abdominal pain with HIPEC. The rates of other adverse events were too small to show a significant difference. Sun and colleagues' meta-analysis (2012) also examined the effectiveness and safety of gastrectomy combined with HIPEC versus gastrectomy alone in patients with advanced gastric cancer with serosal invasion but without distant metastases or peritoneal carcinomatosis. The analysis included 10 trials with a total of 1,062 patients. The primary outcome was overall survival defined as the time from treatment to the last follow-up or death. Similar to Mi et al's analysis, the pooled results indicate that surgery combined with HIPEC may improve the overall survival for patients and prevent peritoneal local recurrence. There pooled results do not show a significantly higher risk of complications associated with HIPEC, but again the numbers were too small to provide sufficient statistical power. The two meta-analyses had had generally valid methodology and analysis. However, they had only 5 trials in common despite almost similar literature search dates. The trials included were small, all were conducted in Asia, and many were performed in the late 1980s and early 1990s and the procedures used may be currently outdated. In addition, there was no standardized agent or dose used for HIPEC; different chemotherapeutic agents were used among the trials and at different doses. The most commonly used agents in the trials were mitomycin C and cisplatin given alone, in combination together, or in combination with other agents. A small phase III RCT (Yang et al, 2011) conducted in Japan, evaluated the efficacy and safety of cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal therapy (HIPEC using mitomycin C and cisplatin) for the treatment peritoneal carcinomatosis (PC) from gastric cancer. The study randomized 68 participants to receive CRS combined with open HIPEC or CRS alone. The primary outcome was overall survival. After a median follow-up of 32 months (range 7.5-83.5 months), the results showed that patients in the CRS and HIPEC had significantly better overall survival compared to those who underwent CRS with no HIPEC. The numbers of serious adverse events were higher in the HIPEC group but were too small to allow any conclusion. *HIPEC for diffuse malignant peritoneal mesothelioma (DMPM):* Baratti and colleagues (2009) analyzed data from a prospective database for 70 patients with DMPM who were treated with cytoreduction surgery and HIPEC by the same surgical team from 1996 to 2008 at a cancer institute in Italy. Disease progression was the primary outcome of the study. This occurred among 38 (54.28%) of the participants after a median follow-up of 43 months. The median time to disease progression (TTP) among these patients was 9 months and the median survival from progression was 8 months. Failure pattern was categorized as peritoneal progression, which occurred among 31 (81.58%) patients, liver metastasis in one patient, abdominal lymph node involvement in 2, and pleural seeding in 4 patients. Residual tumor ≤ 2.2 mm was the only independent risk factor for disease progression. Progressive disease was treated with second HIPEC in 3 patients, debulking in 4, systemic chemotherapy in 16, and supportive care in 15. A multivariate analysis showed that time to progression < 9 months, poor performance status, and supportive care correlated to reduced survival from progression. These results should be interpreted with caution as the study was small, observational, conducted in a single center, and had no comparison or control group. *HIPEC for Pseudomyxoma peritonei (PMP)* In a retrospective study, Chua and colleagues (2012) reported on the outcome of nearly 2,300 patients from 16 institutions worldwide that were treated with cytoreductive surgery (CRS) and HIPEC over an 18-years period for pseudomyxoma peritonei (PMP) that arose from the appendix. The study was based on data from the Peritoneal Surface Oncology Group International registry. The median survival was 16.3 years, and the median progression-free survival was 8.2 years, with 10-year survival rate of 63% and a 15-year survival rate of 59%. The postoperative mortality rate after cytoreductive surgery and HIPEC was low (2%), but 24% of patients experienced major complications and 10% of patients required surgery for their complications. Data on quality of life were not provided. A multivariate analysis indicated that prior chemotherapy treatment, peritoneal mucinous carcinomatosis (PMCA) histopathological subtype, major postoperative complications, high peritoneal cancer index, and debulking surgery were independent predictors for a poorer progression-free survival. Use of HIPEC was associated with a favorable progression-free survival. Older age, major postoperative complications, debulking surgery, prior chemotherapy treatment, and PMCA histopathological subtype were independent predictors of a poorer overall survival. Elias and colleagues (2010) also conducted a retrospective

analysis of data from a registry with 301 patients with PMP treated with CRS and HIPEC between 1993 and 2007 in 18 French speaking centers in Europe and Canada. The mean follow-up was 88 months, the 5-year and 10-year overall survival rates were 73% and 54.8% respectively. The 5-year disease-free survival was 56%. 4.4 % of the patients died postoperatively, 40% had a grade 3-4 complication. 17.5% of all patients required a re-operation due to complications. These results of these retrospective analyses should be interpreted with caution due to the methodological limitations of retrospective studies, and lack of control groups. Conclusion: There is some evidence from small RCTs conducted in Asia, and meta-analyses pooling their results that cytoreductive surgery combined with intraperitoneal hyperthermic chemotherapy may improve the overall survival in patients with advanced gastric cancer without macroscopic peritoneal carcinomatosis or distant metastases. There is insufficient evidence to determine the subgroup of patients with gastric cancer who would benefit most from HIPEC as the effectiveness of HIPEC may depend on size and depth of micrometastases. There is insufficient evidence to determine the optimal regimen for HIPEC. There is insufficient evidence to determine the efficacy of HIPEC in patients with peritoneal carcinomatosis from gastric cancer. There is insufficient evidence to determine the safety of HIPEC or its effect on the quality of life in patients with gastric cancer with or without dissemination to the peritoneum. There is insufficient evidence to determine the safety and efficacy of HIPEC for the treatment of other peritoneal malignancies, whether of a primary origin or peritoneal carcinomatosis secondary to cancer in other organs within the peritoneal cavity.

Articles: The literature search for studies on the efficacy and safety of HIPEC in patients with pseudomyxoma peritonei, GI cancers (other than colorectal cancer) identified two recent meta-analyses of RCTs, two older ones, and a phase III RCT on HIPEC for patients with gastric cancer. The search did not reveal any RCTs that evaluated HIPEC for primary peritoneal malignancies, or other peritoneal disseminations from other cancers evaluated in this review. The published studies were mainly small prospective or retrospective case series with no comparison or control groups. The two more recent meta-analyses and the RCT that evaluated the efficacy and safety of HIPEC for gastric carcinoma were selected for critical appraisal.

Mi DH, Li Z, Yang KH, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomized controlled trials. *Int J Hyperthermia*. 2013; 29:156-167. [See Evidence Table](#). Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. *BMC Cancer*. 2012; 12:526. [See Evidence Table](#). Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol*. 2011; 18:1575-1581. [See Evidence Table](#).

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of Gastric, DMPM, and PMP cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Medicare – Considered not medically necessary for use of hyperthermia with chemotherapy

Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
77600	Hyperthermia, externally generated; superficial (ie, heating to a depth of 4 cm or less)
77605	Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
77610	Hyperthermia generated by interstitial probe(s); 5 or fewer interstitial applicators
77615	Hyperthermia generated by interstitial probe(s); more than 5 interstitial applicators
77620	Hyperthermia generated by intracavitary probe(s)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

**To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).

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Date Created	Date Reviewed	Date Last Revised
04/19/2007	04/02/2007, 04/16/2007 ^{MDCRPC} , (reinitiated policy document) 11/06/2012 ^{MDCRPC} , 03/05/2013 ^{MDCRPC} , 10/01/2013 ^{MPC} , 01/07/2014 ^{MPC} , 11/04/2014 ^{MPC} , 09/01/2015 ^{MPC} , 07/05/2016 ^{MPC} , 05/02/2017 ^{MPC} , 03/06/2018 ^{MPC} , 03/05/2019 ^{MPC} , 03/03/2020 ^{MPC} , 03/02/2021 ^{MPC} , 03/01/2022 ^{MPC} , 03/07/2023 ^{MPC}	03/01/2022

^{MDCRPC} Medical Director Clinical Review and Policy Committee

^{MPC} Medical Policy Committee

Revision History	Description
08/02/2016	Removed the diagnosis, Pseudomyxoma Peritonei (PMP), from the non-covered list
05/22/2020	Added CPT codes 77600, 77610, 77615, 77620 and removed 96446.
03/01/2022	Added ovarian cancer to the list of medically necessary diagnoses.