Transworld Research Network
37/661 (2), Fort P.O.
Trivandrum-695 023
Kerala, India

Cytoreductive Surgery in Gynecologic Oncology: A Multidisciplinary Approach, 2010: 73-99
ISBN: 978-81-7895-484-4 Editor: Yusuf Yildirim

5. Hyperthermic intraperitoneal chemotherapy (HIPEC) in optimally cytoreduced peritoneal carcinomatosis of gynecology origin: Does it provide survival advantage?

Eelco de Bree, Dimitris D. Tsiftsis and John Melissas
Department of Surgical Oncology, Medical School of Crete – University Hospital Herakleion, Greece

Abstract. Among the gynecological malignancies, ovarian cancer is most frequently associated with diffuse peritoneal carcinomatosis. Rarely, peritoneal carcinomatosis is caused by other gynecological malignancies, including endometrial, fallopian tube and primary peritoneal cancer as well as malignant mixed mesodermal tumors. Despite progress in cytoreductive surgery and systemic chemotherapy and consequently significant improvement of survival in advanced ovarian cancer, still the majority of patients will ultimately die from this disease. Hence, besides development of novel more effective drugs, alternative routes of administration have been studied. Intraperitoneal chemotherapy is associated with a major pharmacokinetic advantage, with high locoregional drug concentrations and low systemic toxicity. Optimal cytoreductive surgery is a prerequisite because of its limited penetration depth. The addition of postoperative intraperitoneal instillation chemotherapy to the management of primary advanced ovarian

Correspondence/Reprint request: Dr. Eelco de Bree, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71110 Herakleion, Greece. E-mail: debree@edu.uoc.gr

cancer has been demonstrated to be beneficial in randomized trials and meta-analysis. Intraoperative application of intraperitoneal chemotherapy has the advantage of improved distribution of the drug solution through the peritoneal cavity and exposure of the entire seroperitoneal surface to the agent. Moreover, intraoperatively it can be combined with hyperthermia by heating the drug solution. Intraperitoneal instillation of certain drugs and hyperthermia are both better tolerated when the patient is under general anesthesia. Hyperthermia is cytotoxic itself and enhances the efficacy of many chemotherapeutic drugs. Hyperthermic intraperitoneal chemotherapy (HIPEC) has been demonstrated to be feasible and associated with acceptable morbidity. Unfortunately, there are no data from randomized trials available to asses its role in the management of gynecological malignancies with peritoneal dissemination. Cautious extrapolation of data from simple intraperitoneal instillation chemotherapy and data from phase II and non-randomized comparative studies suggest that HIPEC delivered at the time of surgery for ovarian cancer has definite potential. Further investigation is necessary and only a randomized trial design will adequately answer the question whether the addition of HIPEC actually prolongs survival in selected patients with peritoneal dissemination of ovarian and other gynecological cancer, conditions where outcome remains so poor with conventional therapy.

Introduction

Among the gynecological malignancies, ovarian cancer is most frequently associated with diffuse peritoneal carcinomatosis. Rarely, peritoneal carcinomatosis is caused by other gynecological malignancies, including endometrial, fallopian tube and primary peritoneal cancer as well as malignant mixed mesodermal tumors. Ovarian cancer is the second most frequently gynecological malignancy and the eighth most frequent cancer among females with approximately two thirds of the patients presenting with advanced disease, i.e. peritoneal carcinomatosis and/or hematogenous metastases. Ovarian cancer is the fifth most frequent cause of death from cancer and responsible for 6% of all cancer deaths in females. [1] Progress in the treatment of this disease is evident, with an improvement in survival rate during the last 30 years. In the 1960s, the 5-year survival rate for ovarian cancer was 30%, whereas recent statistics indicate an increase to 45% [1]. Improvement of the quality of cytoreductive surgery as well as development of novel drugs and new chemotherapy regimens are the main contributors to this improvement. Prior to 1993, chemotherapy of choice for advanced ovarian cancer was cisplatin or carboplatin in combination with a classic alkylating agent like cyclophosphamide. Since the mid-1990s cytoreductive surgery and systemic combination chemotherapy with a platinum compound and a taxane have become the standard of care for this disease [2], although a recent trial [3] indicated that in some women systemic chemotherapy with carboplatin alone may provide equivalent disease control with a favorable toxicity profile.

Despite this progress in systemic chemotherapy, most ovarian cancer patients will ultimately die from their disease. Hence, besides development of novel more effective drugs, alternative routes of administration have been studied. Recently, the addition of intraperitoneal chemotherapy to the management of advanced ovarian cancer has been demonstrated to be potentially beneficial [4,5].

The rationale for intraperitoneal chemotherapy

Although usually considered as systemic disease, peritoneal carcinomatosis can be better understood as regional dissemination. Ovarian cancer with tumor implants on peritoneal surfaces may remain confined to the peritoneal cavity for a prolonged period of time. This means that even though it is considered certainly a poor prognostic sign, it is not proof of distant metastases, providing a rationale for regional cancer treatment. Patients with additional hematogenous metastases are usually excluded from such regional treatment modalities, since systemic disease is insufficiently treated by a regional approach and should be treated in a systemic way [6].

Intraperitoneal chemotherapy is a regional treatment modality that has been used for peritoneal carcinomatosis already since 1955 [7]. During the last decades it has subjected to an increasing number of experimental and clinical investigations. The major advantage of intraperitoneal chemotherapy is the regional dose intensity provided, which may overcome the obstacle of relative drug resistance. Assuming the above mentioned dose-effect relation, this will result in a higher efficacy of the cytotoxic drug. The prerequisites for effective intraperitoneal chemotherapy are summarized in table 1 and discussed below.

The pharmacokinetic advantage

Following intraperitoneal delivery high regional drug concentrations can be achieved, while systemic drug levels are low. The concentration differential arises because of the relatively slow rate of movement of the drug from the peritoneal cavity into the plasma (peritoneal clearance). This pharmacokinetic process is based on the characteristics of the *peritoneal-plasma barrier*, which maintains the continuous high ratio of chemotherapeutic drug concentration between peritoneal cavity and plasma [8,9]. The physical nature of the peritoneal-plasma barrier has not been fully elucidated. At present, it is suspected that a complex diffusion barrier exists that consists of peritoneal mesothelium, subserosal tissue and blood vessel walls. The capillary wall appears to offer the dominant resistance to

Table 1. Usual preconditions and patient selection for effective intraperitoneal chemotherapy.

• Absence of hematogenous metastases • Adequate general condition of patient • Lysis of intra-abdominal adhesions • Minimal residual disease after cytoreductive surgery • Large volume carrier solution • Adequate drug choice (see table 2)

the transfer of large molecules. Absence of significant alterations in pharmacokinetics after extensive resections of peritoneum [10], suggests that the mesothelium and peritoneal interstitium impede their movement to a lesser extent. The movement of large drug molecules and hydrophilic agents through this barrier is limited, while the high drug extraction by the liver after absorption from the peritoneal cavity and transport to the portal vein system provides decreased systemic drug exposure. The area under the concentration versus time curve (AUC) gradient of the drugs from the peritoneal cavity to peripheral blood expresses most adequately the pharmacological advantage of intraperitoneal drug administration. Depending on their molecular weight, their affinity to lipids, and first-pass effect and clearance by the liver, the intraperitoneal to plasma drug AUC ratio may exceed a factor of 1000, as observed for taxanes and other drugs. The ratio of maximal intraperitoneal to peak plasma drug levels may reach a similar level [6].

An additional advantage is that the blood drainage of the peritoneal surface through the portal vein to the liver provides, besides the already mentioned first-pass effect, an increased exposure of potential hepatic micrometastases to cytotoxic drugs administered intraperitoneally [11]. Certain drugs are also transported through lymphatics to the systemic circulation and consequently higher drug exposure is achieved in the lymph than in plasma. This provides a strong rationale for treatment of concurrent occult or clinical lymph node metastases by intraperitoneal chemotherapy [12].

Drug tumor penetration depth

High intraperitoneal drug concentration and exposure are the two main factors affecting the treatment of free intraperitoneal tumor cells. However, the AUC for peritoneal fluid may not be correlated with the drug amount in tumor deposits. For invasive peritoneal tumor deposits of adenocarcinoma, which grow towards the subperitoneal space, it is more important to achieve satisfactory local tissue penetration and concentration of the drug rather than

high intraperitoneal fluid drug concentrations only [13]. The agent has to penetrate the peritoneal tumor as well as at the site of the peritoneal cavity as into the peritoneal layer and subperitoneal tissue.

A disadvantage of intracavitary chemotherapy remains to be the limited tissue penetration by the therapeutic agent. Unfortunately, for many agents it is difficult to accurately measure tissue penetration depth and concentration after intraperitoneal chemotherapy and, when possible, there is a large inter-individual variation. Nevertheless, the penetration depth of drugs that are intraperitoneally delivered is estimated to be 3 to 5 mm. at maximum [14-19]. This implies the need for meticulous cytoreductive surgery to precede intraperitoneal delivery of drugs. Hence, intraperitoneal chemotherapy may be indicated only following 'optimal' resection of peritoneal disease, leaving no or very small macroscopic disease behind; generally it is not beneficial in cases in which optimal cytoreductive surgery is not achieved and more than minimal residual disease is left behind [6]. Techniques and other aspects of cytoreductive surgery in ovarian and other gynecological cancer are discussed in detail in other chapters of this book.

Intraperitoneal chemotherapy may be combined simultaneously with systemic chemotherapy to optimize treatment efficacy in case of residual tumor after cytoreductive surgery. The intraperitoneally delivered cytotoxic agent penetrates the residual tumor nodules from the site of the peritoneal surface, while intravenous drug administration provides drug distribution by capillary blood flow into the tumor deposits [20-22]. For the same reason, substantial drug absorption from the peritoneal cavity to the systemic compartment may be even beneficial when it leads to adequate plasma concentrations without major systemic toxicity. Hence, peritoneal fluid to plasma maximal concentration and AUC ratios of certain agents may not accurately represent the pharmacokinetic advantage of intraperitoneal drug administration.

Timing of intraperitoneal chemotherapy

Homogeneous distribution and drug exposure to the entire seroperitoneal surface is required for optimal efficacy. This implies the need for lysis of intra-abdominal adhesions and the use of large volumes of fluid containing the chemotherapeutic agent. Intraperitoneal chemotherapy has been administered in the preoperative, intraoperative, and early and late postoperative period. From a distributional point of view, the optimal time is either prior or during surgery to avoid limitation of homogenous distribution by postoperative adhesion formation. Preoperative administration has the objective to facilitate subsequent cytoreductive surgery, but requires small-volume disease and lack

of extensive adhesions from previous operations. Intraperitoneal chemotherapy is generally used intra- or postoperatively, because the peritoneal surface is usually grossly affected and cytoreductive surgery is required. Intraoperative and early postoperative intraperitoneal chemotherapy are intended to consolidate the effect of surgery by destroying residual small tumor noduli and microscopic intraperitoneal malignant cell nests. In postoperative intraperitoneal chemotherapy, drugs are preferably administered during the first postoperative days, before any new surgery-related adhesions are produced. Late postoperative intraperitoneal chemotherapy, longer than 2 weeks after surgery, is probably associated with diminished therapeutic effect, due to uneven peritoneal distribution, caused by postoperative adhesions, and peritoneal cavity access catheter related problems [6,3,24].

Hyperthermia

Besides the realization of optimal conditions for homogenous drug distribution, another advantage of intraoperative application of intraperitoneal chemotherapy is the ability to perform this treatment modality under hyperthermic conditions, which are poorly tolerated by a conscious patient. The selective effect of hyperthermia on malignant cells and its ability to enhance the efficacy of chemotherapeutic agents make it a valuable adjunct to intraperitoneal chemotherapy in the management of peritoneal carcinomatosis [6,25].

The direct cytotoxic effect of heat has been known since ancient times [6,26]. There is an abundance of experimental and clinical evidence to indicate that malignant cells are selectively destroyed by hyperthermia in the range of 41^{o}C to 43^{o}C. The cellular and molecular basis for this selectivity has been well studied [25-27].

Additionally, hyperthermia enhances chemotherapy efficacy in a number of ways [25]. The combination of heat and chemotherapeutic drugs frequently results in increased cytotoxicity over that predicted for an additive effect. The synergism between both kinds of treatment may be caused by several factors, including increased drug uptake in malignant cells, altered cellular metabolism and cellular drug pharmacokinetics, increased drug penetration in tissue, temperature-dependent increases in drug action and inhibition of repair mechanisms. In many cases, this enhancement of activity and penetration depth of drugs is already seen above 39-40^{o}C [25].

Not all drugs exhibit a synergism with heat, but several agents have been shown to have an apparently improved therapeutic index and efficacy when used with hyperthermia in *in vitro* and *in vivo* experimental studies.

Generally, the highest thermal enhancement ratios have been observed for alkylating agents like melphalan, cyclophosphamide and ifosfamide [28]. There has been some concern regarding lack of thermal enhancement or even an antagonistic effect of hyperthermia on the cytotoxic effect of paclitaxel in *in vitro* studies [29]. However, in these studies, drug concentrations and duration of exposure to the drug and to heat resembled more the conditions of systemic chemotherapy with a period of external heating of the target area. It seems that at high paclitaxel drug concentrations under mild hyperthermia for 2 hours, conditions similar to those during HIPEC, is associated with enhancement and certainly not with impairment of cytotoxicity [29].

During hyperthermic intraperitoneal chemotherapy (HIPEC) mild hyperthermia is achieved by heating the drug carrier solution. The desired intra-abdominal temperature differs between centers and varies generally from 40 to 44^{o}C. Heat used during HIPEC has a limited penetration depth, emphasizing also here the need for adequate cytoreductive surgery. In a recent study [30],[30] a wide inter-individual variability was noted and a temperature of 39^{o}C or higher was reached to a mean depth of 3.1 mm at the beginning and 5.1 mm at the end of the procedure, when the intraperitoneal temperature fluctuated between 40^{o}C and 41^{o}C.

Techniques for intraperitoneal chemotherapy

Uniform exposure of all surfaces within the peritoneal cavity is of critical importance. In postoperative intraperitoneal instillation chemotherapy, infusion of large volumes of fluid (at least 1-2 liters) is necessary to achieve this goal. Access to the peritoneal cavity for instillation of chemotherapeutic solutions is usually achieved by placement of a Tenckhoff catheter or a subcutaneous implantable port and catheter (Port-A-Cath) system. After infusion, the patient is instructed to change frequently body position to promote exposure to the entire seroperitoneal surface. At completion of the treatment, the solution is drained out of the abdominal cavity [31-33].

For HIPEC, after completion of cytoreductive surgery, temperature probes are placed to monitor intra-abdominal temperature and to allow correction of the perfusion pattern in case of unequal thermal distribution. Inflow and outflow catheters are placed in the abdominal cavity. The abdominal cavity is completely filled with the carrier solution, usually being normal saline or dextrose-based peritoneal dialysis solutions. The perfusion is performed using a roller pump, which is connected to a heat exchanger. The cytotoxic drug is added to the perfusate when the target intra-abdominal temperature is reached. At the end of HIPEC, virtually the whole drug amount is removed by drainage of the perfusate, preventing further systemic absorption. Comprehensive

discussion of the different chemoperfusion techniques is behind the scope of this chapter, but the two main techniques, the 'open abdomen technique' and the 'closed abdomen technique', are briefly summarized. During the 'closed abdomen technique' the abdominal skin is temporary closed water tight. Closure of the skin only allows exposure of the remaining laparotomy wound to the perfusate, diminishing the risk of wound recurrence. The abdomen is manually agitated during the perfusion period to promote uniform heat and drug distribution. At the end of the procedure the solution is drained and the abdominal wall is closed in a standard fashion. Advantages of the method are limited heat loss, prevention of drug evaporation, decreased risk of contamination and maintenance of a tight surgical field. The closed abdomen technique seems a safer technique for the theatre personnel due to the minimal drug exposure to them. The main disadvantage is the possible lack of uniform distribution of the perfusate. Others use the 'open abdomen technique' in an attempt to optimize exposure of the abdominal organs and the parietal peritoneum to the perfusate. The skin surrounding the abdominal incision is sutured to a retractor ring placed above the anterior surface of the abdomen, causing an elevated rim around the open abdominal cavity. In this way, a 'Coliseum' or 'soup bowl-like' container is created for instillation of the peritoneal perfusate. The principle benefit of this 'Coliseum technique' is the achievement of better exposure of the seroperitoneal surfaces and adequate heat and drug distribution through the entire abdominal cavity by manual stirring of the perfusate, manipulation of the mobile abdominal contents and repositioning of the inflow catheter. Disadvantages of the technique are that the open abdomen naturally leads to heat loss and the exposure of operating room personnel and especially the surgeon, to the cytotoxic drug. Finally, perfusion with an open abdominal cavity may results in incomplete exposure of the laparotomy wound and of the intestine floating on the fluid surface to the perfusate, resulting in a higher incidence of early wound recurrence and possibly an increased occurrence of malignant bowel obstruction. Although each technique has certain advantages and disadvantages, there are yet no sufficient data available to demonstrate one of the methods to be more effective [24].

Drug choice

The choice of the chemotherapeutic drug is very important and certain aspects have to be considered (table 2). It is important for the agent to lack severe local toxicity after intraperitoneal administration. Moreover, the drug should have a well established activity against the gynecological malignancy treated. Drugs that have to be metabolized systemically into their active form are inappropriate for intraperitoneal use. Whereas in instillation intraperitoneal

Table 2. Specific features of cytotoxic agents favorable for intraperitoneal delivery.

- Lack of local toxicity of the agent
- Documented activity against malignancy to be treated
- No need for metabolism into active form
- Experimental or clinical evidence for concentration- or exposure-dependent cytotoxicity of the agent
- Slow clearance from the peritoneal cavity (i.e. high molecular weight, water rather than lipid solubility)
- Significant and rapid hepatic metabolism to non-cytotoxic metabolite (first-pass effect from the liver)
- Rapid renal clearance
- Direct cytotoxic agent (no antimetabolites; only for HIPEC)
- Synergistic effect with hyperthermia (only for HIPEC)

chemotherapy all categories of active drugs can be used, in HIPEC-procedures a direct cytotoxic agent is needed. Anti-metabolites are not suitable for this application, because the exposure duration is too short to be effective. Experimental or clinical evidence should be available suggesting that a concentration- or exposure-dependent cytotoxicity exists for the certain drug. Otherwise, when low target drug levels are equally effective, conventional systemic chemotherapy may be sufficient. Agents with a large molecular weight have more favorable pharmacokinetics, because of limited and delayed absorption from the peritoneal cavity. Drugs highly metabolized in the liver to non-toxic metabolites are preferred because the first-pass effect from the liver decreases further the systemic drug exposure. Additional rapid renal clearance of the drug that has passed the liver may decrease systemic drug exposure. Finally, existence of synergistic effect of the drug with hyperthermia is preferred for HIPEC. *In vivo* studies on different agents indicate that the drug of choice at physiological temperatures may not be the drug of choice at elevated temperatures [34]. A theoretical prerequisite for HIPEC is the heat stability of the drug that is to be administered, but fortunately nearly all drugs are stable under these moderate hyperthermic conditions [6,35].

For ovarian cancer and other gynecologic malignancies various drugs have been used for intraperitoneal chemotherapy (table 3) [35]. As mentioned before, antimetabolites as methotrexate, 5-fluorouracil, floxuridine and gemcitabine are not effective in intraoperative intraperitoneal chemotherapy, while lack of thermal enhancement makes etoposide not favorable for HIPEC [35]. Most experience with intraperitoneal chemotherapy for gynecological cancer is obtained with platinum-derivates as cisplatin and carboplatin and

Table 3. Results of pharmacokinetic studies on intraperitoneal administration of various drugs, effective in ovarian cancer [35].

Drug	**$C_{max\ i.p.}$ / $C_{max\ plasma}$**	**$AUC_{i.p.}$ / AUC_{plasma}**
Melphalan	93	17-63
Cisplatin	10-36	12-22
Carboplatin		15-20
Mitomycin-C	100	13-80
Adriamycin	249-474	162-230
Mitoxantrone		100-1400
Methotrexate	72	
5-fluorouracil	1000	117-1400
Floxuridine		1000-2700
Gemcitabine		791
Topotecan		54
Etoposide		2-9
Paclitaxel	800-1000	550-2300
Docetaxel	45-200	150-3000

Mean ratios of studies are mentioned. C = concentration, max = maximal, i.p. = intraperitoneal, AUC = area under concentration versus time curve

taxanes like paclitaxel and docetaxel, drugs that are most effective in systemic chemotherapy for ovarian cancer. Because of their most favorable pharmacokinetic profile and the probable thermal enhancement of its cytotoxicity, taxanes as paclitaxel and docetaxel seems to be rather attractive agents for HIPEC [29,36]. Results of pharmacokinetic studies on intraperitoneal administration of drugs used for gynecological malignancies with peritoneal carcinomatosis are summarized in table 3 [35]. Although mitoxantrone, 5-fluorouracil and floxuridine have pharmacokinetics superior than for example that of platinum compounds, they have not been widely used because their cytotoxic effect on ovarian cancer cells is considerably inferior.

Duration of intraperitoneal chemotherapy

While in pre- or postoperative instillation peritoneal chemotherapy the drug solution is usually left in the peritoneal cavity for 4 to more than 24 hours, the duration of HIPEC has been arbitrary and varies from 30 minutes to 2 hours in different centers. No definite data are available to support a certain time period, but taking into account results from pharmacokinetic and experimental hyperthermic studies and taking maximal advantage of drug availability and heat effect, the optimal perfusion duration seems to be

90 to 120 minutes [6]. Some, in an attempt to shorten operation time, to decrease costs and meanwhile to obtain an optimal peritoneal fluid AUC, advocate a shorter duration (30 minutes) with higher drug doses [37].

Eligibility and indications for intraperitoneal chemotherapy

In order to undergo cytoreductive surgery and intraperitoneal chemotherapy, eligible patients must be sufficient healthy to withstand the surgery and chemotherapy, especially in case of HIPEC. Usually, disease should be confined to the peritoneal cavity and systemic disease should be absent, because intraperitoneal chemotherapy does not treat systemic metastases adequately. Further of major importance is that, when after surgery tumor deposits are left behind, they should not exceed 5 mm in diameter, because of the already mentioned limited penetration depth. Preoperative assessment to identify patients whose disease is not likely to be optimally resectable would enable such patients to avoid morbidity of unnecessary surgery. Although several studies have investigated the accuracy of imaging studies in determining the resectability of ovarian cancer, the factors associated with prediction of suboptimal surgery vary between studies and centers, probably reflecting the surgical philosophy at individual institutions [38]. The level of surgical expertise is of major importance with regard to the operability of advanced ovarian cancer and this will ultimately determine the chance of optimal cytoreductive surgery [39].

There are five time-points in the natural history of gynecological cancer with peritoneal dissemination at which cytoreductive surgery and intraperitoneal chemotherapy can be performed, the latter being either simple instillation intraperitoneal chemotherapy or HIPEC: for primary disease (first-line treatment), which includes during front-line treatment, after interval cytoreductive surgery following initial induction chemotherapy and as consolidation treatment, or for persistent and recurrent disease (second line treatment). Superior outcome is to be expected in the first settings, when disease is mostly chemo-sensitive, and worse in the latter settings, when in a significant portion of patients disease is expected to be resistant to chemotherapy.

An alternative indication is the palliation of debilitating malignant ascites, wherefore HIPEC is highly effective. [40,41]. This indication will not be discussed in detail, but is also extremely effective when performed by minimal invasive surgery in patients who are not candidates for cytoreductive surgery [42,43].

Advantages and disadvantages of HIPEC versus intraperitoneal instillation chemotherapy

HIPEC has some advantages over simple intraperitoneal instillation chemotherapy. As discussed above, the most important is the superior distribution of the heated drug solution through the peritoneal cavity and homogenous exposure of the entire seroperitoneal surface to both drug and heat [6]. Further, residual tumor is at the smallest possible volume and treatment would be usually delivered many days to weeks prior to the usual time when postoperative intraperitoneal chemotherapy is given. Another advantage of intraoperative use is that intraperitoneal chemotherapy can be administered with mild hyperthermia, which is directly cytotoxic and enhances the efficacy and penetration depth of many drugs [6,25], but is poorly tolerated by a patient who is awake. Finally, intraperitoneal administration of some agents, including cisplatin and paclitaxel, may cause severe abdominal pain, which is often the dose limiting factor and is better tolerated intraoperatively [44-50].

An argument which may be used against the application of HIPEC instead of instillation intraperitoneal chemotherapy is the substantially shorter tumor exposure time (usually 1-2 hours versus 24 hours). However, experimental studies have demonstrated that even short time exposure of tumor cells to high drug concentrations, as during HIPEC, is extremely sufficient to induce extended cell growth arrest and tumor cell death [51-53]. Another disadvantage is that HIPEC can usually be applied only a single time or the most again when secondary surgery is performed, while simple intraperitoneal instillation chemotherapy is given repetitively. However, it has to be noted, that in a significant number of patients who are considered to be treated with intraperitoneal instillation chemotherapy, treatment can not be started or has to be discontinued because of peritoneal access catheter complications, as obstruction, dysfunction, bowel perforation and infection [54]. Moreover, HIPEC does not exclude postoperative use of intraperitoneal instillation chemotherapy.

Results of intraperitoneal instillation chemotherapy for ovarian cancer

Intraperitoneal instillation chemotherapy has been studied much more extensively than HIPEC. Nowadays, there is clear evidence that addition of intraperitoneal instillation chemotherapy to systemic chemotherapy might be beneficial for primary ovarian cancer patients with peritoneal carcinomatosis,

who underwent optimal cytoreductive surgery. In a recent meta-analysis of different treatment strategies for ovarian cancer [55], addition of intraperitoneal chemotherapy to the management of advanced ovarian cancer was demonstrated to result in significant improvement of survival. When treatment regimens were compared with intravenous single drug chemotherapy which involves neither platinum nor taxane, hazard ratio for death was lowest for platinum-taxane chemotherapy with at least one agent given intraperitoneally (0.45; 95% confidence interval 0.33-0.61). Platinum-based combination intravenous chemotherapy with intraperitoneal chemotherapy with a platinum-compound was associated with a relative risk of death was inferior and similar to that of intravenous platinum-taxane chemotherapy (0.60; 95% confidence interval 0.46-0.79 vs. 0.58; 95% confidence interval 0.49-0.69). Survival differences were inferior for other treatment regimens. Results were similar when analysis was limited to first-line treatment.

In the past, two large randomized trials (GOG 104 and 114) [56,57] have demonstrated a clear benefit for intraperitoneal instillation chemotherapy in small residual primary ovarian cancer. However, an old systemic chemotherapy regimen and addition of intravenous carboplatin administration only in the experimental arm were important criticisms of these studies. While previously platinum-compounds had been used for intraperitoneal chemotherapy, during the last 15 years paclitaxel has been intraperitoneally administered for the treatment of primary and recurrent advanced ovarian cancer in different studies with favorable pharmacokinetic and promising clinical results. [29] Hence, intraperitoneal administration of paclitaxel was included in the latest large multicentric randomized trial on intraperitoneal chemotherapy for optimally cytoreduced primary ovarian cancer (GOG 172) [44]. Significantly improved survival was noted for the use of intraperitoneal chemotherapy with paxlitaxel and cisplatin. This study revealed an improvement in median progression-free survival from 18.3 to 23.8 months by intraperitoneal chemotherapy and a relative recurrence risk of 0.80 ($p=0.05$) in favor of intraperitoneal treatment when compared with conventional intravenous chemotherapy. Overall survival data followed a similar trend favoring intraperitoneal chemotherapy with a median overall survival of 65.6 versus 49.7 months and a relative death risk of 0.75 ($p=0.03$). This is one of the largest benefits ever observed for a new therapy in gynecologic oncology. Based on the results of this study and meta-analysis of the results of this and seven other trials [58], in 2006 the National Cancer Institute issued a clinical announcement recommending that women with primary stage III ovarian cancer who undergo optimal surgical cytoreduction should be considered for intraperitoneal chemotherapy [59,60]. The referred meta-analysis was criticized by the inclusion of a consolidation treatment

study among front-line treatment trials. A subsequent systematic review and meta-analysis [50], from which this consolidation treatment study was excluded, demonstrated still a significant overall survival benefit of the addition of intraperitoneal chemotherapy during primary treatment of women with stage III epithelial ovarian cancer (relative risk, 0.88; 95% confidence interval, 0.81-0.95). Concern exists regarding the adverse events and peritoneal access catheter-related complications with intraperitoneal chemotherapy, which were significantly more common and often dose-limiting than observed during intravenous treatment alone [50,58]. This needs to be considered well when deciding on the most appropriate treatment for each individual woman. Incidence of catheter-related complications, however, has been dramatically reduced by adequate training of nursing and medical personnel, correct use of the catheter system as well as increased experience [54]. Appropriate clinical and institutional multidisciplinary facilities are needed for the save delivery of this treatment in optimally cytoreduced patients.

For other indications than following primary cytoreductive surgery, no randomized trials examining the role of intraperitoneal chemotherapy in ovarian cancer have been performed. However, encouraging results from phase II studies on intraperitoneal instillation chemotherapy as salvage treatment for persistent or recurrent peritoneal disease, as consolidation treatment after negative second-look surgery and as adjuvant treatment for stage I and II disease have been reported [31-33].

Results of HIPEC for gynecological cancer

Although randomized controlled trials have demonstrated a significant benefit of HIPEC in colon cancer with peritoneal dissemination and in high-risk gastric cancer [61-63], unfortunately there are no results of such a study for ovarian cancer. The Italian Society of Integrated Locoregional Therapy (SITILO) initiated a randomized trial to asses the additional role of HIPEC in persistent ovarian cancer [64], but the study was closed prematurely due to lack of accrual. Hence, only data of phase I and II HIPEC studies concerning patients with primary and recurrent ovarian cancer with peritoneal spread are available so far for assessment of its additional benefit. Results of such studies have been summarized in table 4. Since most frequently HIPEC is offered to patients with recurrent and persistent disease, a majority of them having chemotherapy resistant disease, less promising results may be awaited. Heterogeneity among ovarian cancer patients makes interpretation of results and comparison with non-randomized control groups difficult, underlining the need for phase III trials. This heterogeneity of patient populations

Table 4. Results of HIPEC for ovarian cancer with peritoneal carcinomatosis.

First author	Year	N	Indication (N)	Drug used	Morbidity	Mortality	Follow-up (months)	Median survival (months)	1-yr OS	3-yrs OS	5-yrs OS	postop. syst. chemo (N)	Remarks
Kober [65]	1996	12	various indications	Cisplatin	> 44%*	8%*	9 (mean)	11	-	-		9	i.p. recurrence 0%
Orlando [66]	1998	18	consolidation treatment	cisplatin or paclitaxel or carboplatin+VP16	no major	0%	28 (median)	-	-	84%,	-	NS	i.p recurrence 11%
Fujimura [67]	1999	6	1st-line therapy	cisplatin based	8%*	0%	7 (median)	-	60%	20%	-	6	RR 50%
Steller [68]	1999	6	1st-line treatment (5), 2nd-line treatment (1)	Carboplatin	67% grade III/IV hemato	0%	15 (median)	-	-	-	-	6	6 alive, 5 NED
Cavaliere [69]	2000	20†	2nd-line treatment	Cisplatin	40%* 15% reop.*	13%*	20 (mean)*	-	50% (2-yrs)	-	-	NS	heavily pretreated
Van der Vange [70]	2000	5	2nd-line treatment	Cisplatin	no major	0%	-	-	-	-	-	2	1 alive NED at 43 months, 4 DOD after 4-24 months Heavily pretreated
Nicoletto [71]	2000	11	2nd-line treatment++	Mitoxantrone	no major	0%	42 - 57	-	-	-	-	NS	30% RR, 3 alive++, 2 NED++, totally 25 x HIPEC
Hager [42]	2001	36	2nd-line treatment	cisplatin, carboplatin or mitoxantrone	mild	0%	≥ 40	-	65%	30%	16%	NS	Heavily pretreated, no cytoreductive surgery, totally 168 x HIPEC
De Simone [72]	2003	21	re-recurrence	Cisplatin	17% major	9%	-		23% (2-yrs)	50%	-	NS	
		13	1st recurrence	Cisplatin	15% major	8%							
De Bree [40]	2003	19	2nd-line treatment	Docetaxel	60%, mainly minor	10%	30 (mean)	54	79%	63%	42%	17	considerably pretreated, 1 patient 2 x HIPEC
Kecmanovic [73]	2003	11	1st-line treatment (8), 2nd-line treatment (3)	Adriamycin	-	9%	-	22	-	-	-	NS	all pts. EPIC
Chatzigeorgiou [41]	2003	20	2nd-line treatment	Cisplatin	15% major	10%	-	with OCS 29 with SCS 7	-	-	-	15	14 pts. with early recurrent disease
Chatzigeorgiou [74]	2004	27	1st-line treatment	Cisplatin	4% major	0%	-	with OCS 42 with SCS 10	-	-	-	NS	2 pts. stage IV
Piso [75]	2004	19	1st-line treatment (8), 2nd-line treatment (11)	cisplatin (16) or mitoxantrone (3)	36% 16% reop.	5%	24 (median)	33#	-		15%	9	9 pts with liver metastases 11 pts EPIC
Zanon [76]	2004	30	2nd-line treatment	cisplatin	17% major	3%	19 (mean)	28	60% (2-yrs)	-	15%	NS	

Table 4. Continued

Look [77]	2004	28[+]	1st-line treatment (4), 2nd-line treatment (24)	cisplatin+adriamycin or mitomycin+5-FU	11% major	0%	27 (median)	46	60% (2-yrs)	-	-	13	12 pts. HIPEC, 13 pts. EPIC
Ryu [78]	2004	57	at secondary surgery	carboplatin and interferon-α	28% major	4%	47 (mean)	26	-	-	63%	most	5-yr OS 54% for stage III (n=35), outcome measured from primary surgery
Reichman [79]	2005	13	1st-line treatment (4), 2nd-line treatment (9)	Cisplatin	-	0%	14 (median)	not reached	-	55%	-	NS	
Gori [80]	2005	29	consolidation treatment	Cisplatin	3% surgical	0%	56 (mean)	64	-	-	65%	NS	
Yoshida [81]	2005	10	primary treatment and consolidation treatm.	cisplatin, mitomycin and etoposide	-	-	-	70	-	-	-	10	
Rasagliesi [82]	2006	40	2nd line treatment	cisplatin+mitomycin/ adriamycin	20%	0%	26 (median)	41[#]	-	-	15%	NS	
Hadi [83]	2006	6	NS	cisplatin (1) or mitomycin (5)	39%	6%*	-	-	83%	33%	-	NS	+EPIC
Rufian [84]	2006	33	1st-line treatment (19), 2nd-line treatment (14)	Paclitaxel	36%	0%	-	48[#]	89% 84%	46% 51%	37% 51%	33	survival rates for 1st line and 2nd line treatment respectively
Bae [85]	2007	67	positive 2nd look (15), consolidation tr. (52)	carboplatin (45) or paclitaxel (22)	30% GI 21% hematol	0%	62 (mean)	-	-	-	66%	67	survival rate is for stage III (n=44), outcome measured from primary surgery
Helm [86]	2007	18	2nd line treatment	cisplatin (15) or mitomycin (3)	≥22% major	6%	-	31	-	-	-	12	
Cotte [87]	2007	81	2nd line treatment	Cisplatin	14% major	2%	47 (median)	28	-	-	-	43	heavily pretreated
Lentz [88]	2007	17	1st-line treatment (11), 2nd-line treatment (6)	Carboplatin	6% surgical	0%	-	-	-	-	-	17	
Di Giorgio [89]	2008	47	1st-line treatment (22), 2nd-line treatment (25)	Cisplatin	21% major	4%	-	30[#]	-	-	17%	45	
Spiliotis [90]	2008	12[**]	NS	cisplatin+adriamycin	42%* 8% reop.*	8%	22 (mean)*	12[#]	54%	-	-	NS	
De Bree [36]	2008	10	1st-line treatment (3), 2nd-line treatment (7)	Paclitaxel	38%*	0%	-	-	-	-	-	7	

N = number of patients, [+] = 18 patients ovarian cancer, 10 patients papillary serous carcinoma of the peritoneum, [++] = one patient with stage IB ovarian cancer treated by HIPEC as consolidation treatment, * = for the entire group of patients with various primary tumors treated by cytoreductive surgery and HIPEC or early postoperative intraperitoneal chemotherapy, ** = 10 ovarian and 2 uterine cancer patients, [†] = HIPEC or early postoperative intraperitoneal chemotherapy, hemato = hematological, reop. = reoperation, [#] = mean, NS = not stated, OCS = optimal cytoreductive surgery, SCS= suboptimal; cytoreductive surgery, OS = overall survival rate, postop. syst. chemo = postoperative systemic chemotherapy, i.p.= intraperitoneal, RR = response rate, NED = no evidence of disease, DOD = died of disease, EPIC = early postoperative intraperitoneal chemotherapy, pts. = patients,

and differences of the treatment regimens among the studies do also not allow proper comparison of results among these HIPEC studies and meta-analysis. Indications vary and series include patients with primary ovarian cancer, recurrent/persistent disease or both. Further, other patient selection criteria like age, performance status, tumor load, probability of completeness of cytoreductive surgery and other, may differ considerably. Particularly, there is an enormous inter-individual variety in peritoneal tumor load, varying from some small superficial tumor nodules on the peritoneal surface next to the primary tumor site to a peritoneal cavity full of large invasive tumor deposits. Since the HIPEC-procedure has not been standardized yet, this treatment method varies substantially among centers regarding duration of the perfusion, intra-abdominal temperature during hyperthermia, open or closed abdomen technique, selection and dosage of the chemotherapeutic agents. Probably in most, but not all, patients, systemic chemotherapy was administered after cytoreductive surgery and HIPEC, making it nearly impossible in a non-randomized setting to demonstrate whether survival benefit was due to the addition of this procedure or that this was achieved anyhow by systemic chemotherapy only. Finally, the surgeon as a variable parameter leads to potential inconsistency of quality of cytoreductive surgery [39], making comparison between different series unreliable as the quality of surgical cytoreduction is a highly important undependable parameter for outcome, as discussed in a separate chapter of this book.

Recently, a systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer identified fourteen studies with adequate quality to be analyzed [91]. Rates of significant morbidity associated with this treatment modality were low, ranging from 5% to 36%. Hematological toxicity was reported up to 15%, depending substantially on its definition, technique, drug and dose. Renal toxicity was observed in 0-8% of cases and is associated with the use of platinum compounds. Pulmonary complications were seen infrequently and include embolus, pleural effusion, pneumonia and central vein thrombosis. Surgical complications were encountered frequently and related to extensive surgery. The most significant were anastomotic leak, intestinal perforation, abscess, fistula, sepsis, bleeding and wound infection/dehiscence. Reoperation for complications was required in 0-16% of cases. Especially the combination of intestinal perforation or anastomotic leakage with leucopenia is often fatal. In the analyzed series, the median mortality rate was 3% (range 0%-10%) and might be decreased by improved patient selection. The median overall survival in series with primary and/or recurrent disease ranged from 22 to 54 months and the median disease-free survival from 10 to 26 months.

Patients with optimal cytoreduction seemed to have the greatest benefit. In a study in which HIPEC was incorporated during planned secondary surgery after primary cytoreductive surgery and conventional systemic chemotherapy, a 5-year overall survival of 63-66% was noted. In series consisting of patients with recurrent and persistent ovarian cancer only, estimated 5-year overall survival was 15% and 42%. The authors concluded that HIPEC following cytoreductive surgery is a treatment option for patients with ovarian cancer that is worthy of further investigation and that selection criteria for patients most likely to benefit need to be defined.

Despite the difficulty in reliable evaluation as discussed earlier, some investigators attempted to compare their outcome after addition of HIPEC with those obtained by traditional treatment in non-randomized control groups. Ryu et al. [78] compared in a retrospective study the results of 57 stage Ic-III ovarian cancer patients treated by surgical cytoreduction and HIPEC at secondary surgery (second-look or secondary cytoreductive surgery) with those of 60 similar patients who underwent during the same period of time conventional surgical cytoreduction and systemic chemotherapy only. Five-year overall survival was significantly better for the HIPEC-group (63.4% vs. 52.8%, p=0.0078). The additional benefit of HIPEC was most obvious in stage III ovarian cancer patients (5-year overall survival rate 53.8% vs. 33.3%, p=0.0015), while the overall survival difference was not significant in stage Ic and II disease (p=0.63). For stage III ovarian cancer patients whose tumor was reduced to less than 1 cm in diameter during a second procedure, the 5-year survival rate 65.6% in patients who underwent HIPEC and 40.7% in control patients (p=0.0046). In multivariate analysis, HIPEC was an independent prognostic factor that was not affected by surgical staging, residual tumor size after secondary surgery or patient age (p=0.0176).

In the same center, a second non-randomized comparative study was performed, including 96 patients with ovarian cancer stage Ic, II and III [85]. All patients underwent primary surgical cytoreduction and systemic chemotherapy, followed by secondary surgery after initial response. Secondary operation consisted of either secondary cytoreductive surgery when response was partial or second-look surgery when a clinical complete response was achieved. In 29 cases this was followed by systemic chemotherapy only (control group), while in 67 patients HIPEC with paclitaxel (n=22) or carboplatin (n=45) preceded additional systemic chemotherapy. Patient groups were comparable regarding age, histological type, disease stage, completeness of primary surgical cytoreduction and number of chemotherapy cycles per patient. No statistically significant difference in survival was observed for stage Ic and II disease, while outcome

was considerably superior after HIPEC in stage III disease. Three-year progression-free survival was 56.3% for the HIPEC-group versus 16.7% for the control group (p=0.003) and 5-year overall survival 66.1% versus 32.8% (p=0.0003). The difference in survival outcome between the patients who received paclitaxel and those who received carboplatin during HIPEC was not significant (5-year overall survival 84.6% versus 63.0%, p=0.41). It has to be noted, that the number of patients in both HIPEC-groups was small to show any statistically significant difference. For the relative risk of disease progression yielded from multivariate analyses, hazard ratio for HIPEC with paclitaxel was 0.281 (p=0.004) an that of HIPEC with carboplatin 0.433 (p=0.008). Like HIPEC with carboplatin (hazard ratio: 0.396, p=0.0004), HIPEC with paclitaxel considerably decreased the risk of death (hazard ratio: 0.197, p=0.025).

Gori et al. [80] investigated the effect of HIPEC as consolidation treatment in 29 stage IIIb and IIIc ovarian cancer patients, following cytoreductive surgery and systemic chemotherapy, in a multicentric prospective trial. They compared outcome with that of a control group of 19 similar patients who refused second-look operation and subsequent HIPEC. Disease stage, completeness of cytoreduction, histological grade and histological type were comparable for both groups of patients. Disease-free and overall survival were superior after HIPEC (median: 57.1 vs. 46.4 months and 64.4 vs. 60.1 months, respectively), but the differences were statistically not significant, possibly due to the small number of patients included in their analysis.

Little experience exists regarding HIPEC for other gynecologic malignancies. Helm et al. [92] reported unexpectedly long survival in five patients treated by cytoreductive surgery and HIPEC for peritoneal recurrence of endometrial carcinoma. Others have reported encouraging results of HIPEC for malignant mixed mesodermal (or malignant mixed Müllerian) tumors [93,94]. Although fallopian tube carcinoma and primary cancer of the female peritoneum, have been frequently included in clinical trials concerning intraperitoneal instillation chemotherapy for ovarian cancer [32,44], only a few cases have been reported to be treated by HIPEC for such indications [77,95,96].

Conclusions and future directions

Generally, it seems that HIPEC is well tolerated and associated with acceptable morbidity, when patient selection is appropriate and adequate experience is gained in a referral center. However, the most essential question is whether it provides survival advantage. As mentioned before, unfortunately

there are no data from randomized trials available to asses the definite benefit of incorporation of HIPEC in the management of ovarian cancer. However, the precedent for treatment at different natural history time-points of ovarian cancer has been set by many relatively small phase I/II studies and further study is needed. The variety in details of HIPEC treatment and the heterogeneity of the patients are such that comparison to historical controls is unreliable and only a randomized trial design will adequately answer the question whether the addition of HIPEC actually prolongs survival in patients with peritoneal dissemination of ovarian cancer. It will be extremely difficult to accomplish such a study, since it would require several hundreds patients for each single indication and thorough collaboration between many centers.

In absence of evidence from randomized trials and with difficulties in interpretation of non-randomized HIPEC-studies, cautious extrapolation of outcome data from randomized trials and meta-analyses concerning simple intraperitoneal instillation chemotherapy in ovarian cancer may be validated. Taking into account the mentioned advantages of HIPEC when compared with intraperitoneal instillation chemotherapy, it is to be expected that HIPEC offers similarly survival benefit for patients with primary ovarian cancer with peritoneal spread with no or small residual disease after cytoreductive surgery. Likewise, it is probably an effective treatment at other natural history time-points. Comparative non-randomized studies have demonstrated improved outcome by performing HIPEC at secondary surgery (i.e. secondary cytoreductive surgery or second-look surgery) in initially stage III ovarian cancer. Data on HIPEC for other gynecological malignancies are too sparse to draw any conclusion.

Despite the overwhelming evidence, unfortunately the medical community has not widely accepted the use of simple intraperitoneal instillation chemotherapy in optimally cytoreduced stage III ovarian cancer. Reluctance towards this treatment modality exists probably due to several reasons. Firstly, it is a completely novel and different treatment method. Further, it is more demanding than conventional intravenous treatment, since it is more time consuming and requires more effort from nursing and medical staff. Moreover, the already mentioned initial concern regarding toxicity and complications may have resulted in a reserved attitude towards this technique. However, accumulation of experience and adequate training of involved personnel have led to gradually reduction of toxicity and complications, although optimal technique, agent, dose and schedule have still to be defined. Another reason that intraperitoneal chemotherapy has not become popular is the persisting use of cisplatin by most investigators, despite the availability of new drugs that are probably more efficient. Moreover, the medical community and the pharmaceutical industry have put

emphasize on development and intravenous administration of novel agents instead of the use of an alternative delivery route. These issues have to be kept in mind to understand and to attempt to avoid similar reluctance of the medical community towards the incorporation of HIPEC in the treatment of ovarian cancer, especially when well designed studies may offer adequate evidence for its efficacy in the future. Well designed and collaborative studies, treatment in referral centers, adequate patient selection, accurate training and use of new attractive agents as paclitaxel and docetaxel are some of the key issues to attempt to get HIPEC universally accepted.

Most recently, results of the Ovary Consensus Panel convened for the 5th International Workshop on Peritoneal Surface Malignancy (December 2006, Milan) have been reported [97]. Although there was some disagreement regarding indication criteria, they concluded that HIPEC delivered at the time of surgery for ovarian cancer has definite potential. The experts agreed that growing literature documents its relative tolerability and supports the continuation of further research regarding the role of HIPEC in the treatment of ovarian cancer, a disease where outcome remains so poor with conventional therapy.

References

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. CA Cancer J Clin 2008; 58: 71-96.
2. McGuire WP III, Markman M. Primary ovarian cancer chemotherapy: current standards of care. Br J Cancer 2003; 89 suppl 3: S3-S8.
3. The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 2002; 360: 505-515.
4. Trimble EL, Christian MC. Intraperitoneal chemotherapy for women with advanced epithelial ovarian carcinoma. Gynecol Oncol 2006; 100: 3-4.
5. Kyrgiou M, Salanti G, Pavlidis N et al. Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments. J Natl Cancer Inst 2006; 98: 1655-1663.
6. de Bree E, Tsiftsis DD. Principles of perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. Recent Results Cancer Res 2007; 169: 39-51.
7. Weisberger AS, Levine B, Storaasli JP. Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. J Am Med Assoc 1955; 159: 1704-1707.
8. Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. Cancer Treat Res 1996; 82: 53-63.
9. Flessner MF. The transport barrier in intraperitoneal therapy. Am J Physiol Renal Physiol 2005; 288: F433-F442.
10. de Lima Vazquez V, Stuart OA, Mohamed F, Sugarbaker PH. Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics. Cancer Chemother Pharmacol 2003; 52: 108-112.

11. Speyer JL, Sugarbaker PH, Collins JM et al. Portal levels and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. Cancer Res 1981; 41: 1916-1922.
12. Lindner P, Heath DD, Shalinsky DR et al. Regional lymphatic drug exposure following intraperitoneal administration of 5-fluorouracil, carboplatin, and etoposide. Surg Oncol 1993; 2: 105-112.
13. de Bree E, Witkamp AJ, Zoetmulder FAN. Intraperitoneal chemotherapy for colorectal cancer. J Surg Oncol 2002; 79: 46-61.
14. Ozols RF, Locker GY, Doroshow JH et al. Pharmacokinetics of adriamycin and tissue penetration in murine ovarian cancer. Cancer Res 1979; 39: 3209-3214.
15. McVie JG, Dikhoff T, Van der Heide J et al. Tissue concentration of platinum after intraperitoneal cisplatinum administration in patients. Proc Am Assoc Cancer Res 1985; 26: 162.
16. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. Cancer Chemother Pharmacol 1991; 28: 159-165.
17. Fujimoto S, Takahashi M, Kobayashi K et al. Cytohistologic assessment of antitumor effects of intraperitoneal hyperthermic perfusion with mitomycin C for patients with gastric cancer with peritoneal metastasis. Cancer 1992; 70: 2754-2760.
18. Panteix G, Guillaumont M, Cherpin L et al. Study of the pharmacokinetics of mitomycin C in humans during intraperitoneal chemohyperthermia with special mention of the concentration in local tissues. Oncology 1993; 50: 366-370.
19. van der Vaart PJM, van der Vange N, Zoetmulder FAN et al. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: Pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. Eur J Cancer 1998; 34: 148-154.
20. Hofstra LS, Bos AME, de Vries EGE et al. Kinetic modelling and efficacy of intraperitoneal paclitaxel combined with intravenous cyclophosphamide and carboplatin as first-line treatment in ovarian cancer. Gynecol Oncol 2002; 85: 517-523.
21. Markman M, Kulp B, Peterson G et al. Second-line therapy of ovarian cancer with paclitaxel administered by both the intravenous and intraperitoneal routes: Rationale and case reports. Gynecol Oncol 2002; 86: 95-98.
22. Rothenberg ML, Liu PY, Braly PS et al. Combined intraperitoneal and intravenous chemotherapy for women with optimally debulked ovarian cancer: Results from an Intergroup Phase II trial. J Clin Oncol 2003; 21: 1313-1319.
23. Averbach AM, Sugarbaker PH. Methodologic considerations in treatment using intraperitoneal chemotherapy. Cancer Treat Res 1996; 82: 289-309.
24. Witkamp AJ, de Bree E, van Goethem AR, Zoetmulder FAN. Rationale and technique of intra-operative hyperthermic intraperitoneal chemotherapy. Cancer Treat Rev 2001; 27: 365-374.
25. Sticca RP, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. Surg Oncol Clin N Am 2003; 12: 689-701.
26. Overgaard J. Effects of hyperthermia on malignant cells in-vivo, a review and hypothesis. Cancer 1977; 39: 2637-2646.

27. Cavaliere R, Ciocatto EC, Giovanella BC et al. Selective heat sensitivity of cancer cells. Biochemical and clinical studies. Cancer 1967; 20: 1351-1381.
28. Takemoto M, Kuroda M, Urano M et al. The effect of various chemotherapeutic agents given at mild hyperthermia on different types of tumours. Int J Hyperthermia 2003; 19: 193-203.
29. de Bree E, Theodoropoulos PA, Rosing H et al. Treatment of ovarian cancer using intraperitoneal chemotherapy with taxanes: from laboratory bench to bedside. Cancer Treat Rev 2006; 32: 471-482.
30. van Ruth S, Verwaal VJ, Hart AA et al. Heat penetration in locally applied hyperthermia in the abdomen during intra-operative hyperthermic intraperitoneal chemotherapy. Anticancer Res 2003; 23: 1501-1508.
31. Fujiwara K, Armstrong D, Morgan M et al. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. Int J Gynecol Cancer 2007; 17: 1-20.
32. Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. Lancet Oncol 2003; 4: 277-283.
33. Hofstra LS, de Vries EGE, Mulder NH, Willemse PHB. Intraperitoneal chemotherapy in ovarian cancer. Cancer Treat Rev 2000; 26: 133-143.
34. Urano M, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. Int J Hyperthemia 1999; 15: 79-107.
35. de Bree E, Tsiftsis DD. Experimental and pharmacokinetic studies in intraperitoneal chemotherapy: From laboratory bench to bedside. Recent Results Cancer Res 2007; 169: 53-73.
36. de Bree E, Rosing H, Filis D et al. Cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy with paclitaxel: a clinical and pharmacokinetic study. Ann Surg Oncol 2008; 15: 1183-1192.
37. Elias DM, Sideris L. Pharmacokinetics of heated intraoperative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis. Surg Oncol Clin N Am 2003; 12: 755-769.
38. Axtell AE, Lee MH, Bristow RE et al. Multi-institutional reciprocal validation study of computed tomography predictors of suboptimal primary cytoreduction in patients with advanced ovarian cancer. J Clin Oncol 2007; 25: 384-389.
39. Eisenkop SM, Spiros NM, Lin WC. “Optimal” cytoreduction for advanced epithelial ovarian cancer: a commentary. Gynecol Onol 2006; 103: 329-335.
40. de Bree E, Romanos J, Michalakis J et al. Intraoperative hyperthermic intraperitoneal chemotherapy with docetaxel as second-line treatment for peritoneal carcinomatosis of gynaecological origin. Anticancer Res 2003; 23: 3019-3028.
41. Chatzigeorgiou K, Economou S, Chrysafis G et al. Treatment of recurrent epithelial ovarian cancer with secondary cytoreduction and continuous intraoperative intraperitoneal hyperthermic chemoperfusion (CIIPHCP). Zentralbl Gynakol 2003; 125: 424-429.
42. Hager ED, Dziambor H, Hohmann D et al. Intraperitoneal hyperthermic perfusion chemotherapy of patients with chemotherapy-resistant peritoneal disseminated ovarian cancer. Int J Gynecol Cancer 2001; 11 (suppl 1): 57-63.

43. Garafallo A, Valle M, Garcia J, Sugarbaker PH. Laparoscopic intraperitoneal hyperthermic chemotherapy for palliation of debilitating malignant ascites. Eur J Surg Oncol 2006; 32: 682-685.
44. Armstrong DK, Bundy BN, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. New Eng J Med 2006; 354: 34-43.
45. Markman M. Intraperitoneal Taxol. Cancer Treat Res 1996; 81: 1-5.
46. Markman M, Rowinsky E, Hakes T et al. Phase I trial of intraperitoneal taxol: a Gynecologic Oncology Group study. J Clin Oncol 1992; 10: 1485-1491.
47. Fushida S, Furui N, Kinami S et al. [Pharmacologic study of intraperitoneal paclitaxel in gastric cancer with peritoneal dissemination]. Gan To Kagaku Ryoho 2002; 29: 2164-2167.
48. Hofstra LS, Bos AME, de Vries EGE et al. Kinetic modelling and efficacy of intraperitoneal paclitaxel combined with intravenous cyclophosphamide and carboplatin as first-line treatment in ovarian cancer. Gynecol Oncol 2002; 85: 517-523.
49. Francis P, Rowinsky E, Schneider J et al. Phase I feasibility and pharmacologic study of weekly paclitaxel: a Gynecologic Oncology Group pilot study. J Clin Oncol 1995; 13: 2961-2967.
50. Elit L, Oliver T, Covens A et al. Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer. A systemic review with metaanalysis. Cancer 2007; 109: 692-702.
51. Rupniak HY, Whelan RD, Hill BT. Concentration and time-dependent inter-relationships for antitumour drug cytotoxicities against tumour cells in vitro. Int J Cancer 1983; 32: 7-12.
52. Michalakis J, Georgatos SD, de Bree E et al. Short term exposure of cancer cells to micromolar doses of paclitaxel, with or without hyperthermia, induces long term inhibition of cell proliferation and cell death in vitro. Ann Surg Oncol, 2007; 14: 1220-1228.
53. Michalakis J, Georgatos SD, Romanos J et al. Micromolar taxol, with or without hyperthermia, induces mitotic catastrophe and cell necrosis in HeLa cells. Cancer Chemother Pharmacol 2005; 56:615-622.
54. Walker JL, Armstrong DK, Huang HQ et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. Gynecol Oncol 2006; 100: 27-32.
55. Kyrgiou M, Salanti G, Pavlidis N et al. Survival benefits with diverse chemotherapy regimens for ovarian cancer: a meta-analysis of multiple treatments. J Natl Cancer Inst 2006; 98:1655-1663.
56. Alberts DS, Liu PY, Hannigan EV et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. New Engl J Med 1996; 335: 150-155.
57. Markman M, Bundy B, Alberts DS et al. Phase III study of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001; 19: 1001-1007.

58. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cohcrane Database Syst Rev 2006; 25: CD005340.
59. http://www.cancer.gov.
60. Trimble EL, Christian MC. Intraperitoneal chemotherapy for women with advanced epithelial ovarian carcinoma. Gynecol Oncol 2006; 100: 3-4.
61. Verwaal V, 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.
62. de Bree E, Witkamp AJ, Zoetmulder FA. Peroperative hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced gastric cancer. Eur J Surg Oncol, 2000; 26: 630-631.
63. Yan TD, Black D, Sugarbaker PH et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol 2007; 14: 2701-2713.
64. Deraco M, Raspagliesi F, Kusamura S. Management of peritoneal surface component of ovarian cancer. Surg Oncol Clin N Am 2003; 12: 561-583.
65. Kober F, Heiss A, Roka R. Diffuse and gross peritoneal carcinomatosis treated by intraperitoneal hyperthermic chemoperfusion. Cancer Treat Res 1996; 82: 211-219.
66. Orlando M, Huertas E, Salum G et al. Intraperitoneal hyperthermic chemotherapy as consolidation treatment for ovarian cancer in pathological complete remission. Proc Am Soc Clin Oncol 1998; 17: #1432.
67. Fujimura T, Yonemura Y, Fujita H et al. Chemohyperthermic peritoneal perfusion for peritoneal dissemination in various abdominal malignancies. Int Surg 1999; 84: 60-66.
68. Steller MA, Egorin MJ, Trimble EL et al. A pilot phase I trial of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. Cancer Chemother Pharmacol 1999; 43: 106-114.
69. Cavaliere F, Perri P, Di Filippo F et al. Treatment of peritoneal carcinomatosis with intent to cure. J Surg Oncol 2000; 74: 41-44.
70. van der Vange N, van Goethem AR, Zoetmulder FAN et al. Extensive cytoreductive surgery combined with intra-operative intraperitoneal perfusion with cisplatin under hyperthermic conditions (OVHIPEC) in patients with recurrent ovarian cancer: a feasibility pilot. Eur J Surg Oncol 2000; 26: 663-668.
71. Nicoletto MO, Padrini R, Galeotti F et al. Pharmacokinetics of intraperitoneal hyperthermic perfusion with mitoxantrone in ovarian cancer. Cancer Chemother Pharmacol 2000; 45: 457-462.
72. De Simone M, Costamagna D, Scuderi S et al. Cytoreduction and hyperthermic antiblastic peritoneal perfusion (CIIP) in recurrent ovarian carcinoma (abstract). 14th International Congress on Anti-Cancer Treatment, Paris, 1-4 February 2003, abstract book page 183.
73. Kecmanovic DM, Pavlov MJ, Kovacevic PA et al. Cytoreductive surgery for ovarian cancer. Eur J Surg Oncol 2003; 29: 315-320.

74. Chatzigeorgiou KN. [The contribution of intraoperative hyperthermic administration of chemotherapeutic drugs during continuous perfusion of the peritoneal cavity in the treatment of peritoneal carcinomatosis]. Thesis. Alexandropouli, 2004.
75. Piso P, Dahlke M-H, Loss M, Schlitt HJ. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis. World J Surg Oncol 2004; 2: 21-28.
76. Zanon C, Clara R, Chiappino I et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. World J Surg 2004; 28: 1040-1045.
77. Look M, Chang D. Sugarbaker PH. Long-term results of cytoreductive surgery for advanced and recurrent epithelial ovarian cancers and papillary serous carcinoma of the peritoneum. Int J Gynecol Cancer 2004; 14: 35-41.
78. Ryu KS, Kim JH, Ko HS et al. Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. Gynecol Oncol 2004; 94: 325-332.
79. Reichman TW, Cracchiolo B, Sama J et al. Cytoreductive surgery and intraoperative hyperthermic chemoperfusion for advanced ovarian carcinoma. J Surg Oncol 2005; 90: 51-56.
80. Gori J, Castano R, Toziano M et al. Intraperitoneal hyperthermic chemotherapy in ovarian cancer. Int J Gynecol Cancer 2005; 15: 233-239.
81. Yoshida Y, Sasaki H, Kurokawa K et al. Efficacy of intraperitoneal continuous hyperthermic chemotherapy as consolidation therapy in patients with advanced epithelial ovarian cancer: a long-term follow-up. Oncol Rep 2005; 13: 121-125.
82. Rasaglieri F, Kusamura S, Campos Torres JC et al. Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: The experience of National Cancer Institute of Milan. Eur J Surg Oncol 2006; 32: 671-675.
83. Hadi R, Saunders V, Utkina O et al. Review of patients with peritoneal malignancy treated with peritonectomy and heated intraperitoneal chemotherapy. Aust NZ J Surg 2006; 76: 156-161.
84. Rufian S, Munoz-Casares FC, Briceno J et al. Radical surgery-peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. J Surg Oncol 2006; 94: 316-324.
85. Bae JH, Lee JM, Ryu KS et al. Treatment of ovarian cancer with paclitaxel- or carboplatin-based intraperitoneal hyperthermic chemotherapy during secondary surgery. Gynecol Oncol 2007; 106: 193-200.
86. Helm CW, Randall-Whitis L, Martin RS 3rd et al. Hyperthermic intraperitoneal chemotherapy in conjunction with surgery for the treatment of recurrent ovarian carcinoma. Gynecol Oncol 2007; 105: 90-96.
87. Cotte E, Glehen O, Mohamed F et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for chemoresistent and recurrent advanced epithelial ovarian cancer: Prospective study of 81 patients. World J Surg 2007; 31: 1813-1820.
88. Lentz SS, Miller BE, Kucera GL, Levine EA. Intraperitoneal hyperthermic chemotherapy using carboplatin: a phase I analysis in ovarian carcinoma. Gynecol Oncol 2007; 106: 207-210.

89. Di Giorgio A, Naticchioni E, Biacchi D et al. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer 2008; 113: 315-325.
90. Spiliotis J, Tentes AAK, Vaxevanidou A et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal carcinomatosis. Preliminary results and cost from two centers in Greece. J BUON 2008; 13: 205-210.
91. Bijelic L. Jonson A, Sugarbaker PH. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. Ann Oncol 2007; 18: 1943-1950.
92. Helm CW, Toler CR, Martin RS III et al. Cytoreduction and intraperitoneal heated chemotherapy for the treatment of endometrial carcinoma recurrent within the peritoneal cavity. Int J Gynecol Cancer 2007; 17: 204-209.
93. Müller H, Nakchbandi V. Cytoreductive surgery plus intraperitoneal hyperthermic perfusion is an effective treatment for metastasized malignant mixed mesodermal tumours (MMMT) – report of six cases. Eur J Surg Oncol 2004; 30: 573-577.
94. de Bree E, Romanos J, Relakis K, Tsiftsis DD. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant mixed mesodermal tumours with peritoneal dissemination. Eur J Surg Oncol 2005; 31: 111-112.
95. Maluf FC, Carvalho JP, Carvalho FM et al. Aggressive multimodality treatment in transitional cell carcinoma of the parafallopian tube: report of 2 cases and review of the literature. Gynecol Oncol 2006; 102: 381-385.
96. Ajisaka H, Yonemura Y, Bando E et al. Long-term survival of a patient with primary papillary serous carcinoma of the peritoneum treated by subtotal peritonectomy plus intraoperative chemohyperthermia. Hepatogastroenterology 2002; 49: 1027-1029.
97. Helm CW, Bristow RE, Kusamura S et al. Hyperthermic intraperitoneal chemotherapy with and without cytoreductive surgery for epithelial ovarian cancer. J Surg Oncol 2008; 98: 283-290.