Clinical Policy Bulletin:
Hyperthermia in Cancer Therapy

Number: 0278

Policy

I. Aetna considers the following procedures medically necessary:
   A. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy for the treatment of pseudomyxoma peritonei.
   B. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal mesothelioma.
   C. Regional hyperthermic melphalan perfusion in members with stage II, IIIA, and stage III in-transit extremity melanoma.
   D. Sequential radiation -- local/regional external hyperthermia only for superficial recurrent melanoma, locally advanced/recurrent breast cancers and cervical lymph node metastases from head and neck cancer.

II. Aetna considers hyperthermia experimental and investigational for all other indications including the following applications because of insufficient evidence regarding its effectiveness in these conditions:
   A. Deep hyperthermia alone or in combination with radiation therapy.
   B. Hyperthermic intrapleural chemotherapy for intrapleural mesothelioma.
   C. Hyperthermic administration of intraperitoneal chemotherapy for appendiceal carcinoma without pseudomyxoma, bladder cancer, clear cell carcinoma of the ovary, colon cancer, colorectal signet ring carcinoma, desmoplastic small round cell tumor, gastric cancer, goblet carcinoid tumor, hepatocellular carcinoma, ovarian cancer, pancreatic cancer, small bowel adenocarcinoma, thymic carcinoma, or uterine leiomyosarcoma.
   D. Regional hyperthermic melphalan perfusion in stage I, IIIB and IIIB extremity melanoma, as well as regional hyperthermic perfusion for extremity melanoma in conjunction with any other chemotherapy.
   E. Interstitial, intra-cavitary, and intraluminal hyperthermia.
   F. Whole body hyperthermia for testicular cancer and other indications.
G. Intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy (peritoneal carcinomatosis) for indications other than pseudomyxoma peritonei or peritoneal mesothelioma.

H. Regional hyperthermic perfusion for indications (e.g., non-small cell lung cancer) other than extremity melanoma.

I. Superficial hyperthermia for paranasal sinus and nasal cavity cancer.

J. Transrectal ultrasound hyperthermia for prostate cancer.

Note: Stages of melanoma (0 to IV) can be found in the following link: http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-staging

Background

Several studies support the hypothesis that hyperthermia appears to potentiate the tumoricidal effects of radiation therapy. Radiation therapy and hyperthermia probably act independently. Studies have suggested a potential synergistic response to radiation therapy and hyperthermia versus radiation therapy alone.

The goal of hyperthermia in cancer therapy is to produce tumor tissue temperatures above 41 to 42 degrees centigrade. Above this temperature, heat has a direct cytotoxic effect on both normal and tumor cells and also has a radiosensitizing effect by preventing repair of sublethal and potentially lethal radiation damage. Heat can also potentiate the cytotoxic effect of a variety of chemotherapeutic agents.

There are several different heating systems used. The 3 physical modalities employed for power deposition in local and regional clinical hyperthermia are (i) ultrasound, (ii) electromagnetic fields, and (iii) electromagnetic radiation. In addition, there are 3 methods of inducing hyperthermia interstitially: (i) radiofrequency needle electrodes, (ii) coaxial microwave antennas, and (iii) hot sources.

Hyperthermia has been shown to potentiate the effect of radiation therapy in the treatment of superficial lesions (less than 3 cm in depth). Clinical experience has largely been limited to treatment of recurrent, metastatic superficial melanomas, chest wall recurrence of breast cancer and cervical lymph node metastases from head and neck cancers. Tumor depth is a critical factor when combining radiation therapy and hyperthermia. Lesions less than 3 cm from the surface treated with radiation therapy and hyperthermia have been shown to have a significantly greater complete response rate compared to the complete response rate of lesions greater than 3 cm deep.

Guidelines on breast cancer from the National Comprehensive Cancer Network (NCCN, 2009) include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastases. The NCCN guidelines explain that there have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences (Vernon et al, 1996; Jones et al, 2005). The
NCCN guidelines state that, while there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone (Jones et al, 2005). However, no differences in overall survival have been demonstrated. The NCCN guidelines state that delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (e.g., the monitoring of temperatures and management of possible tissue burns). The NCCN Panel thus recommended the use of hyperthermia be limited to treatment centers with appropriate training, expertise and equipment. The NCCN guidelines noted that the addition of hyperthermia generated substantial discussion and controversy among the NCCN panel members and is a category 3 recommendation (the recommendation is based upon any level of evidence but reflects major disagreement). The NCCN's clinical practice guideline on melanoma (version 2.2013) recommends the use of hyperthermic perfusion/infusion with melphalan for "stage III in-transit" melanoma (category 2A recommendation).

The results of clinical studies combining hyperthermia and radiotherapy in the treatment of melanoma have been complex and somewhat conflicting (e.g., Shidnia et al, 1990; Engin et al, 1993; Overgaard et al, 1995). A randomized trial of radiotherapy with or without external hyperthermia was conducted by the European Society for Hyperthermic Oncology in 70 patients with metastatic or recurrent melanoma (Overgaard et al, 1995). The addition of hyperthermia to radiotherapy increased the complete response rate from 35% to 62%, and 2-year local control rates from 28% to 46%. However, only 14% of patients received the prescribed protocol treatment because of "equipment difficulties", and survival did not differ between the 2 groups.

Hyperthermia plus chemotherapy appears to result in increased cell toxicity due to net increase in DNA damage after exposure to hyperthermia and chemotherapy. Regional hyperthermic melphalan isolated limb perfusion for stage II and IIIA extremity melanoma has become routine practice. Isolated hyperthermic melphalan limb perfusion of stage II and IIIA extremity melanomas has been shown to be effective in prospective, randomized trials. Surgery plus regional hyperthermic melphalan perfusion versus surgery alone decreased recurrences and improved survival significantly in several randomized studies. Also, a comparison of responses after melphalan hyperthermic therapeutic limb perfusion versus melphalan normothermic limb perfusion for extremity melanoma showed a clear advantage in response rates. Although hyperthermic perfusion of stage IIIB and IIIB extremity melanoma shows a trend toward improvement in survival, well controlled trials will be necessary to document the effectiveness of this technique in node-positive patients. Similarly, while adjuvant treatment of stage I extremity melanoma shows a trend toward improved 5-year survival, well-controlled studies needed to confirm this observation.

Local or systemic hyperthermia alone has not been shown to be an effective cancer treatment. Although interstitial radiation-hyperthermia appears promising, well controlled trials comparing radiation therapy alone versus combined interstitial radiation-hyperthermia are needed. Whole body heating is a complex, labor-intensive technique that is difficult to accomplish and clinically impractical.
Emami et al (1996) reported on a randomized trial that found no benefit to interstitial radiation-hyperthermia in comparison with interstitial radiotherapy alone on tumor regression or control in accessible lesions. From January 1986 to June 1992, 184 patients with persistent or recurrent tumors after previous radiotherapy and/or surgery, which were amenable to interstitial radiotherapy, were accessioned to a protocol developed by the Radiation Therapy Oncology Group (RTOG). A total of 173 cases were analyzed (87 patients in the interstitial radiotherapy group and 86 in the interstitial radiation-hyperthermia arm). The investigators stated that the 2 arms were well-balanced regarding stratification criteria. Most tumors were in the head and neck (40 % in the interstitial radiation therapy group and 46 % in the interstitial radiation-hyperthermia group), and pelvis (42 % and 43 %, respectively). Eighty-four percent of patients in both arms had prior radiation therapy (40 Gy or more); 50 % and 40 %, respectively, had prior surgery, and 34 % in each arm had prior chemotherapy. The investigators said that the dose of radiation therapy administered was dependent on the previous radiation dose and did not exceed a total cumulative dose of 100 Gy.

Hyperthermia was delivered in 1 or 2 sessions, either before or before and after interstitial implant. According to the investigators, the intended goal of the hyperthermia was to maintain a minimal tumor temperature of 42.5 degrees C for 30 to 60 mins. The investigators reported that there was no difference in any of the study end points between the 2 arms. Complete response was 53 % and 55 % in both arms. Two-year survival was 34 % and 35 %, respectively. Complete response rate for persistent lesions was 69 % and 63 % in the 2 treatment arms as compared with 40 % and 48 % for recurrent lesions. The investigators reported that a set of minimal adequacy criteria for the delivery of hyperthermia was developed. When these criteria were applied, only 1 patient had an adequate hyperthermia session. Acute grade 3 and 4 toxicities were 12 % for interstitial radiation therapy and 22 % for interstitial radiation-hyperthermia therapy. The investigators reported that late grade 3 and 4 toxicities were 15 % for interstitial radiation therapy and 20 % for interstitial hyperthermia radiation therapy. The difference was not significant. The investigators concluded that interstitial hyperthermia, as applied in this randomized study, did not show any additional beneficial effects over interstitial radiotherapy alone. The investigators stated that delivery of hyperthermia remains a major obstacle (since only 1 patient met the basic minimum adequacy criteria as defined in this study). The investigators stated that the benefit of hyperthermia in addition to radiation therapy still remains to be proven in properly randomized prospective clinical trials after substantial technical improvements in heat delivery and dosimetry are achieved.

In a multi-institutional, prospective, randomized trial sponsored by the International Atomic Energy Agency, Mitsumori et al (2007) examined if the combination of hyperthermia (HT) and radiotherapy (RT) improves the local response rate of locally advanced non-small cell lung cancer (NSCLC) compared with that obtained by RT alone. A total of 80 patients with locally advanced NSCLC were randomized to receive either RT alone or radiation RT plus HT. The primary endpoint was the local response rate. The secondary endpoints were local progression-free survival (PFS) and overall survival (OS). The median follow-up period was 204 days for all patients and 450 days for surviving patients. There were no significant differences between the 2 arms with regard to local response rate (p = 0.49) or OS rate (p = 0.868). However, local PFS was significantly better...
in the RT plus HT arm (p = 0.036). Toxicity was generally mild and no grade 3 late toxicity was observed in either arm. The authors concluded that although improvement of local PFS was observed in the RT plus HT arm, this prospective randomized study failed to show any substantial benefit from the addition of HT to RT in the treatment of locally advanced NSCLC.

In a phase II clinical study, Maluta et al (2007) evaluated feasibility and results in terms of biochemical PFS, OS, and treatment toxicity profile of HT combined with RT in locally advanced high risk prostate cancer. A total of 144 patients with locally advanced prostate cancer (LAPC) were enrolled in this study. They were treated using conformal RT (CRT) plus local HT (LHT) and androgen suppression therapy (AST). Treatment modalities consisted of: (i) CRT with a mean dose of 74 Gy (2 Gy/fraction/5 fractions per week); (ii) LHT: 1 session per week during the 1st, 2nd, 3rd, and 4th week of the RT course; (iii) AST was administered as neoadjuvant and adjuvant therapy in more than 60 % of patients. The median follow-up time was 51.7 months. Four patients were lost at follow-up. Of 140 evaluated patients, 4 died because of inter-current diseases and 12 because of progression of disease. Patients were evaluated in terms of 5-year OS (87 %), and 5-year biochemical PFS (49 %). No significant side effects, except symptoms related to AST have been reported. No late grade 3 toxicity occurred. The authors concluded that in advanced high-risk prostatic cancer, HT is feasible and well-tolerated. It may be useful to enhance the RT efficacy at intermediate dose in order to avoid higher doses of irradiation which increases acute and late sequelae. The advantage of LHT combined with CRT should be confirmed by a randomized phase III trial, comparing irradiation plus AST with or without HT.

A number of studies have evaluated the use of hyperthermia combined with chemotherapy for cervical cancer. A multi-institutional prospective randomized controlled trial sponsored by the International Atomic Energy Agency found no benefit to radiotherapy in combination with regional hyperthermia over radiotherapy alone in rate of local control of cervical cancer (Vasanthan et al, 2005). A total of 110 patients with biopsy-proven, locally advanced cervical carcinoma were randomized to treatment by radiotherapy with or without hyperthermia. The patients were stratified by institution, stage, and histologic type. Each patient received external beam radiation therapy and brachytherapy. For the patients randomized to receive hyperthermia, a minimum of 5 sessions (60 mins each, once per week) were administered, employing a radiofrequency (RF) capacitive heating device. The median follow-up period was 466 days for all the patients and 512 days for the surviving patients. The authors stated that the 2 arms were well-balanced with regard to the patient factors, tumor factors, and treatment factors. The OS rate at 3 years was 73.2 %, and the local control rate was 68.5 %. There were no significant differences between the patients treated with or without hyperthermia, either with regard to the survival (p = 0.1893) or the rate of local control (p = 0.58). The authors reported that survival was significantly worse among the patients with stage IIb disease who received hyperthermia (p = 0.0162) although there was no difference in their rate of local control (p = 0.7988). The authors explained that further analysis is necessary to determine if the difference in survival is due to a greater incidence of distant metastases or some other cause. Acute grade 2 to 3 toxicity was seen in 10 of 55 patients (18 %) treated by hyperthermia and in 2 of 55 of the patients (4 %) treated without hyperthermia (p = 0.01). There authors reported that there was no significant
difference in the late toxicity observed in the 2 arms. The authors concluded that this prospective randomized study failed to show any benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced cervical cancer. The authors found that acute toxicity was significantly greater among the patients receiving hyperthermia, and the survival was significantly worse among the stage IIb patients receiving hyperthermia even though there was no difference in the local control rate.

In a phase II study, Richel et al (2004) examined the efficacy and toxicity of whole-body hyperthermia with carboplatin chemotherapy in persons with metastatic or recurrent cervical cancer. Twenty-one of 25 participants were evaluable for response: 1 complete remission, 6 partial responses, stable disease in 9 patients and progression in 5, leading to a response rate of 33%. The investigators reported that 3 of 4 evaluable chemotherapy pre-treated patients progressed, while this was seen in only 2 of 17 chemotherapy-naive patients. The median survival is 7.8 months (range of 1.3 to 43+) and no patients were lost to follow-up. The investigators reported that grades 3/4 toxicities were common: leukopenia in 35%, thrombopenia in 61% and anemia in 22% of all treatments. The investigators stated that excessive, partly reversible renal toxicity was seen in 2 patients (grades 3 and 4). The investigators concluded that the efficacy of whole body hyperthermia and carboplatin in recurrent and/or metastatic cervical cancer seems comparable to that of other palliative chemotherapy regimens in this disease. The investigators stated that the considerable toxicity, though largely manageable, includes unexpected and severe unacceptable renal toxicity, and that this regimen seems less suitable for palliative care.

The Dutch Deep Hyperthermia Trial showed that combining radiotherapy with hyperthermia improved local control rates and survival over radiotherapy alone in women with locally advanced cervical carcinoma (Van der Zee et al, 2000; Franckena et al, 2008). It is not known, however, whether radiotherapy and hyperthermia results in superior outcomes to radiotherapy and chemotherapy, which is the current standard of care for advanced cervical carcinoma. Franckena et al (2008) reported on the long-term results of the Dutch Deep Hyperthermia Trial after 12 years of follow-up. From 1990 to 1996, a total of 114 women with locoregionally advanced cervical carcinoma were randomly assigned to RT or RT+HT. The RT was applied to a median total dose of 68 Gy. The HT was given once-weekly. The primary end point was local control. Secondary end points were OS and late toxicity. At the 12-year follow-up, local control remained better in the RT+HT group (37% versus 56%; p = 0.01). The authors reported that survival was persistently better after 12 years: 20% (RT) and 37% (RT+HT; p = 0.03). Grade 3 or higher radiation-induced late toxicities were reported to be similar in both groups.

Harima et al (2001) reported on a small (n = 40) randomized controlled clinical trial of RT versus RT+HT in persons with advanced cervical carcinoma, and found improvements in response and 3-year local relapse-free survival with the addition of HT. A total of 40 patients with stage IIb cervical carcinoma were treated with external beam radiotherapy to the pelvis, combined with iridium 192 high-dose-rate intracavitary brachytherapy. Patients were randomly assigned to radiotherapy alone or radiotherapy plus 3 sessions of hyperthermia. The investigators reported that a complete response was achieved in 50% of patients treated with RT versus
80% in patients receiving radiotherapy plus hyperthermia. There was also a trend toward improvement in 3-year OS and disease-free survival (DFS) among patients who were treated with RT+HT (58.2% and 63.6%) versus RT alone (48.1% and 45%), but the differences were not statistically significant. The authors reported that the 3-year local relapse-free survival of the patients who were treated with RT+HT (79.7%) was significantly better than that of the patients treated with RT (48.5%) (p = 0.048). The authors noted that RT+HT did not significantly add to toxicity over RT alone.

Current guidelines recommend the use of chemotherapy plus radiotherapy for advanced cervical cancer (e.g., NCCN, 2009; NCI, 2008). Although it has been noted that the addition of hyperthermia to radiotherapy appears to improve response rates and 3-year survival by a magnitude similar to that observed in chemoradiotherapy studies in cervical cancer, Westermann et al (2005) has noted that the reported randomized clinical trial experience of chemotherapy studies (n = 2,192 patients) far exceeds that for radiation therapy plus hyperthermia (n = 154 patients). Ongoing studies are examining the potential benefits of adding hyperthermia to radiotherapy and chemotherapy in advanced cervical carcinoma (Westermann et al, 2005).

A number of studies have examined the use of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy as a treatment for pseudomyxoma peritonei, a rare cancer arising from low-grade adenocarcinomas of appendiceal, ovarian, or peritoneal origin. Reported outcomes of cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for this rare condition are markedly superior to that reported for cytoreduction alone and other conventional treatments for this condition (Sugarbaker and Chang, 1999; Stewart et al, 2005; Elias et al, 2008).

Although some authorities (Esquivel et al, 2007) have recommended use of HIPEC for patients with recurrent and/or metastatic colon cancer with peritoneal involvement, this recommendation is based upon uncontrolled studies. There are a lack of phase III studies demonstrating improved outcomes with the use of hyperthermia compared to non-hyperthermic administration. The sole randomized controlled clinical trial randomly assigned 105 patients with peritoneal carcinomatosis from appendiceal (n = 18) or colorectal (n = 87) cancer to either standard treatment with systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery, or aggressive cytoreduction (debulking) and hyperthermic intraperitoneal chemotherapy followed by the same systemic chemotherapy regime (Verwaal et al, 2003). After a median follow-up period of 22 months, the median survival was 12.6 months in the standard therapy arm and 22 months in the hyperthermic intraperitoneal chemotherapy arm. The study has been criticized because the HIPEC group differed from the standard therapy group not only in the use of intraperitoneal hyperthermic chemotherapy, but also in surgical debulking. It is possible that the important treatment was the surgical debulking, and the HIPEC made little difference.

Guidelines from the National Comprehensive Cancer Network (2009) state that the NCCN colon cancer guidelines panel considers the treatment of disseminated carcinomatosis with cytoreductive surgery (i.e., peritoneal stripping surgery) and
peri-operative HIPEC to be investigational and does not endorse such therapy outside of a clinical trial.

Minicozzi and co-workers (2008) estimated the post-operative morbidity and mortality and short-term outcome of treatment of the peritoneal carcinomatosis (PC) by CRS and HIPEC. A total of 24 patients with PC or positive cytology at peritoneal washing were treated. Primary tumor was ovarian carcinoma in 10 patients: 4 cases presented peritoneal surface malignancies (PSM) after any time from hysteroadnexectomy related to primary tumor, 6 cases synchronous PSM. Primary tumor was gastric cancer in 7 patients: the peritoneal washing was positive in 4 cases and, during follow-up following gastrectomy, another 2 cases presented PSM. One patient was previously treated with ovariectomy for ovarian mass that resulted a Krukenberg's tumor of gastric cancer. Primary tumor was pseudomixoma peritonei (PMP) in 4 patients; CRS and HIPEC was performed as 1st-line therapy in only 1 patient. Three patients were previously treated for colon carcinoma; HIPEC was performed via the abdomino-pelvic cavity for 60 mins using a closed abdomen technique. The drugs used were mitomycin C (3.3 mg/m2/L) and cisplatin (25 mg/m2/L). The intra-cavitary mean temperature was 41.8 degrees C. The mean peritoneal cancer index was 14. Post-operative major complications occurred in 7 cases (28 %), post-operative minor complications occurred in 8 cases (32 %). No patients died in the post-operative period. Mean hospital stay was 11.5 days (6 to 35 days). After a median follow-up of 8 months (range of 2 to 34), 14 (58 %) patients were alive and 13 were disease-free. The authors concluded that these findings are consistent with other studies for the high rate of post-operative morbidity associated with treatment, but they achieved best results on mortality and post-operative hospital stay. The authors concluded that CRS associated with HIPEC is a good therapeutic option especially in ovarian-related carcinoma and PMP.

Scaringi et al (2008) evaluated the role of HIPEC, associated or not to CRS in the treatment of different stages of advanced gastric cancer (AGC). A total of 37 patients with AGC who underwent 43 HIPEC were included in this study. Hyperthermic intraperitoneal chemotherapy used mitomycin-C and cisplatin for 60 to 90 mins at 41 to 43 degrees C intra-abdominal temperature. The main endpoints were long-term survivals, morbidity and mortality rates. Eleven patients had no demonstrable sign of PC and constituted the prophylactic-group, while 26 patients had macroscopic PC (PC-group). Five patients were Gilly 1 or 2 (nodules less than 0.5 cm) and 21 Gilly 3 or 4 (nodules greater than or equal to 0.5 cm). In the PC-group a complete curative CRS was achieved before HIPEC in 8 (PC-curative subgroup) and a palliative HIPEC in 18 patients (PC-palliative subgroup). The overall 30-days mortality was 5 % (2 patients). Two patients in the prophylactic group died within 6 months after hospital discharge (overall mortality 11 %). The estimated risk of death per procedure was 9 %. Ten patients (27 %) presented 1 or more complications. The median survival was 23.4 months in the prophylactic group, and 6.6 months in the PC-group (p < 0.05). The median survival in the PC-curative subgroup was 15 versus 3.9 months in the PC-palliative subgroup (p = 0.007). The median survival according to Gilly classification was significantly different (Gilly 1 and 2 versus Gilly 3 and 4, 15 versus 4 months, respectively, p = 0.014). The global recurrence rates between the prophylactic group and the PC-curative subgroup at 2 years were 36 % versus 50 %, respectively. The median delay to recurrence was 18.5 versus 9.7 months,
respective. The authors concluded that HIPEC might be useful to improve the survival in selected patients with AGC only when a complete CRS can be achieved. Despite encouraging data, prospective studies, based on larger cohorts of patients are needed to evaluate the role of this procedure as a prophylactic treatment in patients with AGC.

Spiliotis et al (2008) reported their experience in the combined treatment of PC using CRS plus HIPEC. This prospective study included patients with PC from gynecological, gastric and colon cancer, treated in 2 centers. Cytoreductive surgery included the peritoneectomy procedures described by Jacquet and Sugarbaker as well as multi-visceral resections in order to achieve a complete macroscopical cancer eradication. The HIPEC that followed was performed via the open abdomen technique. A total of 24 patients (3 men and 21 women, mean age of 60 years) were treated. Twelve patients had PC from ovarian cancer, 7 from colon, 3 from gastric and 2 from uterine cancer. The mean duration of the procedure was 7.83 hours (range of 5 to 12.30). Macroskopically, complete cytoreduction (CC) was achieved in 18 (75 %) patients. Two (8.3 %) patients died in the first 30 days. The overall morbidity was 42 % and 2 patients were re-operated. The mean follow-up was 22 months (range of 3 to 36). The overall 1-year survival was 59.1 %; concerning the gynecological cancers it was 53.8 % (mean survival of 11.7 months) and for gastrointestinal cancers it was 44.4 % (mean survival of 9.5 months). The authors concluded that their findings suggested that the combined treatment of CRS plus HIPEC for PC is associated with acceptable mortality and morbidity and offers an improved survival in these patients.

Di Giorgio et al (2008) examined the use of CRS (peritoneectomy procedures) combined with HIPEC in the treatment of diffuse PC from ovarian cancer. A total of 47 patients with primary advanced or recurrent ovarian cancer and diffuse PC were enrolled; 22 underwent primary and 25 secondary CRS plus immediate HIPEC followed by systemic chemotherapy. The overall mean Sugarbaker peritoneal cancer index was 14.9 (range of 6 to 28). A mean of 6 surgical procedures were required per patient (range of 4 to 10). In 87.3 % of the patients debulking achieved optimal cytoreduction (Sugarbaker completeness of cytoreduction [CC] score 0 to 1), whereas in 12.7 % it left macroscopic residual disease (CC-2 or CC-3). Major complications developed in 21.3 % of the patients and the in-hospital mortality rate was 4.2 %. The mean OS was 30.4 months, median survival was 24 months, and mean DFS was 27.4 months. Five-year survival was 16.7 %. Uni-variate (log-rank test and analysis of variance) and multi-variate analyses (Cox proportional-hazard model) identified the CC score as the main factor capable of independently influencing survival. The authors concluded that peritoneectomy procedures combined with HIPEC offer promising long-term survival in patients with diffuse peritoneal ovarian carcinomatosis. They achieved high adequate primary and secondary surgical cytoreduction rates with acceptable morbidity and mortality.

Verwaal et al (2008) noted that the treatment of PC is based on CRS followed by HIPEC and combined with adjuvant chemotherapy. In 2003, a randomized trial was finished comparing systemic chemotherapy alone with CRS followed by HIPEC and systemic chemotherapy. This trial showed a positive result favoring the studied treatment; and has now been updated to a minimal follow-up of 6
years to show long-term results. For all patients still alive, the follow-up was updated until 2007. In the original study, 4 patients were excluded -- 2 because of no eligible histology/pathology and 2 because of major protocol violations. After randomization, 4 patients in the HIPEC arm and 6 in the control arm were not treated using the intended therapy, 1 patient because of withdrawal, 1 because of a life-threatening other malignant disease and the others because of progressive disease before initiation of the treatment. During the follow-up, 1 patient was crossed-over from the control arm and underwent CRS and HIPEC for recurrent disease, after the assigned treatment was completed. The data from these patients were censored at the moment of the cross-over. Progression-free and disease-specific survival were analyzed using the Kaplan Meyer test and compared using the log rank method. The long-term results were studied in more detail to evaluate efficacy and toxicity. At the time of this update, the median follow-up was almost 8 years (range of 72 to 115 months). In the standard arm, 4 patients were still alive, 2 with and 2 without disease; in the HIPEC arm, 5 patients were still alive, 2 with and 3 without disease. The median PFS was 7.7 months in the control arm and 12.6 months in the HIPEC arm (p = 0.020). The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm (p = 0.028). The 5-year survival was 45 % for those patients in whom a R1 resection was achieved. The authors concluded that with 90 % of all events having taken place up to this time, this randomized trial shows that CRS followed by HIPEC does significantly add survival time to patients affected by PC of colorectal origin. For a selected group, there is a possibility of long-term survival.

Elias and colleagues (2009) compared the long-term survival of patients with isolated and resectable PC in comparable groups of patients treated with systemic chemotherapy containing oxaliplatin or irinotecan or by CRS plus HIPEC. All patients with gross PC from colorectal adenocarcinoma who had undergone CRS plus HIPEC were evaluated. The standard group was constituted by selecting patients with colorectal PC treated with palliative chemotherapy during the same period, but who had not benefited from HIPEC because the technique was unavailable in the center at that time. A total of 48 patients were retrospectively included in the standard group and were compared with 48 patients who had undergone HIPEC and were evaluated prospectively. All characteristics were comparable except age and tumor differentiation. There was no difference in systemic chemotherapy, with a mean of 2.3 lines per patient. Median follow-up was 95.7 months in the standard group versus 63 months in the HIPEC group. Two-year and 5-year overall survival rates were 81 % and 51 % for the HIPEC group, respectively, and 65 % and 13 % for the standard group, respectively.

Median survival was 23.9 months in the standard group versus 62.7 months in the HIPEC group (p < 0.05, log-rank test). The authors concluded that patients with isolated, resectable PC achieve a median survival of 24 months with modern chemotherapies, but only CRS plus HIPEC is able to prolong median survival to roughly 63 months, with a 5-year survival rate of 51 %.

In a phase II clinical study, Lim et al (2009) evaluated the toxicities and treatment response of intra-operative HIPEC in patients with advanced epithelial ovarian cancer. Intra-operative HIPEC (cisplatin 75 mg/m(2), 41.5 degrees C, 90 mins) was performed in 30 patients with residual tumor of less than 1 cm after CRS between January 2007 and February 2008. All the patients received adjuvant
chemotherapy with combination platinum and taxane. Adverse events and responses to primary treatment were evaluated and scored as follows: grade I, observation; grade II, medical treatment; grade III, intervention; and grade IV, re-operation or admission to the intensive care unit. No deaths or grade IV morbidities were observed. A total of 107 adverse events were identified in 30 patients (grade I, 40; grade II, 46; grade III, 21). The most common adverse events affected the hematological system (n = 26), followed by the gastrointestinal system (n = 23). Most adverse events were anemias requiring transfusion and nausea/vomiting requiring medication. Twenty-eight patients (93%) experienced complete remission, and 2 patients (7%) had progressive disease. The authors concluded that HIPEC after extensive CRS for ovarian cancer is a procedure with acceptable morbidity that patients can tolerate. They stated that more follow-up is needed to determine the effect of HIPEC on survival.

In a review on ovarian cancer, Hennessy and colleagues (2009) stated that early data suggested that HIPEC is promising, but this treatment is still highly investigational. Furthermore, Ferron et al (2009) noted that scientific evidence on the use of HIPEC for ovarian cancer remains poor. Much more research is still needed to elucidate unanswered questions. Before this technique can be routinely used, some controversial aspects have to be defined: (i) which drug is the best to deliver and at what temperature, (ii) is it necessary to use mono- or poly-chemotherapy regimens, (iii) which is the time-point for HIPEC in the natural history of ovarian cancer: at front-line therapy, at interval debulking following initial neo-adjuvant chemotherapy, at consolidation following front-line therapy, or at the time of recurrence. Chua and colleagues (2009) stated that a randomized trial is needed to establish the role of HIPEC in ovarian cancer.

There is some evidence that cytoreductive surgery with intra-operative chemotherapy and hyperthermia may be of help in some individuals with peritoneal mesothelioma, which is a rare disease, but increasing in frequency. The incidence is about 1 per 1,000,000 and approximately 1/5 to 1/3 of all mesotheliomas are peritoneal. Because of its unusual nature, the disease has not been clearly defined either in terms of its natural history, diagnosis, or management.

Sebbag et al (2000) discussed results of treatment of 33 patients (10 women and 23 men) with peritoneal mesothelioma. Patients were treated by a uniform strategy involving CRS with peritonectomy procedures and peri-operative intraperitoneal chemotherapy (cisplatin, doxorubicin). Median survival was 31.0 months; overall projected survival at 3 years was 56%. The most significant positive predictive factors of survival were: female sex (p = 0.003), low prior surgical score (p = 0.002), completeness of cytoreduction (p = 0.0002) and second-look surgery (p = 0.019). The morbidity rate for this combined treatment was 33% and the peri-operative mortality rate was 3%. These investigators concluded that although peritoneal mesothelioma is rare, progress in its management has occurred. Survival has been extended and selection factors by which patients may be allocated to aggressive management strategies have been defined.

Sugarbaker et al (2002) reviewed a single institution's experience with 51 patients prospectively treated over the past decade with increasingly aggressive local/regional protocols. Peritoneal mesothelioma patients generally present with
2 types of symptoms and signs: (i) those with abdominal pain, usually localized and related to a dominant tumor mass with little or no ascites, and (ii) those without abdominal pain, but with ascites and abdominal distention. Pathologically, a positive immunostain for calretinin has markedly increased the accuracy of diagnosis. Prognosis as determined by clinical presentation, the completeness of cytoreduction, and gender (females survive longer than males) appears to be improved by the use of intraperitoneal chemotherapy. Over the past decade, the management of these patients has evolved similarly to ovarian cancer treatment and now involves CRS, heated intraoperative intraperitoneal chemotherapy (HIIC) with cisplatin and doxorubicin, and early post-operative intraperitoneal paclitaxel. These perioperative treatments are followed by adjuvant intraperitoneal paclitaxel and second-look cytoreduction. Prolonged DFS and reduced adverse symptoms with the current management strategy are documented by a high complete response rate as assessed by a negative second-look. This multi-modality treatment approach with cytoreductive surgery and intraperitoneal chemotherapy has resulted in a median survival of 50 to 60 months. Peritoneal mesothelioma is an orphan disease that is treatable with expectations for “potential” cure in a small number of patients if diagnosed and treated early with definitive local/regional treatments. A prolonged high quality of life is possible in the majority of patients.

Sethna et al (2003) described their experience with 5 cases (4 females and 1 male) of cystic peritoneal mesothelioma. All of these patients were treated with CRS and peritonectomy procedures and HIIC. The authors concluded that cystic peritoneal mesothelioma should no longer be referred to as “benign” cystic mesothelioma. An aggressive approach with complete disease eradication is the correct goal of treatment. From the authors’ experience, CRS to remove all visible tumor and intraperitoneal chemotherapy to control microscopic residual disease will help patients with peritoneal cystic mesothelioma to remain symptom- and disease-free over an extended time period with a single surgical intervention. Disease eradication may prevent the transition to an aggressive and fatal disease process.

Diffuse malignant peritoneal mesothelioma (DMPM) is a subset of peritoneal mesothelioma with a poor clinical outcome. Deraco et al (2006) performed a prognostic analysis in a cohort of DMPM patients treated homogeneously by CRS and intraperitoneal hyperthermic perfusion (IPHP). A total of 49 DMPM patients who underwent 52 consecutive procedures were enrolled onto the study. Cytoreductive surgery was performed according to the peritonectomy technique, and the IPHP was performed with cisplatin plus doxorubicin or cisplatin plus mitomycin C. These investigators evaluated the correlation of the clinicopathologic variables (previous surgical score, age, sex, performance status, previous systemic chemotherapy, carcinomatosis extension, completeness of cytoreduction, IPHP drug schedule, mitotic count [MC], nuclear grade, and biological markers [epidermal growth factor receptor, p16, matrix metalloproteinase 2 and matrix metalloproteinase 9]) with overall and progression-free survival. The mean age was 52 years (range of 22 to 74 years). The mean follow-up was 20.3 months (range of 1 to 89 months). Regarding the biological markers, the rates of immunoreactivity of epidermal growth factor receptor, p16, matrix metalloproteinase 2, and matrix metalloproteinase 9 were 94 %, 60 %, 100 %, and 85 %, respectively. The strongest factors influencing OS were completeness of cytoreduction and MC, whereas those for PFS were performance...
status and MC. No biological markers were shown to be of prognostic value. The authors concluded that completeness of cytoreduction, performance status, and MC seem to be the best determinants of outcome. These data warrant confirmation by a further prospective formal trial. No biological markers presented a significant correlation with the outcome. The over-expression of epidermal growth factor receptor, matrix metalloproteinase 2, and matrix metalloproteinase 9 and absent or reduced expression of p16 might be related to the underlying tumor kinetics of DMPM and warrant further investigation with other methods.

Kusamura et al (2006) analyzed morbidity and mortality of CRS and IPHP in the treatment of peritoneal surface malignancies. A total of 205 patients (50 with peritoneal mesothelioma, 49 with pseudomyxoma peritonei, 41 with ovarian cancer, 32 with abdominal sarcomatosis, 13 with colon cancer, 12 with gastric cancer, and 8 with carcinomatosis from other origins) underwent 209 consecutive procedures. Four patients underwent the intervention twice because of disease relapse. There were 70 men and 135 women. Mean age was 52 years (range of 22 to 76 years). Cytoreductive surgery was performed by using peritonectomy procedures; IPHP through the closed abdomen technique was conducted with a pre-heated (42.5 degrees C) perfusate containing cisplatin + mitomycin C or cisplatin + doxorubicin. Major morbidity rate was 12 %. The most significant complications were 23 anastomotic leaks or bowel perforations, 4 abdominal bleeds, and 4 sepses. Operative mortality rate was 0.9 %. On logistic regression model multi-variate analysis, extent of cytoreduction (odds ratio [OR], 2.88; 95 % confidence interval [CI]: 1.29 to 6.40) and dose of cisplatin for IPHP greater than or equal to 240 mg (OR, 3.13; 95 % CI: 1.24 to 7.90) were independent risk factors for major morbidity. Ten patients presented with grade 3 to 4 toxicity. The authors concluded that CRS + IPHP presented acceptable morbidity, toxicity, and mortality rates, all of which support prospective phase III clinical trials.

According to the National Cancer Institute's guideline on the treatment of malignant mesothelioma (2009), "[i]ntrapleural or intraperitoneal administration of chemotherapeutic agents (e.g., cisplatin, mitomycin, and cytarabine) has been reported to produce transient reduction in the size of tumor masses and temporary control of effusions in small clinical studies. Additional studies are needed to define the role of intracavitary therapy". Furthermore, although the NCCN guidelines on malignant pleural mesothelioma (2011) recommend cisplatin as a 1st-line drug for inoperable mesothelioma, there is no recommendation for either hyperthermic or intrapleural administration.

Baratti et al (2010) noted that unlike novel molecular-targeted therapies for metastatic gastrointestinal stromal tumors (GIST), conventional treatments for peritoneal sarcomatosis (PS) are mostly ineffective. As with carcinomatosis of epithelial origin, a rationale base supports an aggressive loco-regional treatment of PS, but the use of CRS and HIPEC in this setting is still controversial. These researchers assessed the outcome of clinically and pathologically homogeneous subsets of patients with PS uniformly treated by CRS and HIPEC. A prospective database of 37 patients who underwent CRS and close-abdomen HIPEC with cisplatin and doxorubicin or mitomycin-C was reviewed. PS originated from GIST (pre-imatinib era) in 8 patients, uterine leiomyosarcoma (ULS) in 11, retroperitoneal liposarcoma (RPLP) in 13, and other sarcoma in 5. Cytoreductive surgery was macroscopically complete in 28 patients (75.7 %). Operative
mortality was 3.7 % and morbidity 21.6 %. After median follow-up of 104 (range of 1 to 131) months, peritoneal disease progression occurred in 16 patients, distant metastases in 5, and both in 13. For all patients, median OS was 26.2 months; 7 patients were alive at 46 to 130 months (ULS, n = 4; RPLP, n = 2; GIST, n = 1). Retroperitoneal liposarcoma had the best OS (median of 34 months) but 100 % peritoneal relapse; GIST had dismal overall, local-regional-free and distant-free survival; ULS had the higher proportion of long survivors and best local-regional-free survival. The authors concluded that overall, results of CRS and HIPEC did not compare favorably to those of conventional therapy. In a subgroup analysis, the combined approach did not change GIST and RPLS natural history. The interesting results with ULS may warrant further investigations.

Esquivel et al (2011) noted that CRS and HIPEC are being widely used in the treatment of patients with peritoneal surface malignancies. The open procedure has been associated with high grade III and IV morbidity and prolonged hospitalization. In this study, these researchers evaluated laparoscopic CRS and HIPEC in patients with limited peritoneal surface malignancies. Patients with peritoneal surface malignancies and no gross evidence of carcinomatosis on the computed tomographic scan were enrolled to undergo laparoscopic CRS and HIPEC. They aimed to assess the feasibility, safety, and outcome of this procedure. Post-operative complications were reported according to the National Cancer Institute Common Toxicity Criteria. From October 2008 to January 2010, a total of 14 patients were enrolled into the protocol. Of the 14 patients, 1 patient was found with extensive carcinomatosis at the time of laparoscopy and had no surgical procedure; 13 patients had a complete cytoreduction and HIPEC, 10 (77 %) laparoscopically and 3 (23 %) were converted to an open procedure. There was 1 grade 3 morbidity (10 %) and 1 patient (10 %) in the laparoscopy group experienced a grade 4 complication, needing a re-operation for an internal hernia. Mean length of hospital stay was 6 days for those completed laparoscopically, 8 days for those converted to an open procedure and 8 days for a matched cohort of patients with an upfront open procedure. The authors concluded that this initial investigative stage demonstrated the feasibility and safety of CRS and HIPEC via the laparoscopic route in selected patients with low-tumor volume and no small bowel involvement mainly from appendiceal malignancies. They stated that longer follow-up and additional studies are needed to evaluate its long-term effectiveness.

In a systematic review, Lammers et al (2011) evaluate the effectiveness of chemohyperthermia (C-HT) as a treatment for non-muscle-invasive bladder cancer (NMIBC). The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken. Relevant conference abstracts and urology journals were also searched manually. Two reviewers independently reviewed candidate studies for eligibility and abstracted data from studies that met inclusion criteria. The primary end-point was time to recurrence. Secondary endpoints included time to progression, bladder preservation rate, and adverse event (AE) rate. A total of 22 studies met inclusion criteria and underwent data extraction. When possible, data were combined using random effects meta-analytic techniques. Recurrence was seen 59 % less after C-HT than after mitomycin C (MMC) alone. Due to short follow-up, no conclusions can be drawn.
about time to recurrence and progression. The overall bladder preservation rate after C-HT was 87.6%. This rate appeared higher than after MMC alone, but valid comparison studies were lacking. Adverse events were higher with C-HT than with MMC alone, but this difference was not statistically significant. The authors concluded that published data suggested a 59% relative reduction in NMIBC recurrence when C-HT is compared with MMC alone. Chemohyperthermia also appears to improve bladder preservation rate. However, due to a limited number of randomized trials and to heterogeneity in study design, definitive conclusions cannot be drawn. In the future, C-HT may become standard therapy for high-risk patients with recurrent tumors, for patients who are unsuitable for radical cystectomy, and in cases for which bacillus Calmette-Guérin treatment is contraindicated.

Hurwitz et al (2011) presented long-term results from a phase II study that evaluated the effectiveness of transrectal ultrasound hyperthermia plus radiation with or without androgen suppression for the treatment of locally advanced prostate cancer. Patients with clinical T2b-T3bN0M0 disease (according to 1992 American Joint Committee on Cancer [AJCC] criteria) received radiation plus 2 transrectal ultrasound hyperthermia treatments. After the first 4 patients, 6 months of androgen suppression were allowed. The study was designed to assess absolute improvement in the 2-year disease-free survival rate compared with the short-term androgen suppression arm in Radiation Therapy Oncology Group (RTOG) study 92-02. A total of 37 patients received a total of 72 hyperthermia treatments. The mean cumulative equivalent minutes (CEM) Temp = 43°C was 8.4 minutes. According to the 1992 AJCC classification, there were 19 patients with T2b tumors, 8 patients with T2c tumors, 5 patients with T3a tumors, and 5 patients with T3b tumors. The median Gleason score was 7 (range of 6 to 9), and the median prostate-specific antigen (PSA) level was 13.3 ng/ml (range of 2 to 65 ng/ml). Thirty-three patients received androgen suppression. At a median follow-up of 70 months (range of 18 to 110 months), the 7-year OS rate was 94%, and 61% of patients remained failure free (according to the American Society for Therapeutic Radiology and Oncology definition for failure free survival). The absolute rate of DFS at 2 years, which was the primary study end-point, improved significantly (84%) compared with a rate of 64% for similar patients on the 4-month androgen suppression arm of RTOG 92-02. When Phoenix criteria (PSA nadir + 2 ng/ml) were used to define biochemical failure, 89% of patients were failure-free at 2 years. The authors concluded that hyperthermia combined with radiation for the treatment of locally advanced prostate cancer appeared to be promising. The current results indicated that further study of hyperthermia for the treatment of prostate cancer with optimal radiation and systemic therapy is warranted.

Suzuki et al (2000) noted that since clear cell carcinoma of the ovary does not respond to conventional platinum-based chemotherapy, the prognosis of recurrent tumors is especially poor. In a 51-year-old female who underwent surgery for clear cell carcinoma of the ovary, a solitary metastatic carcinoma developed in the pelvic cavity 7 months after the initial surgery. The patient underwent a whole pelvic irradiation at a total dose of 65 Gy combined with hyperthermia. Complete remission was achieved 46 months after treatment. A study using gynecologic carcinoma cell lines showed that the mean 50% growth inhibitory dose of radiation was 1.2 +/- 0.4 Gy in several clear cell carcinoma cell lines. The value
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did not significantly differ from those for serous carcinoma cell lines (2.3 +/- 1.2 Gy) and uterine cervical carcinoma cell lines (1.6 +/- 0.4 Gy). The authors stated that currently, no anti-cancer agents are effective for clear cell carcinoma; radiotherapy combined with hyperthermia may be effective for localized tumors.

Desmoplastic small round cell tumor (DSRCT) is a rare intra-abdominal mesenchymal tissue neoplasm in young patients and spreads through the abdominal cavity. Desmoplastic small round cell tumor usually presents with diffuse abdominal metastatic disease similar in gross appearance to carcinomatosis. To date, very aggressive treatment programs have yielded dismal outcomes.

Msiaka et al (2010) stated that prognosis of DSRCT is poor despite a multi-modal therapy including chemotherapy, radiotherapy, and surgical cytoreduction. Hyperthermic intra-peritoneal chemotherapy is considered as an additional strategy in the treatment of peritoneal carcinomatosis; for this reason, these investigators planned to treat selected cases of children with DRSCT using surgical cytoreduction and HIPEC. Peritoneal disease extension was evaluated according to Gilly classification. Surgical cytoreduction was considered as completeness of cytoreduction -- stage 0 of Gilly classification (no macroscopic disease); HIPEC was performed according to the open technique. These researchers described 3 cases: the 2 first cases were realized for palliative conditions and the last one was operated on with curative intent. There was no post-operative mortality. One patient was re-operated for a gallbladder perforation. There was no other complication related to HIPEC procedure. The authors concluded that surgical cytoreduction and HIPEC provide a local alternative approach to systemic chemotherapy in the control of microscopic peritoneal disease in DRSCT, with an acceptable morbidity, and may be considered as a potential beneficial adjuvant waiting for a more specific targeted therapy against the fusion protein.

In a review on “Desmoplastic small round cell tumor: Current management and recent findings”, Dufrene et al (2012) states that “Overall, data supporting the use of HIPEC in patients with DSRCT is limited and this technique is not recommended for the management of patients with DSRCT outside clinical trials”.

National Comprehensive Cancer Network clinical practice guideline on “Non-small cell lung cancer” (NCCN, 2013) does not mention the use of hyperthermia as a therapeutic option.

Mi and colleagues (2013) stated that adjuvant intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) is a therapy that combines thermochemotherapy and intraperitoneal chemotherapy. It is theoretically powerful for patients with advanced gastric cancer (AGC), but there is no evident advantage in clinical practice. These researchers performed a meta-analysis to evaluate the safety and effectiveness of adjuvant IHIC inpatients with resectable locally AGC, and provided the reference for clinical practice and study. These investigators searched the Cochrane Library, PubMed, Embase, Web of Science and Chinese databases (Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wanfang) electronically and also retrieved papers from other sources (tracing related references and communication with other authors). All relevant randomized controlled trials (RCTs) were collected to
compare surgery combined with IHIC to surgery without IHIC for AGC. There were no language restrictions. After independent quality assessment and data extraction by 2 reviewers, meta-analysis was conducted by RevMan 5.1 software. A total of 16 RCTs involving 1,906 patients were included. Compared with surgery alone, combination therapy (surgery plus IHIC) was associated with a significant improvement in survival rate at 1 year (hazard ratio (HR) = 2.99; 95% CI: 2.21 to 4.05; p < 0.00001), 2 years (HR = 2.43; 95% CI: 1.81 to 3.26; p < 0.00001), 3 years (HR = 2.63; 95% CI: 2.17 to 3.20; p < 0.00001), 5 years (HR = 2.49; 95% CI: 1.97 to 3.14; p < 0.00001), and 9 years (HR = 2.14; 95% CI: 1.38 to 3.32; p = 0.0007). Compared with surgery alone, combination therapy was associated with a significant reduction in recurrence rate at 2 years (RR = 0.42; 95% CI: 0.29 to 0.61; p < 0.00001), 3 years (RR = 0.35; 95% CI: 0.24 to 0.51; p < 0.00001) and 5 years (RR = 0.47; 95% CI: 0.39 to 0.56; p < 0.00001).

Intraoperative hyperthermic intraperitoneal chemotherapy was not found to be associated with higher risks of anastomotic leakage, ileus, bowel perforation, myelosuppression, GI reaction and hypoglycemia, but it increased the incidence of abdominal pain (RR = 21.46; 95% CI: 5.24 to 87.78; p < 0.00001). The authors concluded that compared with surgery alone, surgery combined with IHIC can improve survival rate and reduce the recurrence rate, with acceptable safety. However, they stated that safety outcomes should be further evaluated by larger samples and high quality studies. Furthermore, these investigators stated that hyperthermia for intraperitoneal chemotherapy needs more clinical research.

Furthermore, the NCCN clinical practice guideline on “Gastric cancer” (Version 2.2013) does not mention the use of hyperthermic intraperitoneal chemotherapy as a therapeutic option.

National Comprehensive Cancer Network's clinical practice guideline on “Pancreatic adenocarcinoma” (Version 1.2014) does not mention the use of hyperthermic intraperitoneal chemotherapy as a therapeutic option.

Tejani et al (2014) stated that treatment of advanced appendiceal adenocarcinoma at NCCN's member institutions commonly incorporates agents used for colorectal cancer. Guidelines from the NCCN stated that small bowel and appendiceal carcinoma may be treated with systemic chemotherapy according to the NCCN guidelines for colon cancer (Version 2.2015), which states that "the panel considers the treatment of disseminated carcinomatosis with cytotoxic chemotherapy and HIPEC to be investigational and does not endorse this therapy outside of a clinical trial".

Signet ring cell carcinoma (SRCC) is a diffuse type of adenocarcinoma found most often in the glandular cells of the stomach. van Oudheusden et al (2015) noted that SRCC patients have a poor oncologic outcome. These researchers examined if the potential drawbacks of HIPEC outweigh the benefits in patients with peritoneally metastasized SRCC. Patients with PC of colorectal origin referred to 2 tertiary centers between April 2005 and December 2013 were identified and retrospectively analyzed. Data were compared between SRCC histology and other differentiations. A total of 351 patients were referred for CRS + HIPEC among which 20 (5.7%) patients were identified with SRCC histology. CRS + HIPEC was performed in 16 of these 20 (80%) and 252 out of the 331 remaining patients (76.1%). A higher proportion of patients in the SRCC-group were
diagnosed with N2 stage (62.5 % versus 36.1 %, p = 0.04). A macroscopic complete resection was achieved in 87.5 % and 97.2 %, respectively (p = 0.04). Median survival was 14.1 months compared to 35.1 months (p < 0.01). Recurrence occurred in 68.8 % of the SRCC patients and in 43.7 % of the other histology patients (p = 0.05). The authors concluded that patients with SRCC and PC treated with CRS + HIPEC have a poor median survival only slightly reaching over 1 year. In the presence of other relative contraindications, SRCC histology should refrain a surgeon from performing CRS and HIPEC.

Furthermore, NCCN’s clinical practice guideline on “Gastric cancer” (Version 1.2015) does not mention HIPEC as a therapeutic option.

A recent review by Elias et al (2014a) stated that HIPEC for neuroendocrine tumors (NETs) is in the investigational stage. Furthermore, Elias et al (2014b) compared the results of complete cytoreductive surgery (CCRS) of peritoneal metastases from NET with and without HIPEC and reported that they were not able to determine whether HIPEC had a positive or negative impact on outcomes.

Guidelines from the National Cancer Institute on “Gastrointestinal Carcinoid Tumors Treatment (PDQ®)” (2014) have no recommendation for HIPEC. Also, NCCN’s guideline on NETs (Version 1.2015) has no recommendations for the use of HIPEC for carcinoid tumors.

Tabrizian et al (2014) presented a series of patients with peritoneal hepatocellular carcinoma (HCC) treated with CRS +/- HIPEC and evaluated their clinicopathologic characteristics and outcomes. Between 07/2007 to 08/2012, 14 patients with limited disease to the peritoneum underwent CRS; 7 of these patients received additional HIPEC treatment. Primary end-point was OS. Operative treatment was directed for metachronous peritoneal disease in the majority (92.8 %) of patients. Mean intra-operative PCI was 9.9 (± 8.3) and complete macroscopic cytoreduction (CCR 0-1) was achieved in all but 1 case. Overall major morbidity rate (Clavien-Dindo III-IV) at 30 days was 7.1 %. One post-operative death occurred in a patient with extensive tumor burden (PCI = 33, CCR2). Median follow-up after initial surgery was 43.8 months and the median time to metachronous peritoneal recurrence was 23 months. Three-year recurrence rate after peritoneal resection was 100 %. Median survival of the cohort CCR0-1 was 35.6 months. The authors concluded that treatment of peritoneal HCC remains challenging and survival is poor. In well-selected candidates, however, CRS +/- HIPEC may prolong survival compared to systemic therapy alone in patients with peritoneal HCC.

However, NCCN’s clinical practice guideline on “Hepatobiliary cancers” (Version 1.2015) does not mention HIPEC as a therapeutic option.

A recently published review of small intestine neoplasms (Reynolds et al, 2014) stated that the evidence for HIPEC in small bowel adenocarcinoma is anecdotal. The review stated that “The role of more radical resections or metastasectomy for small bowel adenocarcinoma is unclear but anecdotal reports indicate a possible role for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy”.

An UpToDate review on “Treatment of small bowel neoplasm” (Cusack and Overman, 2014) stated that “Long-term survival has been reported after
aggressive cytoreduction surgery and intraperitoneal hyperthermic chemotherapy in a handful of highly selected patients with peritoneal carcinomatosis from a small bowel adenocarcinoma. Experience with this approach, which is more commonly applied to patients with pseudomyxoma peritonei or malignant peritoneal mesothelioma, is very limited. Patients being considered for this approach should be referred to a center with expertise in the management of peritoneal surface malignancies”. The authors recommended systemic chemotherapy for patients with locally advanced unresectable or metastatic small bowel adenocarcinoma.

Also, guidelines from the NCCN stated that small bowel and appendiceal carcinoma may be treated with systemic chemotherapy according to the NCCN guidelines for colon cancer (Version 2.2015); which states that "the panel considers the treatment of disseminated carcinomatosis with cytoreductive surgery and HIPEC to be investigational and does not endorse this therapy outside of a clinical trial”.

An UpToDate review on “Clinical presentation and management of thymoma and thymic carcinoma” (Bezjak et al, 2014) does not mention the use of hyperthermic administration of intraperitoneal chemotherapy as a therapeutic option. Furthermore, the NCCN’s clinical practice guideline on “Thymomas and thymic carcinoma” (version 1.2014) does not mention the use of hyperthermic administration of intraperitoneal chemotherapy as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-9 Codes

**Hyperthermia:**

CPT codes covered if selection criteria are met:

- 77600 Hyperthermia, externally generated; superficial (i.e., heating to a depth of 4 cm or less)
- 77610 Hyperthermia generated by interstitial probe(s); 5 or fewer interstitial applicators
- 77615 more than 5 interstitial applicators

CPT codes not covered for indications listed in the CPB:

- 77605 Hyperthermia, externally generated; deep (i.e., heating to depths greater than 4 cm)
- 77620 Hyperthermia generated by intracavitary probe(s)

Other HCPCS codes related to the CPB:

- J8600 Melphalan, oral 2 mg
- J9245 Injection, melphalan HCl, 50 mg

ICD-9 codes covered if selection criteria are met:
172.0 - 172.9 Malignant melanoma of skin
174.0 - 175.9 Malignant neoplasm of breast
195.0 Malignant neoplasm of head, face, and neck
196.0 Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

158.8 Malignant neoplasm of specified parts of peritoneum
160.2 - 160.5 Malignant neoplasm of maxillary, ethmoidal, frontal, and sphenoidal sinuses
162.2 - 162.9 Malignant neoplasm of lung
171.0 - 171.9 Malignant neoplasm of connective and other soft tissue [desmoplastic small round cell tumor]
183.0 Malignant neoplasm of ovary [clear cell carcinoma]
183.3 Malignant neoplasm of broad ligament of uterus (mesovarium; parovarian region)
183.8 Malignant neoplasm of other specified sites of uterine adnexa
186.0 - 186.9 Malignant neoplasm of testis
197.6 Secondary malignant neoplasm of retroperitoneum and peritoneum
198.6 Secondary malignant neoplasm of ovary

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy:

CPT codes covered if selection criteria are met:

77605 Hyperthermia, externally generated; deep (i.e., heating to depths greater than 4 cm)
77620 Hyperthermia generated by intracavitary probe(s)
96446 Chemotherapy administration into the peritoneal cavity via indwelling port or catheter

CPT codes not covered for indications listed in the CPB:

96440 Chemotherapy administrations into pleural cavity, requiring and including thoracentesis

ICD-9 codes covered if selection criteria are met:
158.0 - 158.9 Malignant neoplasm of retroperitoneum and peritoneum [peritoneal mesothelioma]

197.6 Secondary malignant neoplasm of retroperitoneum and peritoneum [pseudomyxoma peritonei]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

151.0 - 151.9 Malignant neoplasm of stomach

153.0-153.9 Malignant neoplasm of colon

154.0 - 154.8 Malignant neoplasm of rectum, rectosigmoid junction, and anus

157.0 - 157.9 Malignant neoplasm of pancreas

163.0 - 163.9 Malignant neoplasm of pleura [mesothelioma]

182.0-182.8 Malignant neoplasm of body of uterus [leiomyosarcoma]

188.0-188.9 Malignant neoplasm of bladder

**Intraluminal hyperthermia:**

No specific code

**Transrectal ultrasound hyperthermia - no specific code:**

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

185 Malignant neoplasm of prostate

The above policy is based on the following references:


51. Minicozzi A, Borzellino G, Momo EN, et al. Treatment of the peritoneal carcinomatosis by cytoreductive surgery and intraperitoneal hyperthermic
Hyperthermia in Cancer Therapy


Hyperthermia in Cancer Therapy


90. Cusack JC, Jr., Overman MJ. Treatment of small bowel neoplasms. UpToDate Inc., Waltham, MA. Last reviewed December 2104.


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