Intraperitoneal Cancer Therapy

Edited by

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Preface

This collaborative work is the result of a gathering of some of the leaders in the field of intraperitoneal chemotherapy for ovarian cancer and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis at an International Symposium held at the University of Louisville, Kentucky, in May 2005. All the speakers at that symposium have contributed chapters to this work.

Dr John Spratt
1929–2005
Professor of Surgery
University of Louisville
Louisville, KY

The Symposium was held 25 years after Dr. John Spratt, a surgeon at the University of Louisville, reported for the first time ever delivery of hyperthermic intraperitoneal chemotherapy to a male patient with pseudomyxoma peritonei. It is to him that this book is dedicated.

Although much has happened in the intervening quarter century, the revolution has been slow to develop and it is only recently that the tide has turned widely in favor of directing tumoricidal therapy to the peritoneal cavity for the treatment of intraperitoneal malignancies. Oncologists of surgical, gynecologic and medical bents from all over the World have played their part in these developments. We hope that this volume will contribute to a greater understanding of where we are now, how we got here, and where we are going.

C. William Helm
Robert P. Edwards

Acknowledgments

The editors extend their thanks to their editorial assistant, Ms. Leta Weedman, for her guidance and tireless help during the production of this book. We are also indebted to all the contributors who have so eagerly given their energy and time to share their knowledge and experience in this exciting new arena of cancer treatments that will give hope to patients around the world.

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Introduction: Intraperitoneal Chemotherapy for Advanced Ovarian Cancer: Finally, a Standard of Care!

Key Words: Intraperitoneal chemotherapy, ovarian cancer, IP cisplatin, IP paclitaxel, cancer survival

Epithelial ovarian cancer is the fourth leading cause of cancer death in women in the United States, with an estimated incidence of 20,180 and 15,310 deaths in 2006 *(1).* According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the five-year relative survival rates for women with "localized" ovarian cancer is 93.6%, whereas for those with "distant" disease it is 29.1% *(2).* Unfortunately, these data have changed minimally over the past decade.

In comparison to all other common solid cancers (including lung and pancreatic cancers), ovarian cancer is diagnosed far more frequently with "regional" or "distant" disease (i.e., approximately 80% of all new diagnoses) *(1).* These late diagnoses occur because there are no ovarian cancer specific symptoms and because of the propensity for tumor cells that invade through the capsule of the ovary to be swept into the upper abdomen where they can grow in a rich "culture media" of macrophages and lymphocytes *(3).*

Although bioimaging and biomarker technologies have failed to lead to the diagnosis of early stage ovarian cancers (i.e., only about 20% of ovarian cancers are diagnosed in a localized stage), the natural history of distant or advanced disease involves the metastases from ovarian cancer progressing mainly within the intraperitoneal space. Thus, regional approaches to therapy of advanced disease must be considered both rational and vital; however, regional therapy can only be successful in this setting if attention to aggressive cytoreductive surgery is preserved as a centerpiece of ovarian cancer management.

Systemic therapy (i.e., intravenously administered cytotoxic and biologic agents) has always been the favored approach for drug delivery for advanced ovarian cancer. In relation to high-impact progress in the lengthening of survival for women with ovarian cancer, there have been three hallmark

developments in systemic therapy over the past 20 years, including (1) the development of intravenously administered cisplatin and carboplatin in the 1970s and 1980s *(4,5)*; (2) the addition of paclitaxel to cisplatin and carboplatin in the 1990s *(6–8)*; and (3) the administration of cisplatin and paclitaxel by the intraperitoneal routes in the 1990s and early 2000s (Table 1) *(9–11)*.

In the United States over the past decade, the combination of intravenously administered carboplatin and paclitaxel has been the standard treatment of women with stages III and IV ovarian cancer, regardless of disease characteristics or success of surgical debulking *(8)*. This combination of carboplatin plus paclitaxel was tested by both the AGO Ovarian Cancer Study Group (Germany) and by the Gynecologic Oncology Group (GOG-158) comparing it with a cisplatin plus paclitaxel combination *(7,8)*. The outcome of the large phase III trial in the GOG documented better patient tolerability and a non-significant trend toward a higher negative "second-look" exploratory laparotomy rate and longer survival duration associated with the carboplatin/paclitaxel study arm *(8)*. Of considerable interest is that virtually all subsequent trials of this combination in first-line therapy have utilized a carboplatin dose calculated with an AUC (area under plasma concentration · time curve) of no more than 6 μg.hr/mL in contrast to the AUC of 7.5 μg.hr/mL used in GOG-158, mainly to cut down on relatively high rates of grade 4 neutropenia, chronic thrombocytopenia, and moderately severe peripheral neuropathy *(8)*.

Even with the use of a carboplatin AUC calculated dose of 7.5 μg.hr/mL in combination with paclitaxel in GOG-158, the median survival duration of 57 months achieved with this intravenous regimen is considerably lower than the median survivals of 63 and 66 months achieved with the intraperitoneal cisplatin or intraperitoneal cisplatin/paclitaxel arms of GOG-114 and GOG-172, respectively (Table 1) *(10,11)*.

With the publication of GOG-172 in January 2006, the National Cancer Institute issued a "Clinical Announcement," suggesting that women with stage III, optimally debulked (>1 cm individual sized intraperitoneal tumor plaques) be informed of the positive results of the three large, phase III intraperitoneal cisplatin-based trials stating that, "the benefit appears to be approximately a 12-month improvement in median overall survival (range 0–16 months) *(9–12)*. The "Clinical Announcement" goes on to state "of note, the magnitude of improvement in survival is similar to that observed with the introductions of cisplatin and paclitaxel in the treatment of women with ovarian cancer" *(12)*.

As stated in a 2002 editorial in the *Journal of Clinical Oncology,* "we cannot think of any other setting in oncology where the results of three positive phase III trials have not led to widespread adoption of the superior therapy. The time has come for intraperitoneal (IP) chemotherapy to move beyond the setting of clinical trials and into the standard treatment armamentarium for women with

Table 1
Survival Data Related to Gynecologic Oncology Group Trials of Intravenous or Intraperitoneal Platinum Plus Taxane Regimens in Women with Stage III, Optimally Debulked Ovarian Cancer

				Median Survival (months)		
Group Study #	**First author**	**Control Arm**	**Experimental Arm**	**Control**	**Experimental**	***P* value**
GOG-158	Ozols *(8)*	IV cisplatin IV paclitaxel	IV carboplatin IV paclitaxel	49	57	>.05
GOG-114	Markman *(10)*	IV cisplatin IV paclitaxel	IV carboplatin IV paclitaxel IP cisplatin	52	63	.05
GOG-172	Armstrong *(11)*	IV cisplatin IV paclitaxel	IV paclitaxel IP cisplatin IP paclitaxel	50	66	.02

optimally debulked, stage III ovarian cancer. We owe our patients nothing less" *(13).*

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1 Management of Ovarian Cancer: The Theory

Maurie Markman, MD

Summary

The mathematical modeling concepts developed by Robert Dedrick and his colleagues, and subsequent preclinical evaluation, provided a strong framework upon which to build a clinical investigative program examining intraperitoneal (IP) chemotherapy as a management approach in advanced ovarian cancer. These investigative efforts suggested the type of antineoplastic agents that should be explored, the patient populations more likely to benefit, and the limitations and potential toxicities of this novel strategy.

Key Words: Ovarian cancer; intraperitoneal cytotoxic drug delivery; chemotherapy; "Dedrick Model."

1. INTRODUCTION

Ovarian cancer is an ideal tumor to consider for regional therapy, for several reasons. First, although clearly recognized to be a highly "chemosensitive" malignancy, long-term disease-free survival in advanced disease is the exception, rather than the rule *(1)*.

Second, despite the fact the cancer is usually widespread throughout the peritoneal cavity at initial presentation, the disease generally remains confined to the peritoneal cavity (at least in its major clinical manifestations) in most patients during the majority of its *natural history (2,3)*.

Third, although large, "bulky tumor" masses are frequently noted at initial surgical exploration, the cancer uncommonly invades deeply into surrounding tissue.

Finally, there is a long-established tradition of primary surgical cytoreduction in ovarian cancer *(4)*, with the goal of permitting patients to begin cytotoxic chemotherapy with the smallest possible residual tumor volume.

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2. HISTORICAL BACKGROUND

Given the information provided in the Introduction, it should come as no surprise that the direct IP administration of anticancer agents in the treatment of ovarian cancer is far from a "novel concept." Shortly after the "new class" of drugs, the cytotoxic alkylating agents, was introduced into both clinical investigation and practice, this technique of drug delivery was examined as a management strategy in women with ovarian cancer *(5,6)*.

Unfortunately, although the early experience provided evidence for a biological effect of this regional treatment strategy (e.g., reduction in the amount of ascites formation), there was little evidence of an important clinical effect. Tumor masses were rarely observed to decrease in size, and the agents employed in those "early days" were found to be capable of producing considerable local toxicity. Further, it became clear that systemic drug delivery (intravenous or oral) could avoid these negative local effects, as well as the more complex technical requirements associated with IP treatment programs.

Thus, IP chemotherapy became relegated to the setting of occasional use to attempt to control malignant fluid reaccumulation, such as with bleomycin *(7)*. Although successfully employed in many patients for this purpose, and still utilized today, it has never been clear if the observed beneficial outcomes of this strategy have anything to do with direct cytotoxicity of the drugs against the malignant cell population present within the fluid, or are merely the result of a nonspecific sclerosing effect of the agents. (That similar activity is seen when noncytotoxic, but highly irritating, drugs [e.g., tetracycline and talc] are employed in the management of pleural effusions provides support for the conclusion that the major effect is one of inflammation and sclerosis, and not direct cytotoxicity.)

3. "DEDRICK MODEL" OF INTRAPERITONEAL CYTOTOXIC DRUG DELIVERY

In 1978, the publication of a paper by Robert Dedrick and his colleagues at the National Cancer Institute renewed interest in this long-abandoned concept of cancer management *(8)*. In what became a truly landmark paper in the annals of cancer research, Dedrick described a theoretical rationale for the treatment of ovarian cancer by direct delivery of drugs into the peritoneal cavity. Using data regarding the pharmacology of cytotoxic chemotherapeutic agents existing at that time (e.g., cytarabine) and knowledge of the physiology (from prior research in peritoneal dialysis) and anatomy of the peritoneal cavity, the model proposed that regional drug delivery could result in a striking increase in peritoneal cavity exposure, compared with the systemic vascular compartment, for drugs possessing specific biological characteristics.

For example, agents that are extensively and rapidly metabolized during their first passage through the liver would be predicted to exhibit the most impressive pharmacokinetic advantage (difference between cavity and systemic compartment exposure) for regional delivery, as drugs administered directly into the peritoneal cavity enter the portal circulation before entry into the systemic vascular compartment. Further, drugs whose properties would suggest slow clearance from the cavity (e.g., large size or water soluble) would also be predicted to show a greater advantage compared with agents undergoing more rapid cavity clearance (e.g., smaller size or lipid soluble).

In the "Dedrick model," it was suggested that cytarabine, which is a well-established antineoplastic agent for the treatment of acute leukemia that was known to undergo rapid metabolism in the liver, would show a profound pharmacokinetic advantage (1,000-fold) if delivered by the IP route *(8)*. The validity of this analysis was subsequently confirmed in a clinical trial examining single-agent IP cytarabine in the treatment of ovarian cancer *(9)*.

It is important to recognize that by employing cytarabine in this mathematical "model," the National Cancer Institute investigators did not mean to strongly suggest this specific agent should be utilized in the management of ovarian cancer. In fact, cytarabine had previously been shown to possess minimal activity in the treatment of any solid tumor. However, the point of this theoretical modeling exercise was to show that a drug with *biological characteristics* similar to that of cytarabine, but with demonstrated activity in ovarian cancer, would be an excellent candidate agent to be examined for its potential therapeutic efficacy when administered by the IP route.

It is not an exaggeration to state that it was this paper written by Dedrick and colleagues that was responsible for stimulating the interest of several investigators to rigorously explore, in both the preclinical and, ultimately, the clinical setting, a potential role for IP drug delivery in the management of ovarian cancer.

Notably, at the time of the development of the Dedrick model, a clearly appreciated, but highly unwelcome, clinical experience was observed in a group of patients receiving the chemotherapeutic agent methotrexate, which provided support for the relevance of regional cytotoxic drug administration. It was recognized that the presence of ascites could substantially increase the risk of serious toxicity associated with delivery of this drug, as this "third space" fluid produced *a reservoir effect*, slowing the release of the agent into the systemic compartment. Thus, the pharmacokinetic behavior of methotrexate present within the peritoneal cavity was vastly different from that observed when the agent was confined within the systemic circulation.

4. PROPERTIES OF THE "IDEAL CYTOTOXIC AGENT" FOR INTRAPERITONEAL DRUG DELIVERY

As noted, drugs that are *rapidly metabolized* during first passage through the liver, and agents that slowly exit the peritoneal cavity, are more likely to exhibit a favorable pharmacokinetic advantage for cavity exposure after regional delivery, compared to drugs that do not exhibit these properties. Similarly, a biologically "active" drug, which is rapidly cleared from the systemic circulation after it enters the vascular compartment, will show a more favorable advantage than one that is slowly removed (either by metabolization into a non-toxic metabolite or elimination from the body by excretion though the kidneys).

It is also important to state that drugs considered for clinical use must be *active against the tumor type in question*. Stated slightly differently, increasing the exposure of a malignancy 1,000-fold to an antineoplastic agent to which it is completely resistant is unlikely to produce a meaningful clinical effect. Conversely, as has been shown in preclinical model systems in ovarian cancer, cytotoxicity of several agents with known activity in the disease can be markedly enhanced at the concentrations of the drugs possibly achievable with regional delivery, but not safely attainable with systemic administration *(10)*. Characteristics of an ideal drug for IP drug delivery can be found in Table 1.

Another relevant issue is that of unique toxicities that must be considered with regional cytotoxic drug delivery. As noted in very early experiences with IP therapy *(11)*, the peritoneal lining can be quite sensitive to the effects of cytotoxic drugs, leading to abdominal pain, sclerosis, and subsequent bowel obstruction. Thus, even if an agent is known to be active in ovarian cancer, and preclinical models suggest the potential clinical relevance associated with increasing the exposure of drug to tumor through regional delivery,

Table 1
Characteristics of an "Ideal Drug" for Intraperitoneal Administration

1. Inherent activity in the tumor type being treated.
2. Preclinical evidence for enhanced cytotoxicity associated with increasing either (or both) the peak concentration or total AUC vs time curve.
3. Not toxic to the peritoneal lining (nonvesicant).
4. Extensively and rapidly metabolized to a nontoxic form during initial passage through the liver.
5. Quickly cleared after entry from the peritoneal cavity into the systemic compartment.
6. Drug *does not require* metabolism in the liver to become an "active" cytotoxic agent.

it may not be possible to safely employ a particular agent because of unacceptable local toxic effects. For example, it should come as no surprise that an antineoplastic agent that is known to be a *vesicant*, after intravenous administration would produce considerable, and likely unacceptable, local toxicity when delivered directly into the peritoneal cavity *(11)*.

It is relevant at this point in the discussion to note that the issue of the evaluation of unfavorable effects of individual cytotoxic antineoplastic agents and combination chemotherapy regimens used for regional delivery is complicated by the fact that there are additional potential toxicities resulting from the unique requirements of drug administration (e.g., catheter malfunction, catheter erosion into bowel, and bacterial peritonitis), rather than to the agents themselves *(12,13)*.

5. ALTERNATIVE MECHANISMS OF TUMOR CELL KILL RESULTING FROM INTRAPERITONEAL DELIVERY OF CYTOTOXIC ANTINEOPLASTIC AGENTS

Before proceeding to a discussion of the preclinical experience with the concept of IP therapy, it is relevant to note one additional unique aspect of the peritoneal cavity that may potentiate the efficacy of treatment, rather than increase risk. Stimulation ("activation") of local immunological mechanisms, perhaps similar to those responsible for producing a nonspecific inflammatory and sclerosing effect observed with regional drug delivery, may also enhance the "cytotoxicity" of antineoplastic drugs administered intraperitoneally *(14)*.

Although it is very difficult to determine either the specific biological factors responsible for a favorable effect, or the relative contributions of direct cytotoxicity versus an impact of local immunoregulatory mechanisms in this process, it is important to note the potential relevance of this influence.

(The topic of the IP administration of immunological antineoplastic agents is discussed in detail in Chapter 4.)

6. PRECLINICAL EXPERIENCE WITH INTRAPERITONEAL THERAPY OF OVARIAN CANCER

Preclinical evaluation performed in several laboratories provided important support for the concept of IP cytotoxic drug delivery, and also pointed to relevant limitations of this strategy. Studies revealed the potential significance of increasing drug exposure to tumor in defining the added benefits that may be observed after regional therapy *(10)*.

Further, in the case of the use of cisplatin in the treatment of ovarian cancer, provocative data suggested "resistance" to the agent was really quite relative,

and even increasing the concentration by 4–5-fold could convert a "resistant" cell into a "sensitive" one *(15)*. Unfortunately, it was also quite clear that even doubling the dose of cisplatin or carboplatin in the actual treatment of patients was very difficult, resulting in unacceptable toxicities (e.g., neuropathy, emesis, and bone marrow suppression).

In addition, several randomized trials have revealed that doubling the dose of a platinum agent in the treatment of ovarian cancer, although producing increased side effects, does not favorably impact outcome *(16–18)*. Yet, it remained possible that after IP platinum delivery, tumor exposures >10-fold, compared with the systemic compartment, could be observed.

Preclinical studies also supported the concern for the potential local toxicity associated with IP drug delivery (e.g., doxorubicin) *(19)*, an experience subsequently confirmed in clinical trials *(11,20)*.

7. THE ISSUE OF "DEPTH OF PENETRATION"

Finally, several studies revealed perhaps the major limitation of regional drug delivery in the management of ovarian cancer, the *depth of penetration of drugs directly into tumor tissue*. Several model systems, employing a variety of cytotoxic agents (e.g., cisplatin, carboplatin, doxorubicin, and methotrexate) *(21–25)*, demonstrated the drugs were capable of penetrating a distance of only a few cell layers to a maximum of several millimeters from the tumor surface into the solid mass.

Thus, based on this preclinical experience, it would be reasonable to conclude that the ovarian cancer patient populations who might be anticipated to benefit from a regional therapeutic approach would be those with very small-volume IP disease (e.g., microscopic cancer only or macroscopic nodules <0.5 cm in maximal diameter) when the IP treatment program was initiated.

However, it is relevant to also note here several points that may substantially modify the impact of this highly clinically relevant statement.

In fact, the actual "advantage" of IP drug administration is not simply the "total amount of drug" found to reach the cancer after regional delivery, but rather how much drug reaches the cancer *relative to* what is achieved with systemic drug delivery. Thus, when exploring a potential advantage of this approach, it is important to consider the *total amount of drug* reaching the cancer from both *direct diffusion* (from regional delivery) and *capillary flow* (from the systemic circulation), and to then inquire if there is any added effect resulting from the high local concentrations. Thus, if even a few millimeters depth of tumor is exposed to the substantially greater levels of the cytotoxic agent with regional treatment than attainable with systemic drug delivery, there may be a clinically relevant benefit associated with this route of treatment.

This hypothesis assumes that when a cytotoxic agent is administered regionally there will be *no meaningful decrease* in the amount of the active agent that reaches the tumor by capillary flow. In fact, it is important to acknowledge that *if there is a reduction* in the amount of drug delivery to tumor from the vascular department after IP therapy, it is actually possible the overall effectiveness of the treatment program *will be less* than that achieved with intravenous therapy.

How can it be known if a drug *administered regionally* will achieve the *same level* of delivery of drug to tumor through the vascular compartment compared with systemic administration? The first method is to actually measure the level of "active" drug (both peak and area-under-the-concentration-versus time curve [AUC]) within the systemic vascular compartment after either intravenous or regional delivery.

However, a simpler and quite practical method would be to determine if the dose-limiting toxicities of an intraperitoneally administered drug are related to the *local* or *systemic effects* of the agent. For example, if the dose of a particular cytotoxic agent administered into the peritoneal cavity is able to be escalated to the point where the limiting side effect is found to be bone marrow suppression (e.g., carboplatin), it would be quite reasonable to assume that as much of the active (cytotoxic) drug was reaching the systemic compartment (and therefore the tumor, by capillary flow) as when the drug was delivered systemically.

Conversely, for an intraperitoneally administered agent that produces minimal systemic effects at its maximally tolerated dose because abdominal discomfort prevents further dose escalation (e.g., doxorubicin or paclitaxel), it can be appropriately assumed that there will be less systemic exposure to the drug than achieved with intravenous infusion. In such a situation, the particular drug will either have to be delivered *both systemically and regionally*, to achieve a *maximal biological effect*, or it must simply be acknowledged that there will be less delivery of the drug to the cancer by capillary flow than would have been achieved after intravenous administration.

In the case of cisplatin, preclinical data have convincingly shown that *after IP delivery*, a small layer of tumor near the peritoneal surface is exposed to substantially higher concentrations of the agent than can be achieved with intravenous delivery *(21)*. However, the remainder of the tumor volume (beneath this surface area) is exposed to the *same concentration* of the cytotoxic agent as achieved with systemic treatment.

Thus, with IP cisplatin administration, there is a *relative increase* in the exposure of tumor near the surface of the cavity after regional treatment, *without any compromise* to exposure of other portions of the tumor volume. Further, treating patients with IP cisplatin who have even large-volume disease should not be associated with any negative consequences, as systemic delivery of the agent will not be meaningfully reduced.

Interestingly, although cisplatin and carboplatin have been shown to produce identical clinical results when administered systemically in the treatment of ovarian cancer, preclinical data have suggested caution in assuming the same will be the case with IP delivery *(22)*. In fact, probably related to differences in the biological structures/size of the two drugs (as might have been predicted from their unique clinical toxicities), dissimilar profiles emerge for the agents when examining the concentration of "platinum" within tumor tissue after regional administration.

The relevance of these preclinical findings (higher platinum concentrations for cisplatin than carboplatin) at the clinical level remains to be defined. The point to be made here is that it should not simply be assumed these two platinum drugs are "equivalent" for regional treatment of ovarian cancer.

A second point regarding the relevance of tumor volume in influencing the clinical utility of IP chemotherapy specifically relates to its use as a *primary treatment strategy* in advanced ovarian cancer.

Assuming the malignancy is not inherently platinum-resistant (which occurs in 20–30% of ovarian cancers) *(1)*, whereas the percentage of the cancer cell population affected by direct diffusion with the *initial cycle(s)* of a regional treatment program may be quite limited, with *later cycles* the volume of the remaining tumor should be considerably smaller (as a direct result of the cytotoxic effect of platinum entering the systemic compartment). Therefore, if an ovarian cancer patient initiates primary chemotherapy with the largest remaining tumor mass being 2 cm in maximum diameter, a major reduction in the size of the residual nodules should make it possible for the high concentrations of drug in direct contact with the tumor to have a far greater effect in subsequently delivered IP treatment cycles.

(Note: This point may help explain what some have considered to be a paradoxical finding in the initial phase III randomized trial of IP versus intravenous cisplatin as primary chemotherapy of advanced ovarian cancer *(26)*. In this trial, patients with *macroscopic residual disease* appeared to exhibit a *greater* therapeutic benefit from regional treatment, compared to those individuals who initiated therapy with *only microscopic cancer* present. Considering only the issue of depth of penetration, one would not have predicted this finding. However, for those patients who began therapy with larger volumes of disease and had the worst prognosis, the *benefits of direct drug uptake plus delivery of drug by capillary flow may actually have had the greatest impact on the natural history of the disease process*.)

8. CONCLUSION

The mathematical modeling concepts developed by Robert Dedrick and his colleagues *(8)*, and subsequent preclinical evaluation, provided a strong

framework upon which to build a clinical investigative program examining IP chemotherapy as a management approach in advanced ovarian cancer. These investigative efforts suggested the type of antineoplastic agents that should be explored, the patient populations more likely to benefit, and the limitations and potential toxicities of this novel strategy.

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2 Management of Ovarian Cancer: Clinical Trials

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Summary

To date, the accomplishment in the area of regional treatment of ovarian cancer has been a major advance in the management of this difficult malignancy. What began as a hypothesis, based on a theoretical mathematical model, has been translated into a 67-mo median survival for women with small-volume residual advanced ovarian cancer *(1)*.

The three major randomized clinical trials on ovarian cancer are detailed in this chapter. The methodology and outcomes, as well as a critique of their design, are presented. Outcomes of these trials to date are described.

Key Words: Intraperitoneal chemotherapy; ovarian cancer; clinical trials.

1. INTRODUCTION

The provocative modeling studies of Dedrick and colleagues at the National Cancer Institute suggested a strong rationale for the intraperitoneal (IP) administration of cytotoxic agents in treatment of advanced ovarian cancer *(1)*. This stimulated other investigators in several centers to explore the clinical implications of this analysis.

Preclinical evaluation, described in some detail in the previous chapter, helped define the patient populations where this strategy had the realistic potential to favorably impact the course of the illness, and pointed out potential concerns (both theoretical and practical) with this approach.

2. PHASE I TRIALS OF THE IP ADMINISTRATION OF CYTOTOXIC ANTINEOPLASTIC AGENTS

Over the past two decades, the use of several antineoplastic and biological agents has been explored in phase 1 clinical trials. The investigation of biologi-

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Table 1
Pharmacokinetic Advantage of Selected Agents with Known Activity in Ovarian Cancer When Administered Directly into the Peritoneal Cavity

Agent	*Ratio: Peritoneal Cavity to Serum*	
	Peak Concentration	**AUC**
Methotrexate *(2,3)*	92	
5-fluorouracil *(4)*	300	360
Melphalan *(5)*	93	65
Doxorubicin *(6)*	470	
Mitoxantrone *(7)*		1,400
Cisplatin *(8–11)*	20	12
Carboplatin *(12,13)*		18
Paclitaxel *(14,15)*	1,000	1,000

AUC, Area-under-the concentration versus time curve

cal agents such as interferon-alpha, interferon-gamma, and interleukin-2 is discussed in Chapter 4.

Table 1 summarizes the pharmacokinetic profile of selected cytotoxic agents with documented anticancer activity in ovarian cancer when delivered directly into the peritoneal cavity *(2–15)*. As predicted by the Dedrick model, the agents demonstrating the greatest difference between cavity and systemic exposures are drugs known to undergo extensive metabolism in the liver (e.g., 5-fluorouracil, doxorubicin, cytarabine, paclitaxel, and mitoxantrone), whereas drugs that do not exhibit this property have a less impressive pharmacokinetic advantage associated with IP administration (e.g., cisplatin and carboplatin). Agents predicted to slowly exit the cavity, based on their unique structural properties (e.g., paclitaxel), also reveal a substantial difference between cavity and systemic exposures after regional delivery.

However, as discussed in the previous chapter, the *relative differences* between local and systemic drug concentrations after IP drug instillation is only one measure of the potential effectiveness of regional treatment. A second important question is the ability of a drug to reach the malignancy by *capillary flow* after regional treatment.

Although it is reasonable to conclude IP administration results in "only a modest" increase in cavity exposure (10–20-fold) compared with the systemic compartment *(8–13)*, for both cisplatin and carboplatin, substantial concentrations of drug instilled into the peritoneal cavity ultimately reach the systemic circulation, such that this route of drug delivery results in essentially equivalent exposure of the tumor to the agent through capillary flow as achieved with intravenous delivery.

The critical point resulting from this analysis is that the IP administration of either cisplatin or carboplatin should, at a minimum, be *equally as effective as systemic therapy* for ovarian cancer, and any effect of the high local concentrations *may add to the benefits* associated with use of this major class of cytotoxic agents.

However, a very different conclusion is reached when analyzing the potential impact of drugs such as paclitaxel, which are limited in the dose that can be delivered into the peritoneal cavity because of their local toxic effects (e.g., abdominal pain), rather than systemic side effects (e.g., bone marrow suppression). Although rather remarkable concentrations of paclitaxel, relative to the systemic compartment, can be achieved (>1,000-fold), very limited concentrations of the active drug are found in the systemic compartment after regional delivery *(14,15)*. Thus, to achieve optimal utilization of this drug in the management of ovarian cancer, it is reasonable to conclude that the agent should be delivered both locally *and* systemically *(16)*.

An additional conclusion from these phase 1 IP trials was the observation that considerable local toxicity could be observed with use of certain drugs (e.g., doxorubicin) *(6,17,18)*. Thus, despite the pharmacokinetic advantage associated with regional delivery, considerable caution would be advised in the administration of these agents. It might be argued that an alternative form of such agents might be developed that could minimize local toxicity (e.g., liposomal preparation) while permitting tumor within the compartment to be exposed to the high concentrations of the agent, possibly with the use of this delivery strategy *(19)*.

During this era, several combination chemotherapy regimens were also explored in phase 1 IP trials, focusing on agents with known activity in ovarian cancer or where theorized synergy between the drugs was possible *(18,20,21)*. There was a particular appeal with this approach, as it permitted the examination of the clinical relevance of highly concentration-dependent interactions noted in preclinical systems.

However, concerns were also raised by this novel strategy. Adding agents together in the fluid volume to be instilled into the peritoneal cavity had the potential to alter the microenvironment (e.g., pH) such that one drug in the combination might become less cytotoxic against the malignant cells, or another agent, with an acceptable local side-effect profile when delivered regionally by itself, might become quite toxic. Finally, it was recognized that if biological activity (e.g., surgically documented tumor regression) was observed in a clinical trial, it would be essentially impossible to know if the responses resulted from one of the individual drugs or actually represented a *synergistic effect* of the combination.

Significantly, the nature of these early phase trials, and the limited populations available, required that investigators carefully select dosing schedules to

be examined. However, alternative strategies might have been chosen that would have been equally valid from the perspective of both toxicity and potential efficacy. Thus, while the platinum agents were principally explored for IP administration on an every 3–4 wk schedule, daily treatment for several days, or a weekly schedule, would have been acceptable options.

3. UNIQUE PHASE I TRIAL EXPERIENCE WITH IP PACLITAXEL

In the case of paclitaxel, compelling data regarding the mechanism of its cytotoxicity (i.e., strongly cycle-specific) argued for a more frequent regional dosing schedule *(22,23)*. Thus, although the initial phase 1 study examining IP paclitaxel in ovarian cancer used the conventional "every 3 wk" treatment strategy *(14)*, a subsequent phase I trial explored its delivery on a weekly schedule *(15)*. Interestingly, use of a lower dose weekly regimen was found to substantially reduce the toxicity (i.e., abdominal pain) associated with IP paclitaxel *(15)*, which had been previously determined to be dose related *(14)*.

The phase I experience with IP paclitaxel also provides a demonstration of the fact that this route can be utilized not only to substantially enhance the *peak levels* of drug in direct contact with tumor but also to profoundly increase the total exposure (area under the curve [AUC]) of a cytotoxic agent to tumor over prolonged periods of time.

In the phase I trial of weekly IP paclitaxel, measurements were made of the concentration of paclitaxel within the peritoneal cavity *immediately preceding* the next weekly dosing schedule (Table 2) *(15)*. The analysis revealed potentially cytotoxic concentrations of the agent persisted for the entire week after treatment. Thus, in theory, the weekly IP delivery of paclitaxel has the potential to permit at least the surface of the cavity, and malignant cells present in this environment, to be *continuously exposed* to the cycle-specific cytotoxic drug *(22,23)*. Further, this provocative goal was accomplished with both an acceptable systemic and local toxicity profile. (Note: The results of a phase 2 second-line ovarian cancer IP paclitaxel trial, conducted by the Gynecologic

Table 2
Concentration of Paclitaxel After IP Delivery*

Administered Dose	*5–7 d After Instillation*
60 mg/m^2	25 µmol/L
65 mg/m^2	35 µmol/L
65 mg/m^2	20 µmol/L

*Individual patients treated at specified dose levels *(15)*.

Oncology Group based on this observation, will be discussed later in this chapter) *(24)*.

4. IMPACT OF CHANGING CONCEPTS OF OVARIAN CANCER TREATMENT ON IP DRUG DELIVERY STRATEGIES

These phase I studies were conducted over a period of two decades, which partially explains modifications in the concepts of optimizing treatment programs in the IP arena. As data from accumulating clinical trials more clearly defined both the relevance of "dose intensity" and methods to reduce the toxicity of specific agents, these ideas were employed by investigators exploring regional drug delivery strategies. For example, the initial trials of IP carboplatin determined IP dosing based on "mg/m^2" *(12,13)*, whereas later studies used AUC dosing strategies *(25)*.

Further, early phase I (and some phase II) trials of IP cisplatin explored the potential of substantially increasing the administered dose using this route of delivery *(8,18,20,21)*. During this era of drug development in oncology, there was a fundamental belief that "more is better" when delivering cytotoxic agents, and this general treatment philosophy played a major role in many chemotherapeutic approaches in ovarian cancer (and other malignancies).

However, a series of highly *negative* prospective phase III randomized trials in the treatment of ovarian cancer have convincingly demonstrated that this concept is seriously flawed, at least at the concentrations of currently available cytotoxic agents that can be *safely attained* within the *systemic compartment* after intravenous drug delivery *(26–29)*. These trials revealed that by "doubling" the dose intensity of systemically delivered platinum (e.g., cisplatin from 50 mg/m^2 to 100 mg/m^2 and carboplatin from AUC 6 to AUC 12), toxicity substantially increased without any change in survival.

It is critical to emphasize that this negative experience with dose intensity in randomized phase III trials in ovarian cancer relates to what can currently be achieved with *systemic drug delivery*, and does not suggest that the fundamental concept is actually wrong. On the contrary, it is conceivable that at the far higher local drug concentrations achievable locally after IP drug delivery (e.g., 10–20-fold for cisplatin and carboplatin *(8–13)* and >1,000-fold for paclitaxel *(14,15)*), a clinically relevant impact of "dose–response" might be observed.

Thus, conceptually, *maximizing the amount of platinum* achieved within the systemic compartment with IP administration should currently be understood to *not be a goal of regional drug delivery*. Rather, the aim should be to attain a systemic drug concentration that permits sufficient delivery of the platinum agent to the tumor by *capillary flow*, as previously defined in phase III randomized clinical trials *(26–29)*.

5. EVALUATION OF THE BIOLOGICAL ACTIVITY OF IP CYTOTOXIC CHEMOTHERAPY IN THE MANAGEMENT OF OVARIAN CANCER

After the completion of phase I studies, which defined the pharmacokinetic properties and safety of both single-agent and several combination chemotherapy IP programs, investigators in several centers and cooperative groups initiated a series of platinum-based phase II IP efficacy trials in patients with ovarian cancer *(24,30–40)*.

Before briefly reviewing and summarizing the results of these studies, it is important to discuss the method by which "efficacy" was defined. In most *traditional* phase II oncology trials, patients with "measurable" mass lesions, based on physical exam findings or (more commonly) radiographic evaluation, are treated with a particular experimental program, and response is determined based on a prospectively defined percentage of shrinkage of those tumor nodules/masses.

However, although such an approach could have been used to evaluate the effectiveness of an IP regimen in a phase II trial, a decision to perform this type of analysis would have been a serious error. As previously noted, the setting where the benefits of an IP treatment program might be rationally anticipated would be in patients with either documented microscopic IP cancer, or where only very small-volume macroscopic disease was present (<0.5-cm–1-cm tumor masses) when the regional strategy was initiated *(41–43)*. Conversely, extensive preclinical evaluation (discussed in the preceding chapter) had strongly suggested there would be minimal (or no) activity observed after IP therapy of larger macroscopic tumor masses.

Treatment of patients with tumor nodules that could be imaged by a CT scan of the abdomen/pelvis would likely require IP disease of at least 2 cm in diameter, which is far larger than what existing data would suggest is appropriate for successful use of this route of drug delivery. Given this information, how can the biological activity of IP therapy be evaluated? Fortunately, in the management of patients with ovarian cancer, there is long-established and accepted experience, with surgical reassessment after the completion of primary chemotherapy programs ("second-look laparotomy") *(44,45)*.

Thus, in several centers exploring the activity of IP therapy in women with ovarian cancer, patients who had "relatively small-volume disease" at the time of performance of a second-look surgical procedure were treated on an Institutional Review Board (IRB)-approved phase 2 IP chemotherapy trial, and, subsequently, underwent a "third-look" surgery (laparotomy or, more recently, laparoscopy) to evaluate the reduction in tumor volume (compared to what was observed before treatment) or the absence of any histologic evidence of persistent cancer ("negative third-look").

6. PHASE II TRIAL EXPERIENCE WITH IP CISPLATIN IN OVARIAN CANCER

Predictably, based on its central role in the management of ovarian cancer, much of the initial phase II trial effort (both single-agent and combination chemotherapy regimens) in the malignancy focused on cisplatin *(30–37)*.

Further, with few exceptions, the early phase II IP trials in ovarian cancer were directed toward treating women with this strategy as a "second-line" treatment approach. Exploration of the activity of IP cisplatin in this particular clinical setting permitted a most interesting, and rather unique, analysis.

Because essentially all patients entered into the phase II, second-line, IP cisplatin–based trials had received the same agent (or the equivalent drug, carboplatin) delivered intravenously as a component of primary chemotherapy, the activity of *IP cisplatin* could be indirectly compared to the activity of *systemically delivered cisplatin* (or carboplatin). In addition, because the IP delivery followed documentation of the extent of response to the intravenous treatment program, it was reasonable to speculate that any "observed biological activity" of the second-line approach was related to the specific *route of delivery*, rather than only the effect of cisplatin itself, because the "cisplatin effect" would have been seen with the intravenous regimen *(46)*.

It is essential to note that any such comparisons (to be described later in this chapter) are merely "*hypothesis generating*," or supportive of further clinical investigation. In the absence of data from prospective randomized phase III trials examining the impact of treatment on survival, it is completely unknown if the observation of "additional tumor cell kill" actually benefits patients.

As rather accurately predicted by the preclinical studies, substantially more "biological activity" (surgically defined tumor shrinkage, conversion of "positive" second-look laparotomies to "negative" third-look procedures) was observed for second-line IP cisplatin in patients with small-volume disease, compared with those individuals with larger tumor masses *(47)*. This point is emphasized by the extensive published experience of the Gynecologic Cancer program of the Memorial Sloan-Kettering Cancer Center with second-line, cisplatin-based IP chemotherapy in ovarian cancer (Table 3) *(47)*.

In addition, and not necessarily predicted by the previously conducted preclinical evaluations, the accumulating data in this area revealed another highly relevant limitation of IP cisplatin. The Memorial Sloan-Kettering group demonstrated impressive surgically defined biological activity for IP cisplatin in patients with ovarian cancer whose malignancy had previously responded to intravenous cisplatin, but who persisted in having "small-volume residual disease" at the time of a second-look laparotomy *(47)*. However, the group also showed that there was essentially no activity observed with this regional strategy in patients with similarly defined small-volume disease, except where the

Table 3
Surgically Documented Complete Response Rate to Second-Line Cisplatin-Based IP Chemotherapy of Ovarian Cancer *(47)*

	Largest Residual Tumor Mass	
	Microscopic	**>1 cm**
Prior response to intravenous cisplatin	6/13 (46%)	2/16 (13%)
No prior response to intravenous cisplatin	1/4 (25%)	0/23 (0%)

cancer had actually failed to exhibit evidence of a response to the primary cisplatin-based intravenous chemotherapy program.

Thus, these data provide strong support for the concept that the high concentrations of platinum achievable within the peritoneal cavity (10–20-fold greater than present within the systemic circulation) are able to overcome a *modest level of resistance* to the agent, in that additional cell kill is observed when disease is found to persist in the setting of documentation of a *response* to the intravenous treatment. In sharp contrast, where the tumor has shown itself to possess an inherent *major level of resistance*, the concentration of platinum present within the peritoneal cavity after regional drug delivery is unable to produce a biologically relevant effect. Notably, these data are quite consistent with the previously published experience with high dose intravenous chemotherapy and autologous bone marrow transplantation used in the management of ovarian cancer *(48)*.

Several phase II single-agent cisplatin– and combination cisplatin–based IP chemotherapy trials have been reported, with similar levels of observable surgically documented biological activity *(30–37)*. The results of these studies do not suggest the superiority of any particular cisplatin-based regional treatment strategy, including the use of "high dose" IP cisplatin (combined with sodium thiosulfate rescue) *(8,36)*.

Again, in the *second-line setting*, what the data make quite clear is that patients with ovarian cancers that are inherently resistant to platinum (documented by failure to respond to primary chemotherapy), or those with larger volume disease (maximum tumor mass >1 cm in maximum diameter) are highly unlikely to benefit from this therapeutic strategy *(47)*. Conversely, for those individuals whose cancers have responded to initial chemotherapy, but microscopic or small-volume macroscopic disease (<0.5 cm maximum diameter) persists, a substantial percentage of such patients (30–40%) may be anticipated to attain the state of "surgically documented complete response" (if this surgery were performed) after treatment with an IP cisplatin–based regimen.

Unfortunately, evidence of a *biological effect* (e.g., objective tumor shrinkage or conversion of a "microscopically positive" second-look surgery to "micro-

scopically negative third-look surgery") does not necessarily signify that patients have experienced *clinical benefit* (e.g., improved symptoms or progression-free and overall survival) from the strategy. Only appropriately designed prospective randomized phase III trials can definitively address this question.

However, it is interesting to note that several groups have reported an impressive experience with long-term (>4–5 yr) survival for ovarian cancer patients treated with *second-line* cisplatin-based IP chemotherapy *(49–52)*. Whether this favorable outcome reflects the benefits of this management approach, the natural history of disease in a subset of patients with favorable biological characteristics (e.g., initial response to chemotherapy with minimal disease at second-look surgery), or a combination of these two factors remains unknown in the absence of data from a phase III trial.

A final cisplatin-based IP phase II trial experience is worthy of particular mention. Investigators at the Memorial Sloan-Kettering Cancer Center treated a group of ovarian cancer patients who were found to be without histologic evidence of disease at the time of performance of a second-look laparotomy with three cycles of IP cisplatin and etoposide *(53)*. The researchers subsequently compared the risk of documented disease relapse in this population to a contemporaneous "historical control" group at their institution that was in an identical clinical state, and would have been eligible for entry into this phase II trial, but for various reasons (e.g., patient/physician choice) *did not* receive this consolidation strategy. Interestingly, the investigators found that the rate of ultimate relapse was greater (54% vs 39%) in the historical control group *(53)*.

Although it is appropriate to conclude that such published retrospective comparisons to historical controls should generally be ignored, as the most likely explanation for the finding is that the nonrandomized "experimental study arm" population simply had more favorable "baseline clinical characteristics" that could account for this "apparent favorable outcome," the exact opposite was the case in this analysis. In fact, the historical control group, which was found to have the greater risk of relapse, possessed the more favorable baseline features, including having a higher percentage of individuals who were stage II (39% vs 8%), and a lower percentage of individuals with suboptimal disease (20% vs 33%) when primary chemotherapy was initiated.

Again, although not a randomized trial, these data are quite provocative, and suggest another setting where IP cisplatin–based chemotherapy may be rationally employed.

7. NON–CISPLATIN-CONTAINING PHASE II IP CHEMOTHERAPY TRIALS

IP carboplatin has been examined as a single agent, and in several combination chemotherapy programs, with surgically documented activity observed in the settings of both primary and second-line treatment of ovarian cancer *(38–*

40). Overall, the objective response rates are comparable to that seen with IP cisplatin in similar patient populations. However, some concern has been expressed for a potentially lower response rate to carboplatin in the presence of *macroscopic* residual disease, compared to the older platinum drug, when the agents are employed as second-line therapy *(54)*.

The experience with IP paclitaxel is of particular interest. In a Gynecologic Oncology Group phase II trial, paclitaxel was administered on a weekly schedule (60 mg/m^2) for 16 wk *(24)*. Of the 28 patients who initiated regional treatment with *microscopic disease only* (documented at the prior performance of a second-look laparotomy), 17 (61%) attained a surgically documented complete response, in contrast to only 1 in 31 patients (3%) who achieved this state if they started second-line IP paclitaxel with any evidence of *macroscopic cancer*.

These data reinforce the importance of tumor volume in influencing the activity of IP therapy, particularly when relying almost exclusively on direct uptake of the agent from the cavity into the malignant cell population, when there is limited (or no) delivery of the drug through the vascular compartment. Further, this experience emphasizes the relevance of a "combined intravenous/IP" approach when employing paclitaxel, or a cytotoxic drug with similar biological properties *(16)*.

Other single agents explored in phase II IP trials in ovarian cancer included cytarabine *(55)*, mitoxantrone *(56,57)*, 5-fluorouracil *(58)*, and fluoroxidine *(57)*.

8. PHASE III TRIAL OF IP VERSUS INTRAVENOUS CISPLATIN (WITH ALL PATIENTS ALSO RECEIVING INTRAVENOUS CYCLOPHOSPHAMIDE) AS PRIMARY TREATMENT OF SMALL-VOLUME RESIDUAL ADVANCED OVARIAN CANCER

The aforementioned experience with second-line cisplatin-based IP chemotherapy led the Southwest Oncology Group and the Gynecologic Oncology Group to initiate a randomized phase III trial directly, comparing a regimen of IP cisplatin to intravenous cisplatin as primary treatment of small-volume residual advanced ovarian cancer, after an attempt at optimal surgical cytoreduction (Table 4) *(59)*. All patients also received intravenous cyclophosphamide as the second drug in the combination program.

In this trial, small-volume residual disease was defined as the largest remaining tumor nodule, being <2 cm in maximal diameter. The study was well balanced for known prognostic factors in the malignancy.

The trial found that patients treated with the IP cisplatin program experienced a lower incidence of neutropenia, tinnitus, and hearing loss (presumably caused by reduced peak levels of platinum within the vascular compartment and marginally lower total systemic exposure to the agent), but a greater risk of abdomi-

Table 4
Randomized Phase III Trials of IP Versus Intravenous Cisplatin-Based Primary Chemotherapy of Small-Volume Residual Advanced Ovarian Cancer

Study	*Progression-Free Survival (Median in Months)*	*Overall Survival (Median in Months)*	*Control Arm*	*Experimental Arm*
Study 1 *(59)*	–	48 vs 41 ($p = 0.02$) HR 0.76	cisplatin 100 mg/m^2 IV plus cyclophosphamide 600 mg/m^2 IV q 21-d × 6	cisplatin 100 mg/m^2 IP plus cyclophosphamide 600 mg/m^2 IV q 21-d × 6
Study 2 *(62)*	28 vs 22 ($p = 0.02$) HR 0.78	63 vs 52 ($p = 0.05$) HR 0.81	paclitaxel 135 mg/m^2 IV over 24-hours plus cisplatin 75 mg/m^2 IV q 21-d × 6	carboplatin AUC 9 IV q 28-days × 2; followed by Paclitaxel 135 mg/m^2 IV over 24-hours cisplatin 100 mg/m^2 IP (day 2) q 21-d × 6
Study 3 *(16)*	24 vs 18 ($p = 0.05$) HR 0.79	66 vs 50 ($p = 0.03$) HR 0.71	paclitaxel 135 mg/m^2 IV over 24 hours plus cisplatin 75 mg/m^2 IV q 21-d × 6	paclitaxel 135 mg/m^2 IV over 24 hours plus cisplatin 100 mg/m^2 IP (day 2) plus Paclitaxel 60 m/mg^2 IP (day 8) q 21-d × 6

nal pain (principally, mild to moderate in severity). There was no difference in treatment-related mortality between the two treatment arms.

Of considerable importance, patients randomized to receive IP cisplatin experienced superior overall survival compared with systemic delivery of the agent (median: 49 mo vs 41 mo; $p = 0.02$) *(59)*.

9. PHASE III TRIAL OF IP VERSUS INTRAVENOUS CISPLATIN (WITH ALL PATIENTS ALSO RECEIVING INTRAVENOUS PACLITAXEL) AS PRIMARY TREATMENT OF SMALL-VOLUME RESIDUAL ADVANCED OVARIAN CANCER

Despite the impressive impact of IP treatment found in the initial phase III trial, many investigators questioned whether the benefits associated with regional cisplatin drug delivery could be achieved by simply substituting paclitaxel for cyclophosphamide, based on the finding at that time of the superiority of the taxane-containing regimen when used in advanced ovarian cancer *(60,61)*.

Thus, a second phase III trial was initiated by the Gynecologic Oncology Group, the Southwest Oncology Group, and the Eastern Cooperative Oncology Group, which directly compared the "new" systemically administered "gold standard" regimen of intravenous cisplatin plus paclitaxel to an experimental program of intravenous paclitaxel plus IP cisplatin (Table 4) *(62)*. Of note, in this study, small-volume residual advanced ovarian cancer was defined as the largest tumor mass, being <1 cm in maximum diameter.

This trial added a second novel component to the experimental regimen. In an effort to employ the regional therapy in a setting where the "smallest possible tumor volume" was present when IP treatment was initiated (as predicted by the previously described preclinical models and limited clinical experience *(47,63)* to be a rational strategy), patients randomized to this study arm were given two cycles of "moderately high dose" intravenous carboplatin (AUC 9) to *chemically debulk* the tumor before receiving IP cisplatin *(62)*.

Although theoretically a reasonable approach, the initial intravenous carboplatin resulted in an unanticipated incidence of severe and persistent bone marrow suppression (principally thrombocytopenia), such that approximately 20% of the patients randomized to the experimental arm ultimately received up to two courses of IP cisplatin *(62)*. Although not a direct result of the regional treatment, patients experiencing prolonged cytopenias were required to be removed from the investigative program.

Despite this, women randomized to the experimental study arm experienced a statistically significant improvement in both progression-free (28 mo vs 22 mo; $p = 0.02$) and overall survival (63 mo vs 52 mo; $p = 0.05$) *(62)*. Thus, even though *all patients* entered into this study received intravenous paclitaxel, the

use of IP cisplatin *further extended survival*. In this regard, it is interesting to note that this trial was the first randomized study in advanced ovarian cancer to achieve a median overall survival of >5 yr in one of the study arms (IP cisplatin).

It is also important to comment here on a possible specific role for the two courses of "moderately high dose" carboplatin in the observed survival benefits in this trial. As previously mentioned, several randomized phase III trials examining a role for *dose intensity* in the range of the carboplatin dose used in this study have failed to demonstrate any benefit in favorably impacting survival *(26–29)*. Thus, it is highly unlikely that the two courses of carboplatin used before the administration of IP cisplatin had a direct influence on the trial's outcome.

10. PHASE III TRIAL OF INTRAVENOUS CISPLATIN/ PACLITAXEL VERSUS IP CISPLATIN PLUS BOTH IP AND INTRAVENOUS PACLITAXEL

The most recent randomized phase III trial, which was conducted by the Gynecologic Oncology Group, directly compared a regimen of intravenous cisplatin plus paclitaxel (control arm) to an "experimental program" consisting of IP cisplatin plus both IP *and* intravenous paclitaxel as primary chemotherapy of small-volume residual advanced ovarian cancer (Table 4) *(16)*. (The rationale for combining intravenous and IP paclitaxel is discussed earlier in this chapter, as well as in the preceding chapter.)

In an effort to avoid direct interactions between cisplatin and paclitaxel within the instilled treatment volume (and the unknown consequences of such an event), the regionally delivered paclitaxel was administered on day 8 of each 21-d treatment cycle. The largest volume of residual disease permitted for entry into this trial was, again, <1 cm in maximum diameter.

Patients treated on the experimental arm of this phase III trial experienced a higher incidence of several systemic toxicities (e.g., emesis, bone marrow suppression, and neuropathy) and more abdominal discomfort. However, of considerable importance, a *formal quality-of-life analysis* was performed as a prospective component of this trial; although there was a lower measured quality-of-life associated with the IP regimen *during the treatment program*, at the 12-mo follow-up there was no difference between the regimens *(16)*.

Of greatest significance, this study once again revealed that treatment with a cisplatin-based IP program resulted in a highly statistically significant improvement in both progression-free survival (24 mo vs 18 mo; $p = 0.05$) and overall survival (66 mo vs 50 mo; $p = 0.03$), and was the *third randomized phase III trial to reach this conclusion*.

11. IMPLICATIONS OF THE CURRENT IP CHEMOTHERAPY DATA FOR THE PRIMARY CHEMOTHERAPEUTIC MANAGEMENT OF SMALL-VOLUME RESIDUAL ADVANCED OVARIAN CANCER

The data from these three randomized phase III trials have now firmly established a new *standard of care* in the primary chemotherapeutic management of small-volume residual advanced ovarian cancer *(16,59,62)*. Collectively, they indicate that patients treated with cisplatin by the IP route experience a 20%–30% reduction in the risk of death compared with intravenous drug delivery.

These results are similar to those previously documented when paclitaxel was substituted for cyclophosphamide in the management of ovarian cancer *(60,61)*. Of great importance, it is now clear the use of IP cisplatin *adds* to the benefits attained by using intravenous paclitaxel.

However, as is very often the case in oncology, the results of these three landmark trials do raise several highly clinically relevant questions: Is it necessary to employ IP cisplatin at a dose of 100 mg/m^2, or can a somewhat lower dose be utilized to reduce the toxicity of treatment? Can IP carboplatin be substituted for cisplatin? What is the role of IP paclitaxel?

Although definitive answers to these (and other) questions are currently not available, the following are reasonable responses, based on existing data, which may be utilized by oncologists considering IP chemotherapy in this clinical setting.

First, while it is quite appropriate to employ an IP cisplatin dose of 100 mg/m^2, based on the findings of the three randomized phase III trials *(16,59,62)*, it is also rational to argue that moderately lowering the cisplatin dose (75–80 mg/m^2) will *not* reduce the efficacy of treatment (continued high local concentrations, minimal decrease in systemic exposure) *(26–29)*. Further, for many patients, a modest dose reduction may make it possible for the cisplatin-based treatment to be far better tolerated (e.g., reduced emesis and neuropathy).

Second, although IP carboplatin has been successfully employed in the phase II setting *(25)*, including in combination with intravenous paclitaxel, all randomized trials (to date) that have shown a *major survival advantage* have utilized IP cisplatin. Thus, it would be reasonable to conclude that unless a particular patient experiences unacceptable systemic toxicity from cisplatin, or simply refuses to receive the agent, the initial regional treatment program should utilize cisplatin. In the setting of significant cisplatin-related toxicity (e.g., emesis), substitution with IP carboplatin is a highly rational management option *(25)*.

Finally, although IP paclitaxel was utilized in the third randomized trial (showing the greatest impact on survival) *(16)*, the previous two studies that also revealed a favorable effect on overall survival did not employ this agent administered regionally *(59,62)*. Further, it is quite possible that much of the

abdominal pain observed in the most recent trial may have been caused by the paclitaxel *(14,15)*.

Thus, one rational option for management may be to begin the IP treatment program with only the cisplatin delivered regionally. If the initial cycle is tolerated reasonably well, in regard to the development of abdominal discomfort, IP paclitaxel can be added to the second (and future) cycles. However, if even "modest" abdominal pain is noted with IP cisplatin alone, it may be prudent to avoid the addition of regional paclitaxel that may significantly worsen the local discomfort and, in fact, prevent the completion of the planned IP treatment program.

12. FUTURE DIRECTIONS IN THE USE OF IP CHEMOTHERAPY IN THE MANAGEMENT OF OVARIAN CANCER

The results of three large prospective randomized phase III trials have now established IP chemotherapy as the standard of care in the primary chemotherapeutic management of small-volume residual advanced ovarian cancer *(16,59,62)*. Much research remains to be done in this arena, including focusing major efforts to improve methods of drug delivery (discussed in Chapter 5), exploring novel antineoplastic agents administered regionally, and developing innovative strategies to enhance drug penetration and distribution.

Further, based on currently available data and knowledge of the natural history of the course of this disease, it is reasonable to propose the conduct of prospective randomized phase III trials in other settings involving patients with ovarian cancer (Table 5).

In conclusion, what has been accomplished to date in the area of regional treatment of ovarian cancer has been a major advance in the management of this difficult malignancy. What began as a hypothesis based on a theoretical

Table 5
Additional Potential Indications for IP Chemotherapy in the Management of Ovarian Cancer

1. *Primary treatment* of "early-stage" high-risk ovarian cancer (stage IC, stage 2)
2. *Consolidation treatment* following attainment of a surgically defined complete response *(53)*.
3. "*Second-line treatment*" with microscopic/minimal macroscopic residual cancer confirmed at a reassessment surgery in a patient with documented response to primary platinum-based systemic chemotherapy
4. Treatment following a major surgically confirmed response (minimal residual disease) to neoadjuvant chemotherapy.

mathematical model *(1)* has been translated into a 67-mo median survival for women with small-volume residual advanced ovarian cancer. Yet, we are truly only at the "end of the beginning."

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3 A Systematic Review and Meta-Analysis of Randomized Trials

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Summary

Intraperitoneal (IP) chemotherapy for advanced ovarian cancer improves both overall and disease-free survival. In this chapter, we compare the effectiveness of intravenous (IV) to IP chemotherapy. The evidence suggests an improvement in survival if some of the chemotherapy is administered via the IP route. The adverse events principally relate to the presence of a peritoneal catheter, including pain, catheter blockage, gastrointestinal effects, and infection.

A systematic search identified eight relevant randomized trials studying 1,819 women receiving primary treatment for ovarian cancer. Women were less likely to die if they received an IP component to the chemotherapy (hazard ratio = 0.80; 95% confidence interval [CI] = 0.71–0.90). Administering a component of chemotherapy by the IP route also prolongs the disease-free interval (0.79; 0.69–0.90) by almost 9 mo and increases complete response rates. There may, however, be greater pain, fever, and gastrointestinal toxicity, but less ototoxicity, using the IP route.

Key Words: Meta-analysis; randomized trial; clinical trial; IP; chemotherapy; ovarian cancer; epithelial ovarian adenocarcinoma; survival; disease-free survival; complications.

1. INTRODUCTION

This chapter describes and discusses a systematic review and meta-analysis of all known randomized controlled trials, comparing chemotherapy administered entirely by the intravenous (IV) route to regimens in which the chemotherapy was delivered at least partially intraperitoneally for newly diagnosed ovarian cancer *(1)*. It was carried out within the guidelines of the Cochrane Collaboration, which is an international and independent organization dedicated to providing up-to-date and accurate information by preparing, maintaining,

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and promoting the accessibility of systematic reviews of the effects of healthcare interventions, thus, allowing people to make well-informed decisions about patient management *(2)*.

A systematic review aims to answer a clearly formulated question using systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from studies that meet the criteria for review. A meta-analysis takes this one step further and uses statistical methods to combine, analyze, and summarize the results of the included studies.

2. OBJECTIVES

The primary objective of this study was to compare the survival and disease-free interval after chemotherapy administered intravenously or into the peritoneal cavity in newly diagnosed primary epithelial ovarian cancer (EOC). Secondary objectives included determining if there are some patients with EOC who are more or less likely to benefit from this treatment and if there is any difference in quality of life (QOL) for women treated with the alternative forms of chemotherapy.

3. CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Only randomized trials comparing standard IV chemotherapy with chemotherapy that included a component of IP administration were considered for this review. We accepted trials comparing regimens, which included IP treatment, with similar regimens that excluded IP treatment. The data included cases of primary peritoneal, fallopian tube, and EOC. The review excluded the trials studying radiocolloids, gene therapy, biologic therapy, radioisotopes, vascular growth factors, immunomodulating drugs, matrix metalloproteinase inhibitors, and radiolabeled monoclonal antibodies.

The search strategy used for identification of studies followed the Cochrane Gynaecological Cancer Collaborative Review Group search strategy, employing all major international databases.

A highly sensitive search strategy for randomized controlled trials, as described in the Cochrane Reviewers' Handbook, was performed to include a combination of controlled vocabulary and free text terms *(2)*. No limits were set. The *International Journal of Gynecological Cancer and Gynecologic Oncology* from 1998 to 2004 was hand searched. Database searching was augmented by contact with authors active in the field. The "first generation" reference lists of all eligible trials were searched for additional studies. Grey

literature was searched in particular conference proceedings and abstracts through ZETOC and Dissertation Abstracts. We searched for all relevant studies, irrespective of language. A French trial (Zylberberg) was translated, with the assistance of a native speaker, and was included in the review *(3)*. Missing and confusing data relating to results, outcomes, and quality from included studies were sought directly from the investigators. Only Armstrong replied, and mature data from this trial were retrieved before publication. Data from the published GOG 172 study have now been included in the meta-analysis *(4)*.

4. METHODS OF THE REVIEW

After scanning titles and abstracts found through the search, we excluded those thought not to be relevant. We then obtained the full text of potentially relevant studies for assessment of study eligibility. The hazard ratio and its variance summarizing time to recurrence of ovarian cancer and death were extracted from the paper or estimated using Parmar's methods *(5)*. For the time-to-event outcomes, the hazard ratio was used. The generic inverse variance method, a widely applicable approach to meta-analysis involving a weighted average of the effect estimates from the different studies, was used for time-to-death and time-to-recurrence outcomes. Relative risks were calculated for meta-analysis of adverse events.

Survival at 1, 2, 3, 4, and 5 years was computed from data extracted from the original survival curves of 7 randomized trials, and this is presented as an odds ratio. It was impossible to measure censorship precisely from the overall survival analysis, but graphs redrawn with the best-estimated fit of censored data did not impact on the shape or results. Data examining disease-free survival at 1, 2, 3, 4 and 5 years were also calculated with 95% CIs by reconstructing the data from the disease-free survival curves. These data could be adjusted to account for cases that were censored in four studies *(3,4,6,7)*, but Gadducci's data *(8)* were included without adjustment for censorship. The fixed hazard ratio was extracted from the trial report, calculated from existing data, or obtained from the trial author. This was used to calculate the hazard ratio with 95% and 99% CIs for time to death and time to recurrence. The survival curve depicted in this report is a simple summation of the data and is reproduced to provide a pictorial illustration (Fig. 1). Adverse effects of therapy were abstracted. We elected to classify toxicity as severe if it was graded 3 or more. If necessary, different categories of toxicity were combined within trials to facilitate pooling of data from different trials. For example, different authors described ototoxicity differently. Armstrong's paper focused on grade 3 and 4 tinnitus, whereas Kirmani focused on hearing loss. These data were combined to represent a crude

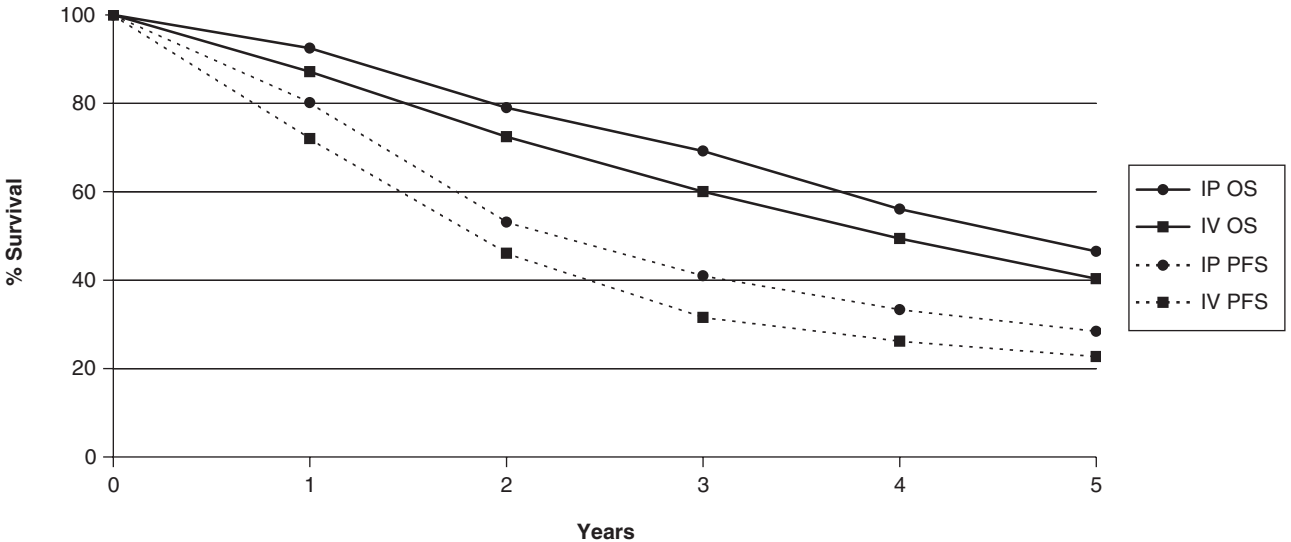

Fig. 1. Crude survival curves for overall survival (OS) and survival without disease (progression-free survival [PFS]) for women treated with intravenous therapy and a combination of IV and IP therapy over 5 yr. The fixed odds ratio (number of participants; 95% CI) for 1, 2, 3, 4, and 5 yr overall survival is 1.8 (1,736; 1.3–2.5), 1.4 (1,734; 1.1–1.8), 1.5 (1730; 1.2–1.8), 1.3 (1728; 1.1–1.6), and 1.3 (1728; 1.1–1.6), respectively, in favor of chemotherapy that includes an IP component.

measure of hearing damage. Any disagreements were resolved by discussion between the two reviewers.

In systematic reviews, heterogeneity refers to variability or differences between studies in the estimates of effects. Tests of statistical heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance alone. The magnitude of this statistical heterogeneity was assessed using the I^2 statistic *(9)*. A fixed effects model was used where there was no evidence of statistical heterogeneity ($I^2 < 25\%$). Where there was substantial heterogeneity ($I^2 > 25\%$), the possible clinical and methodological reasons for this were explored qualitatively, and a random effects model was used. A funnel plot was used, and confirmed that the assumptions underlying the random effects model appear to be valid.

5. DESCRIPTION OF STUDIES

Nine potentially relevant studies were identified and assessed independently by both reviewers. One of the citations compared IP chemotherapy with no further treatment *(10)*, but the types of participants (ovarian cancer patients with a pathologically complete remission after platinum-based IV chemotherapy) did not fit this review's eligibility criteria. Sensitivity analysis was applied to determine if exclusion of this trial would affect the results of the meta-analysis. Data from all randomized patients from the remaining eight trials were made available, and so the main results for this comparison are based on 1,819 patients, which represents 100% of eligible patients from known randomized trials.

Overall survival data were extracted from all but one of the trials *(11)*. Four of the seven trials provided hazard ratios of death in the IP group and included covariates in Cox regression analysis *(4,6,12,13)*. Most included age, tumor type and grade, performance status, and residual disease as covariates before commencing chemotherapy. Six trials displayed Kaplan–Meier survival curves *(4,6–8,12,13)*, and we constructed a survival curve for the Zylberberg trial from individual patient data presented. One paper presented sufficient data to allow calculation of the hazard ratio using Parmar's methods *(8)*. Hazard ratio of death for Kirmani and Zylberberg was estimated from the Kaplan–Meier survival curves.

Disease-free survival data and Kaplan–Meier disease-free survival curves were available from four trials. Two trials presented the calculated hazard ratios *(4,6)*. Gadducci presented sufficient data to allow calculation using Parmar's methods *(8)*, and the hazard ratio of recurrence for Kirmani's paper was estimated from the Kaplan–Meier disease-free survival curves *(7)*. The definitions of recurrence varied amongst these trials. For example, Kirmani used the

Eastern Cooperative Oncology Group definition; Markman and Gadducci used date of entry to date of appearance of disease (clinical or radiological) or date of death from any cause. Seven of the eight included trials that reported adverse effects, with the exception of the trial by Zylberberg. Toxicity criteria included the Southwest Oncology Group, Common Toxicity Criteria, and the World Health Organization, all of which were comparable for the toxicities described. Gadducci used the WHO criteria, but included four grades of alopecia; therefore, these data could not be assimilated because the WHO criteria divide alopecia into only three grades. Quality of life scores were reported in the Armstrong trial using the Functional Assessment of Cancer Therapy scale, with General, Neurotoxicity, Pain, and Ovarian cancer subscales. This was reported at the 2004 annual American Society of Clinical Oncology meeting *(14)*. Subgroup meta-analysis was not performed because data from the subgroups in the various studies were not adequate for meta-analysis. Only Alberts and Armstrong reported survival subgroup analysis including the group of patients with residual tumors <0.5 cm, but insufficient data were available in the Alberts paper to perform the meta-analysis *(4,12)*. However, both suggest that IP chemotherapy is effective, irrespective of residual disease volume. Only the trial by Armstrong assessed QOL as an outcome measure; therefore, no meta-analysis was performed. Catheter-related complications of IP drug administration were discussed in all of the trials, but data retrieved from them were insufficient to produce a meta-analysis. An attempt was made to comprehensively document the numbers of, or reasons for, withdrawal from treatment protocol, but insufficient data were available to report this. A meta-analysis based on RR for withdrawal from treatment could not be performed.

6. RESULTS

Data were available for analysis from up to 1,779 subjects. All trials used different chemotherapeutic regimens and different IP components to the chemotherapy. Many women received IP chemotherapy limited to a few cycles. In the study by Markman, women randomly allocated IP chemotherapy also received a very high dose (AUC 9) of IV carboplatin for two cycles before they received an IP component to the chemotherapy (Table 1). Median length of follow-up was reported in seven of the eight trials (>60 mo *(12)*; 50.4 mo *(4)*; 60 mo *(8)*; 46 mo *(7)*; >60 mo *(6)*; 74 mo *(13)*; and 50 mo *(3)*). Polyzos did not provide data on length of follow-up.

Survival at 1, 2, 3, 4, and 5 years was computed from data extracted from the original survival curves of 7 randomized trials. IP chemotherapy is associated with a survival advantage (Fig. 1) that persists at 5 yr. The hazard ratio calculated from 7 trials (Fig. 2) is 0.80 (95% CI = 0.71–0.90) favoring IP therapy, implying that IP therapy reduces the hazard of death by one fifth.

Table 1
Characteristics of Chemotherapy Administration

Study	*Accrual Period*	*Number of Eligible Participants*	*IV Therapy Given to Both Groups*	*Additional IV Therapy Given to Control Arm*	*Additional Therapy Given to Intervention Arm*	*Course Repetition*
Alberts *(12)*	1986–1992	546	cyclophosphamide 600 mg/m^2 (day 1)	cisplatin 100 mg/m^2 (day 1)	IP cisplatin 100 mg/m^2 (day 1)	3 weekly × 6
Armstrong *(4)*	1998–2001	415	paclitaxel 135 mg/m^2 over 24 h (day 1)	cisplatin 75 mg/m^2 (day 2)	IP cisplatin 100 mg/m^2 (day 2) + IP paclitaxel 60 mg/m^2 (day 8)	3 weekly × 6
Gadducci *(8)*	1989–1996	100	epirubicin 60 mg/m^2 + CTX 600 mg/m^2 (day 1)	cisplatin 50 mg/m^2 (day 1)	IP cisplatin 50 mg/m^2 (day 1)	4 weekly × 6
Kirmani *(7)*	1988–1992	68 for toxicity 62 for survival		cisplatin 100 mg/m^2 + cyclophosphamide 600 mg/m^2 (day 1)	IP cisplatin 200 mg/m^2 + IP etoposide 350 mg/m^2 (day 1)	IV 3 weekly × 6 IP 4 weekly × 6

Table 1
(*Continued*)

Study	*Accrual Period*	*Number of Eligible Participants*	*IV Therapy Given to Both Groups*	*Additional IV Therapy Given to Control Arm*	*Additional Therapy Given to Intervention Arm*	*Course Repetition*
Markman *(6)*	1992–1995	462		paclitaxel 135 mg/m^2 (day 1) + cisplatin 75 mg/m^2 (day 2)	IV carboplatin (AUC 9) × 2 courses, followed 4 weeks later by IV paclitaxel 135 mg/m^2 (day 1) + IP cisplatin 100 mg/m^2 (day 2)	IV 3 weekly × 6 IP carboplatin AUC 9 4 weekly × 2 followed by 3 weekly × 6
Polyzos *(11)*	1990–1996	90	cyclophosphamide 600 mg/m^2 (day 1)	carboplatin 350 mg/m^2 (day 1)	IP carboplatin 350 mg/m^2 (day 1)	3–4 weekly × 6

Yen *(13)*	1990–1995	118	cyclophosphamide 500 mg/m^2 (day 1) + adriamycin or epirubicin 50 mg/m^2 (day 1)	cisplatin 50 mg/m^2 (day 1)	IP cisplatin 100 mg/m^2 (day 1)	3 weekly × 6
Zylberberg *(3)*	1980–1984	20	vinblastine 10 mg + ifosfamide 1 g × 2	adriamycin 35 mg × 2 + fluorouracil 750 mg × 2 + bleomycin 15 mg + cisplatin 100 mg	IV adriamycin 20 mg × 2 + fluorouracil 500 mg × 2 + cisplatin 50 mg IP bleomycin 15 mg + cisplatin 50 mg + fluorouracil 500 mg + adriamycin 30 mg	4 weekly × 10

Table 2
The Relative Risk of Serious Adverse Events If a Component of the Chemotherapy Is Given Intraperitoneally

Severe Adverse Effects (grade 3 and 4)	*Number of Studies*	*Participants*	I^2	*Relative Risk (95% CI)*
Leukopenia	7	1779	82%	R 0.94 (0.75, 1.19)
Thrombocytopenia	7	1779	92%	R 1.16 (0.33, 6.06)
Anemia	4	812	0%	F 0.97 (0.74, 1.26)
Gastrointestinal	4	1045	61%	R 1.60 (1.13, 2.25)
Neurologic	5	1571	76%	R 1.19 (0.64, 2.21)
Fever	4	1503	20%	F 1.92 (1.20, 3.06)
Renal	4	1045	38%	R 2.55 (0.80, 8.10)
Hearing loss/tinnitus	3	1009	0%	F 0.67 (0.46, 0.99)
Fatigue	2	877	0%	F 3.63 (1.95, 6.74)
Pain	2	941	0%	F 8.13 (4.11, 16.10)
Fever	4	1503	20%	F 1.92 (1.20–3.06)
Cardiovascular	2	877	0%	F 1.69 (0.93–3.08)

A risk >1 implies more grade 3 and 4 toxicity with IP therapy. If $I^2 < 25\%$, the trial is statistically homogeneous and the relative risk can be calculated with a fixed-effect model (F) rather than the random effect model (R). Data on hearing loss/tinnitus, fatigue, pain, and cardiovascular adverse events come from dissimilar trials with regard to these outcomes, and these meta-analyses have limited credibility.

Disease-free intervals at 1, 2, 3, 4, and 5 years are also significantly increased in the women given an IP component. The hazard ratio measuring time to recurrence from four available studies is 0.79 (95% CI = 0.69–0.90), favoring women allocated IP chemotherapy. The results do not change if the data from the adjuvant placebo controlled IP trial *(10)* are added to the meta-analysis (hazard ratio for time to death, incorporating data from this study = 0.80; 95% CI = 0.71–0.91). These survival data are all statistically homogeneous.

Most of the toxicity data are difficult to interpret because different regimens in different trials yield different toxicity profiles; this helps explain the heterogeneity in the meta-analyses with regard to these outcomes (Table 2). The study by Markman *(6)* is particularly confounding because women allocated an IP component to their treatment also received an additional very high "priming" dose of IV carboplatin. Data on the risk of thrombocytopenia, leukopenia, renal toxicity, gastrointestinal toxicity, and neurological toxicity are heterogeneous and cannot be combined legitimately. However, data on fever, pain, infection, fatigue, and ototoxicity passed the test of homogeneity. Four trials quote data on fever and the relative risk for grade 3+ toxicity associated with IP chemotherapy is almost doubled (1.92; 95% CI = 1.20–3.06), and the additional risk

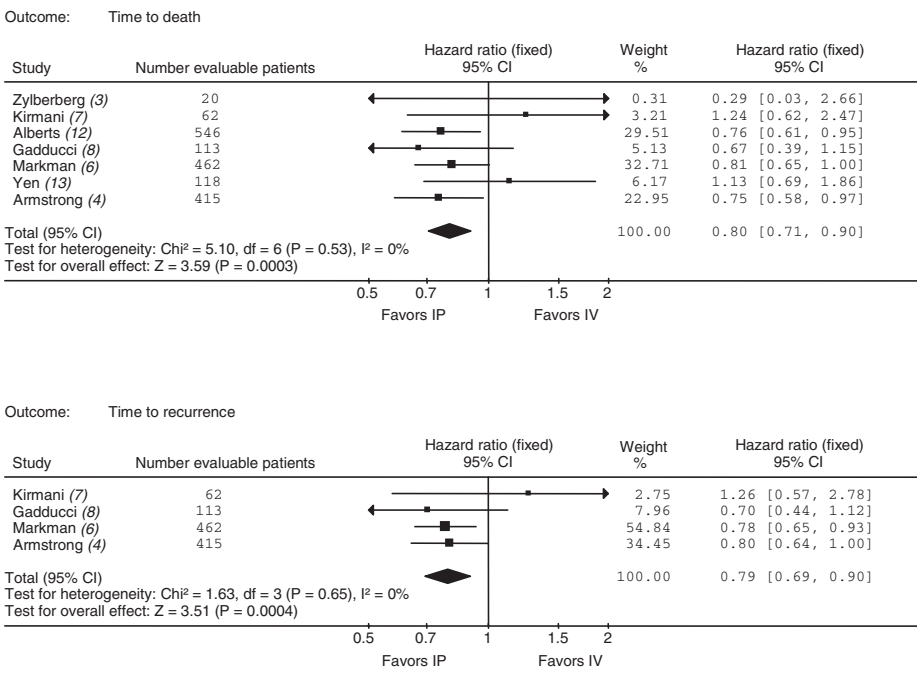

Fig. 2. Forrest plot showing time from randomization to death (above) and time from randomization to recurrent disease (below).

for each woman is 3%. The relative risk of fatigue and pain is 3.6 and 8.13, respectively, but these data are only reported in two trials. The relative risk of severe ototoxicity associated with IP rather than conventional IV therapy is lower (0.67; 95% CI = 0.46–0.99), but this conclusion is based on the post hoc combination of tinnitus and hearing loss after multiple comparisons. Consequently, this apparent advantage to the IP route should be treated with caution. Pulmonary, alopecia, metabolic, pain, lymphatic, and hepatic adverse effects were only reported in two or less studies, and the data are heterogeneous.

Catheter problems are described in most studies. For example, Gadducci used an implanted device (Port-A-Cath), and catheter obstruction occurred in 4 patients (8.7%), bowel perforation in 3 (6.5%), and chemical peritonitis occurred in 4 cases (8.7%) *(8)*. Kirmani also used the Port-A-Cath for 32 women, and there was 1 case of infectious peritonitis and 1 case of chemical peritonitis *(7)*. Polyzos used an IP drug injected rapidly through an IV catheter that was withdrawn immediately after completion *(11)*. Three cases involved infusion into large bowel with ensuing massive diarrhea, and two cases suffered infusion between layers of the abdominal wall. Yen injected through 1 of 2 Tenckhoff catheters implanted at primary surgery, protected by a subcutaneous

tunnel, and reported 1 fatal case of *Staphylococcus epidermidis* peritonitis *(13)*. Armstrong used a variety of implantable peritoneal catheters, and 40 (34%) discontinued IP therapy primarily because of catheter complications *(4)*. They found an association between rectosigmoid colon resection and the inability to initiate IP therapy.

7. DISCUSSION

This chapter analyzes data from trials that compare conventional IV therapy with a regimen where at least one drug was given by the IP route. Data on survival are statistically homogeneous, implying that the data can be legitimately merged. The results show an improved survival, improved disease-free interval, and improved complete response rates associated with administering some of the chemotherapy intraperitoneally. It is worth translating this analysis into clinically important outcomes. A hazard ratio of 0.80 for survival represents an advantage that is greater than the advantage offered by radical surgery. This implies that women who accept surgery will logically ask for IP therapy. IP therapy offers a survival advantage for 1 woman in 12 and an average gain of about 9 mo before any disease recurs. Conversely, 1 woman out of 30 is likely to suffer fever, and an additional 1 in 8 will experience pain from the catheter that she would not have experienced had she received IV chemotherapy alone. It is important to review the data excluded from this analysis to determine if a different analysis would affect the conclusion. Two randomized trials were excluded. Piccart's study randomized 153 patients once they were in complete remission to placebo or 4 courses of adjuvant IP cisplatin. After a median follow-up of 8 yr, the odds ratios (95% CI) for progression-free survival and overall survival favoring the additional IP treatment were 0.89 (0.59–1.33) and 0.82 (0.52–1.29) *(10)*. The second excluded trial compared IP monoclonal radiolabeled antibodies to standard IV consolidation therapy in patients who were in complete remission from ovarian cancer. This showed that IP therapy reduced the onset of recurrent peritoneal disease, but not recurrence in the lymph nodes *(15)*. Data from one included trial *(11)* was not included in the survival analysis because the trial only quotes response rates. The response rate was 75% (33/46; 95% CI 59.7–86.8) with IP therapy, compared to 72% (33/44; 95% CI 56.5–84.0) in the control arm. Median survival for suboptimally debulked disease was 19 mo (IP therapy $n = 18$) and 18 mo (control arm $n = 21$). Survival times for women when the postoperative residuum was <2 cm were 32 mo ($n = 26$) after IP therapy and 30 mo ($n = 25$) in the control arm. The authors were not able to provide sufficient data for hazard ratio calculations.

IP therapy has several understandable disadvantages. Catheters are inconvenient to use, they have a tendency to occlude, and they cause pain and risk introducing infection *(16)*. One series showed that the rate of severe infection

associated with catheters was approximately 10% *(17)*, and only 42% of the subjects were able to complete the allocated 6 cycles of IP therapy in the Armstrong study *(4)*. Direct IP injections or laparoscopic catheter placement may avoid these problems *(18)*, but this is an added inconvenience compared to catheter placement at the time of debulking surgery. Another disadvantage is that we do not know enough about other adverse effects from IP therapy. The meta-analysis does not show any difference in hematological or renal toxicity because the data are heterogeneous, and toxicity will vary according to the regimen used. For example, the renal and platelet toxicity is much greater in Markman's study, but not in others, possibly because Markman used 2 cycles of very high dose (AUC 9) carboplatin to prime women allocated IP chemotherapy.

Several important questions remain unanswered by this systematic review. It does not define the optimal IP drug or drug combination for ovarian cancer. Specifically, the meta-analysis does not focus on the current standard therapy for ovarian cancer, which is carboplatin with or without a taxane. We know from a recent study by Fujiwara that IP carboplatin has similar pharmacodynamics to cisplatin, but there are limited comparative data on the two drugs *(17)*.

Second, review of the existing trials does not allow us to define the optimal technique of drug administration. Should a surgically implanted catheter be used, or repeated independent IP injections, which may cause less pain and infection, but risk malposition of the needle tip with its associated complications?

Third, the problem of timing of administration is not addressed in this review. It is not known if it will be more effective to start injecting the IP agent(s) before debulking surgery as neoadjuvant therapy, at the time of surgery, or delayed for up to 6 wk postoperatively.

The trials do show a statistically and clinically significant survival advantage from giving some of the chemotherapy intraperitoneally. A meta-analysis cannot untangle these components, but a pragmatic conclusion is that chemotherapy is more effective when some is administered intraperitoneally. The new challenge will be to provide this treatment option when little is known about the side effect profile and best regimen. Nevertheless, this is the largest potential advance in survival from ovarian cancer since the introduction of platinum chemotherapy.

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4 Immunobiology and Intraperitoneal Immunobiologics in Ovarian Cancer

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Summary

Advances continue to be made in tumor immunology and in strategies to integrate the growing number of bioimmunotherapeutic molecules into the treatment of ovarian cancer, as well as other malignancies. Extensive studies have provided support for antigen-driven T-cell activation in vivo. The number of known tumor antigen epitopes is expanding, although advances in this area remain behind that of melanoma. Evidence suggests that the tumor environment is contributing to a state of in vivo immunosuppression; however, in vitro experiments and laboratory correlative studies also show that immune suppressor activity might be reversible. These findings could lead to new approaches, such as the use of antibodies or cytokines to overcome the immunosuppressive effects, in addition to the more established surgical and chemotherapeutic debulking.

Both prophylactic and therapeutic bioimmunotherapeutic strategies require pharmacodynamic and immunologic end points that can guide each phase in the development of an effective approach. Review of systemic and intraperitoneal (IP) immunotherapy trials of interferon (IFN) α, IFNγ, and interleukin 2 (IL2), as well as newer agents such as IL12 and Flt3 ligand, overall continues to offer promise of a role for bioimmunotherapy in the treatment of ovarian cancer. Future developments lie in the improved target specificity of activated cells and cell-surface–binding molecules and in a systematic plan for combining chemotherapy with cytokines, growth factors, and polyvalent vaccines that are based on the *in vivo* dynamics of each agent. Another totally different approach, which could set a new paradigm, might be to target cells from the inflammatory immune system, which could contribute to tumor growth, invasion, and metastasis.

Key Words: Bioimmunotherapy; intraperitoneal therapy.

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Developments in bioimmunotherapy have been spurred by advanced knowledge of tumor immunology and the availability of an increasing array of recombinant and other molecules that target specific sites in the immune system.

Cellular immunity incorporates adaptive and innate components. We extensively reviewed the subject in a previous study *(1)*. The dendritic cell (DC) is a key cellular element for processing tumor cell antigens, and it eventually matures to perform three main functions. These functions relate to the activation of cells belonging to the adaptive (CD3+CD4+ T-cell receptor (TCR) αβ and CD3+CD8+TCRαβ+) or innate systems (natural killer [NK], CD3+ TCRγδ, or monocyte [MO]/macrophages [MAs]). The functions include presentation of tumor-derived peptide in the context of the major histocompatibility complex (MHC) to CD4+ and CD8+ T cells complemented by co-stimulation through B7 and other surface molecules, and the production of IL12, which is able to stimulate both adaptive and innate immune systems. Production of IFNγ by certain T cells, NK cells, and T γδ cells is a vital component of both adaptive and innate immunity and participates in both MHC-restrictive killing by CD8+ T cells and the non–MHC-restricted killing exhibited by NK, T-γδ cells, and MAs. Progress has been made in understanding the receptor–ligand interactions of the innate immune cells. Interferon γ may produce antitumor effects through several different mechanisms, including direct inhibition of growth, up-regulation of MHC molecules to make tumor cells better targets for the adaptive system, and induction of superoxides or nitric oxide by MAs activated by IFNγ and tumor necrosis factor (TNF). Interferon-γ also increases activity of the indolamine deoxygenase enzyme that converts tryptophan to kynurenine, which is then converted to hydroxykynurine, which is highly toxic not only to human tumor cells *(2)* but also to activated T cells. IFNγ has antiangiogenic effects, which are probably mediated through the chemokine IP10, but possibly also through down-regulation of the integrin receptor pathways on tumor endothelial cells.

Evidence for specific T-cell activation *in vivo* in ovarian cancer follows criteria that have been set for melanoma, and includes the development of specifically activated T-cell lines or clones from tumor-infiltrating lymphocytes (TILs); demonstration of antigen-dependent and -independent cytokine production upon co-incubation of these T-cell lines or clones with autologous tumor; the demonstration of MHC-restricted tumor cell activity; and, importantly, the clonal expansion of TCRαβ clones, *in vivo*, as we have recently demonstrated *(3)*. However, even the discovery of clonally expanded T cells with tumors *in vivo* does not determine their type of activity *in vivo*.

The number of tumor antigen epitopes in ovarian cancer remains small, relative to that shown in malignant melanoma. Most of the work in ovarian cancer relates to studies conducted with HER2/neu peptides that express HLA A2 motifs, demonstrated by Ioannides *(4,5)*, Peoples *(6,7)*, and extensive studies conducted by Disis *(8)*. More recently, the human telomerase reverse transcriptase protein component of the telomerase enzyme and the alpha folate receptor

has been identified as targets for MHC-restricted activity by sensitized T-cell lines. Other proteins of possible interest in ovarian cancer include mesothelin and its derived peptides, and those derived from the testis proteins, such as NY-ESO. Both CD8+ and CD4+ T cells may recognize different epitopes of NY-ESO. B melanoma antigen and G melanoma antigen are other surface proteins that expand in epithelial ovarian cancer (EOC).

An important question that is relevant to *in vivo* efficacy of epitopes in vaccines is whether a particular epitope can generate human leukocyte antigen (HLA)–restricted peptide that is reactive to T cells that recognize the naturally expressed epitope on the tumor cells *in vivo*. Because HER2/neu has been extensively studied, we examine this issue in relation to HER2/neu as a target for human adaptive immunity.

HER2/neu protein is overexpressed in approximately 10% of ovarian cancer, and its overexpression is associated with a worse prognosis. MHC class 2 peptides, which contain the HLA-A2–binding motifs, have been derived and tested *in vitro* and, in some cases, *in vivo.* T-cell lines have been developed that recognize a peptide-pulsed target that is expressed on a cell line that has been transfected to express HLA-A2. Specific lysis of Epstein–Barr Virus–transformed B cells appeared to be low even at high elevated temperature ratios. Immunization with amino acids 369–377, in addition to Freund's adjuvant, to facilitate the immune response was unable to activate T cells that recognize HER-2^+ cell lines. Thus, in summary, the requirements for generating active specific (either cellular or humoral) immunity in ovarian cancer have to consider the following: that peptides must generate HLA-restricted T cells that recognize multiple naturally expressed epitopes, and thus require polyvalent vaccines; cytotoxicity has to be induced at acceptable effector target ratios, that is, at least 20% at 20 : 1 effector/target ratios. Also, as recently shown by Rosenberg *(9)*, therapy with vaccines may need to include TIL-derived T-cell lines or clones for greater efficacy. All of these factors add to the complexity of active immunotherapy, at least in patients who have established disease. Several antibody-generating vaccines have also been tested *(10)*. These are directed at O-linked mucin glycans, such as sialylated Tn and others. It is critical, however, that such vaccine approaches generate cell surface–reactive antibodies that are able to mediate antibody-dependent cellular toxicity or complement-dependent cytotoxicity. Recently, several inhibitors for complement-mediated killing have been demonstrated on tumor cells. Antibody-generating vaccines might also be combined with cellular therapies, such as activated MAs or NK cells. We have found, however, that activated MO/MA from EOC patients have a defect in FcγR-mediated functions such as antibody-dependent cell-mediated cytotoxicity and phagocytosis *(11)*. Strategies will be needed to overcome immunosuppression *in vivo* to achieve effective active immune-based therapies.

A variety of immunosuppressive factors have already been identified in ovarian cancer patients. The best known are IL10, IL6, transforming growth

factor β (TGFβ) isotope, FAS ligand expression on tumor cells, and probably several others that remain undefined *(12)*. Others have demonstrated that IFNγ transcripts and the TCRζ chain were absent or poorly expressed in solid ovarian tumors *(13)*. Woo and colleagues *(14)* have isolated CD4+, CD25+, and FoxP3+ regulatory T cells from ovarian cancer, and our group recently demonstrated a MA with the IL10+ and TGFβ phenotype *(15)*. The MOs/MAs of the CD14+, IL10+, and TGFβ phenotypes inhibit T cell proliferation, but this effect can be abrogated with αTGFβ and αIL10 neutralizing antibodies *(15)*. A recent study has shown an inverse relation between CD3+ and CD25+ regulatory cells and survival of EOC patients *(16)*. A more recent paper has shown that the ratio of T-regs to CD8+ T cells is important in survival prognostication *(17)*.

An important question is whether immunosuppression in cancer patients can be overcome *in vivo*. In 1991, Greenburg published some key experiments that demonstrated that immunosuppression associated with tumors could be reversed by the debulking effect of chemotherapy *(18)*. It is also possible that CD3ζ chain hypophosphorylation might be reversed through administration of IL2 or the use of TGFβ neutralizing and IL10 receptor antibodies to overcome immunosuppressive activity *in vitro.* It has also been shown that patients with lower CD3ζ expression had lower survival compared to patients with normal expression *(19)*. However, most cytokines, including IL2, have pleiotropic effects on other cell populations; therefore, the effects of these cytokines may not always parallel results of preclinical *in vitro* or animal *in vivo* studies.

A variety of immunotherapeutics have been developed for testing in EOC patients. These include cytokines, cell therapies, antibodies, and vaccines.

Immunotherapy approaches have been categorized by Malcolm Mitchell as prophylactic or therapeutic *(20)*. A similar categorization could be applied in the bioimmunotherapy of ovarian cancer. It is possible that prophylactic approaches will be developed for high-risk populations. For example, a combination of family history of EOC and the presence of BRCA-1 and -2 mutations increase an individual's risk to 16%–44%. It is possible that the mutated antigens could serve as targets for future vaccine strategies. In established cancer, either consolidation or adjuvant approaches, such as vaccines, cytokines, growth factors, antibodies, and other immune-activating molecules, have been tested, but neither consolidation nor adjuvant use of immunotherapy has fully evolved.

Therapeutic immunotherapy approaches in ovarian cancer have largely employed cytokines. The small number of studies that have been done with the interferons in ovarian cancer notwithstanding, significant clinical responses have sometimes been demonstrated with both IFNα and IFNγ. Moreover, a recently reported randomized trial, using IV cisplatin, cyclophosphamide, and subcutaneous (SQ) IFNγ has demonstrated improved progression-free survival over cyclophosphamide alone *(21)*, but this benefit of IFNγ added to paclitaxel and carboplatin was not confirmed in a recently completed randomized trial.

The utilization of IP bioimmunotherapy continues to attract attention. IP injection of cytokines fits with the paracrine model of cytokine action. Lower blood levels of exogenous or endogenous cytokines tend to be associated with lower hematologic and nonhematologic systemic toxicity. The residence time tends to be prolonged, especially with larger molecules. The capillary barrier may be less of a problem, especially in the presence of small-volume disease. Most importantly, there is an opportunity for direct contact between tumor and the different mononuclear cell-effector populations in the peritoneal cavity. There may also be modulation of the tumor microenvironment through the secretion of chemokines and endogenous cytokines. IP therapy delivered through temporary catheters or ports may also provide opportunities to study activity and resistance *in vivo*.

Disadvantages of the IP approach are as follows: the requirement of IP catheter placement and care, the exclusion of patients with significant adhesions, and the necessity to evaluate responses surgically. Both rIFNα and rIFNγ have demonstrated significant responses, particularly in patients with small-volume disease (Table 1) *(22,23)*. In the case of IFNα, responses were noted in patients with platinum-sensitive disease only. The large study conducted by Pujade-Lauraine and co-workers employed IFNγ at a dose of 20 million units, twice weekly, and produced 23 complete responses out of 98 evaluable patients *(24)*. Responses included some patients with macroscopic disease and some with tumors greater than 2 cm.

IFNα has also been combined with cisplatin based on prior activity observed *in vitro* (Table 2). Doses of IFNα were mostly in the range of 25 MU–50 MU, and platinum doses ranged between 45 mg/m^2 and 90 mg/m^2. Berek and Markman have demonstrated that responses to the combination of rIFNα and

Table 1
Intraperitoneal Therapies with Recombinant Interferons

Treatment	*Dose*	*Eval/Resp.*	*Pts. (MRD)*	*CR*	*Surg. Resp. Vis. Tum.*	*PR*
rIFNα 2b (Berek) *(25)*	50 MU weekly	25 (PS) 21 (PR)	46 (5 mm)	4 0	NS NS	3 0
rIFNα 2b (Willemse) *(23)*	50 MU weekly	20	11 (2 cm)	5	1/5	4
rIFNγ (D'Acquisto) *(22)*	0.05–8 MIU/m^2 biweekly	24	3** (5 mm)	0	0/1	0
rIFNγ (Pujade-Lauraine) *(24)*	20 MIU/m^2 biweekly	98	63 (2 cm)	23*	17/88	8

PS, platinum sensitive; PR, platinum resistant; *9 > 5 mm; **2 microscopic disease.

Table 2
Clinical Activity from Intraperitoneal Recombinant Interferon-α with and without Cisplatin in Patients with Ovarian Cancer

Author	*Pt. # (MRD)*	*Dosing*	*Schedule*	*Response*
Nardi	14 (14)	rIFNα50 MU cDDP 90 mg/m^2	biweekly × 4 rpt@ wk 10	CPR-7 (6cyto+)
Berek *(25)*	24 (9)	rIFNα10–50 MU cDDP 45–90 mg/m^2	q 2–3 wk × 6	CPR-2 PPR-3
Markman *(26)*	43 (15)	rIFNα 25 MU cDDP 60 mg/m^2	q 3 wk × 6	1 PR/18 evaluation points
Frasci	41 (18)	rIFNα 30 MU mitoxan 20 mg/m^2 cDDP 75 mg/m^2	q 3 wk × 4	CPR 23/27
Frasci	21 (21)	rIFNα 30 MU carbo 150 mg/mL	q wk × 12	10 CPR < 5 mm 4 CPR > 5 mm

CPR, complete pathologic response; PPR, partial pathologic response; carbo, carboplatin; mitoxan, mitoxantrone.

cisplatin were almost exclusively in patients who were platinum sensitive *(25,26)*. It is possible that additional work on scheduling could be fruitful.

rIFNα and carboplatin have also been administered to a small group of patients with optimally debulked primary ovarian cancer with interesting preliminary results. However, larger studies have not been reported. Recombinant IL2 (rIL2) has been administered alone or in combination with LAK cells, TIL-derived T-cell lines, or T cells to which bifunctional CD3 folate receptor construct has been added (Table 3). Edwards demonstrated that a 24-h infusion produced 9 responses, 5 of which were considered platinum sensitive. Prolonged infusions were found to be too toxic. Taylor's group has also shown that sera from nonresponders incubated with Jurkat cells suppressed CD3ζ expression by 8.3%, compared with 36% for responders *(27)*. Steiss utilized LAK cells after IP priming and has observed some responses. We conducted a trial with IL2- and TIL-derived T-cell lines that were expanded from to 10^{10} to 10^{11}, but observed no objective responses *(28,29)*. It is difficult to do this study with patients with minimum residual disease because of the requirements for large numbers of tumor-associated TIL. Canevari has obtained interesting results from a trial that utilized the bifunctional CD3-folate receptor antibody together with activated T cells and rIL2 *(30)*. These were not specifically activated T cells, and it could not be determined whether the responses were primarily caused by the IL2 or by the combination with the T cells and the a/b construct. Studies with other cytokines continued to provide interesting data. In a recent study, we conducted a phase 1 trial with IP rIL12 (Genetics Institute) in doses that ranged from 3 ng/kg to 600 ng/kg *(31)*. Three patients were

Table 3
IP IL-2 ± Cellular Therapy

Treatment	*Dose*	*Schedule*	*Eval. for Resp.*	*MRD*	*Surgical Response*
rIL2 Edwards	6×10^4 to 3×10^7	24 h infusion 7-d infusion	35	19	*9/35
rIL2 + LAK Steiss	IV priming: 10^5 U/Kg	8 h × 3 d 8 h × 3 d	Ovar 10 Colon 12	9 3	(2PR) (5PR)
rIL2 + TIL Freedman	0.6 MIU + $10^{10}10^{11}$ 0.6 MIU/m^2	×1 d ×3 d	Ovar 8		0
rIL2T-cells + bifunctional CD3-folate receptor Canevari	0.6 MIU	×5 d	Ovar 26	21	(4CR) (3PR)

* 5/9 platinum sensitive.

treated at each dose level. Dose-limiting toxicity occurred in 2 of 4 patients at the 600-ng/kg dose, as manifested by grade 3 elevation of transaminases. Toxicities were manageable, and 10 patients received 300 ng/kg with an acceptable frequency and severity of side effects. Two patients, one with ovarian cancer and one with mesothelioma, had no disease at follow-up laparoscopy. Eight patients had stable disease. At the 300-ng/kg dose, IL12 was cleared from the peritoneal fluid in a biphasic manner with a terminal phase half-life of 18.7 h. Peritoneal fluid levels of IL12, 5 min after injection, ranged from 100 pg/mL to 200 pg/mL. Serum IL12 levels after 300 ng/kg reached approximately 10 pg/mL between 24 h and 36 h. IFNγ was detected in a high proportion of peritoneal fluid samples and in the serum after injection, but the levels in the serum were at least a log lower compared to the peritoneal concentrations. TNF and IL10 levels were also slightly increased in some patients. In one responding patient, there was a reduction in the transcripts for IL10, with a corresponding increase in IFNγ and IP10 transcripts. By quantitative image analysis, we observed a statistically significant decrease in the expression of TGFβ on tumor cells isolated from the peritoneal cavity. We could not demonstrate a significant decrease overall in vascular endothelial growth factor, although individual patients did show a decrease. We have concluded that IL12 at a weekly IP dose of 300 ng/kg was an acceptable clinical and immunobiologic dose. A four-institution phase II clinical trial of IP IL12 was recently concluded. Several patients showed stable disease, but there were no objective responses at laparoscopy. It is also possible that IL12 could be combined in the future with tumor vaccines, as has been done in malignant melanoma.

In another trial, the growth factor Flt3 ligand, which is a fms-like tyrosinase kinase 3 ligand, was studied *(32)*. Flt3 ligand is a hemapoietic growth factor

that stimulates myeloid cells of monocytic and DC lineage. Antitumor activity has been demonstrated in preclinical studies, including an ovarian tumor model. Either IP or SQ injection of Flt3 ligand produced significant increases in white blood cell's MOs and DCs. Interestingly, platelets increased in the washout period. There were few significant toxicities with either the IP or SQ injection routes. Three patients, two with mesothelioma and one with mucinous adenocarcinoma, had stable disease by computed tomography scan that was associated with improvement of symptoms in these patients. Stable disease lasted for at least 8 mo in each patient. Peritoneal fluid or blood samples obtained on day 0 and day 12 were treated with granulocyte MA colony-stimulating factor (GM-CSF) and IL4 according to a standard DC protocol, and then stimulated with soluble CD40L trimer (Immunex). Both blood and peritoneal fluid DCs produced IL12. However, peritoneal fluid DCs produced a more marked increase in IL12 and somewhat lower production of IL10 on day 12. These findings suggested a differentiation toward a DC1 phenotype.

Flt3 ligand is currently unavailable for clinical trials. However, in an ongoing study, we have utilized GM-CSF, which has the potential to mobilize and mature myeloid cells of MO/MA, DC, and granulocytes, in a priming prechemotherapy and postchemotherapy growth factor regimen with carboplatin together with two doses of rIFNγ *(33)*. The combination provides an acceptable toxicity profile. This study will also examine time-to-progression after treatment compared to the prior chemotherapy courses.

The following conclusions can be made about the current status of immunobiologics in persistent or recurrent ovarian cancer. IP IFNα, IFNγ, and IL2 are active in phase II clinical trials. IP rIFNα appears to be active only in platinum-sensitive patients. IP rIFNγ also appears to have activity, even in patients with macroscopic metastases. IP cytokines plus cellular therapy remains very experimental for patients with EOC. It may be possible to identify patients more likely to respond to cytokines, such as IL2 *(19,27)*. Chemobioimmunotherapy studies should continue with novel agents or combinations, while exploring different routes and schedules of administration.

The pluripotential nature of immune inflammatory cells in ovarian cancer is posing a dilemma for future therapy strategies. Should we increase our efforts to utilize adaptive or innate immune systems to destroy ovarian tumors or should we increase our efforts to neutralize or destroy immune cells that contribute to tumor increase and metastasis? New technology, including gene profiling, gene knockdown, and proteomics, may help us to better understand the broader role of these cells *in vivo* and to identify susceptible pathways of these cells *(34,35)*. A recent trial with Yondelis has shown that this marine product, which had clinical activity in ovarian cancer, also inhibited the numbers and activity of MO/MA. It is possible that the targeting of pro-tumor MO/MA could become a paradigm for future strategies in ovarian cancer *(36)*.

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5 Intraperitoneal Chemotherapy: Technique and Complications

Joan L. Walker, MD

1. OPERATIVE TECHNIQUE

Ideally, the intraperitoneal chemotherapy (IP) delivery device is placed at the time of the original diagnostic procedure, when an optimal surgical resection can be completed. The patient, who is appropriately counseled before surgery about her risk of cancer and the treatment options available, should have an IP device placed at the time of surgical resection of the presumed ovarian or primary peritoneal cancer. The pathologic diagnosis and stage is not completely understood in that setting, but good clinical judgment can identify an appropriate candidate for IP chemotherapy. It is safer to place the device and remove it unused at the bedside later, than to forego placement and have to reoperate to place the device at a second procedure. The second procedure to place an IP catheter is an important barrier to initiating IP chemotherapy, and also delays proper treatment.

2. PLACEMENT AT THE TIME OF OPEN LAPAROTOMY

The catheter is tunneled above the fascia from an implantable port location, at the midclavicular line on the inferior costal margin, to a peritoneal entrance point approximately 6 cm lateral to the umbilicus. A tunneling device, which is packaged with the catheter, is ideal for this part of the procedure because it leaves a dissection tract only the width of the catheter. The catheter should be placed over the ascending or descending colon and progress toward the pelvis, depending on where the fewest adhesions are expected to form (Figs. 1 and 2). The catheter should be left long (10 cm–15 cm), so that it will not retract into the subcutaneous tissues (Fig. 3). If the catheter is placed in the upper abdomen, it may become trapped in adhesions that can develop between the liver and the diaphragm after peritoneal stripping, or between the transverse colon and the anterior abdominal

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Fig. 1. Intraperitoneal port placement at initial laparotomy. The tunneling device is guided up through the subcutaneous tissues into the port pocket.

Fig. 2. Intraperitoneal port placement at initial laparotomy. The port has been secured to the reservoir, which is being secured to the fascia above the right costal margin in the midclavicular line. This is a 9.6F single lumen port (Bard Access Systems, Salt Lake City, Utah Order Number-06026870).

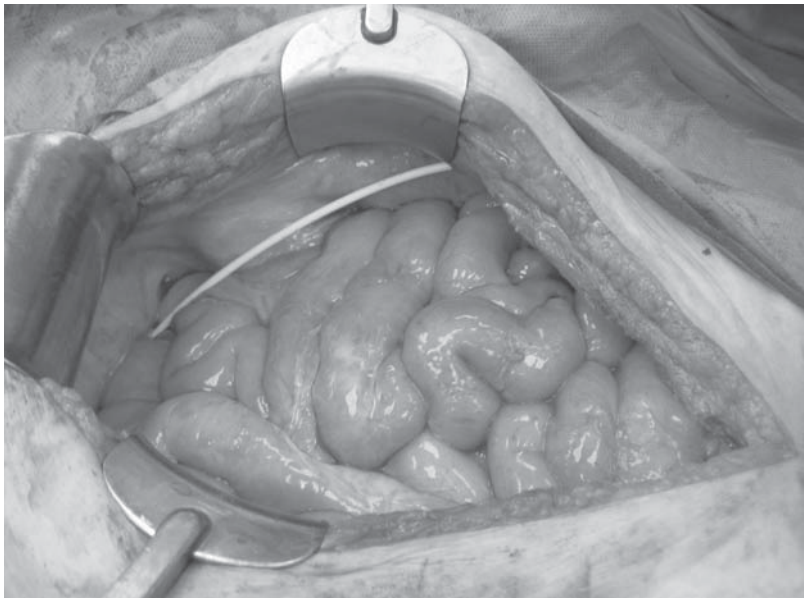

Fig. 3. Intraperitoneal port placement at initial laparotomy. The end of the port is left long.

wall after omentectomy. The catheter should drape into an area of intact peritoneal surfaces, which are less likely to form adhesions. The port pocket is created cephalad to a transverse incision along the lower costal margin in the midclavicular line. The port is sutured with 2-0 polypropylene (Prolene®; Ethicon, Inc., Somerville, NJ) in four corners to prevent future displacement and rotation, which impair Huber needle access into port lumen. The perforation into the peritoneal cavity must be kept as small as possible to prevent ascites or IP chemotherapy fluid from flowing retrograde into the subcutaneous tissues and port pocket. The vagina and the abdominal wall incisions must be closed watertight, with care to avoid leakage of ascites or chemotherapy fluid out of either wound. Care must also be taken not to tangle the catheter into the wound-closure suture. The subcutaneous tissue is closed over the port with 3-0 polyglactin 310 (Vicryl®; Ethicon, Inc.) and the skin is closed with subcuticular 4-0 polyglactin 310 (Vicryl® Ethicon Inc, Somerville, NJ) or 4-0 poliglecaprone (Monocryl®; Ethicon, Inc.) (Fig. 4). The port is accessed with a Huber needle, and the port and the catheter are flushed with 100 U/cc heparinized saline to document flow and maintenance of a patent lumen. This flushing procedure is repeated after each port access procedure for chemotherapy administration.

Controversy continues as to whether the use of adhesion barrier material should be advocated between the bowel and the abdominal wall to improve IP

Fig. 4. The midline and port-site incisions.

chemotherapy fluid distribution. This issue requires further study, and there are many competing products on the market today. Some surgeons are currently placing routine adhesion barriers under the abdominal wound closure, whereas others use these products on other surfaces where the peritoneum has been removed.

The avoidance of foreign body placement at the time of peritoneal cavity contamination with fecal contents is based on good clinical judgment with limited evidence. There is evidence that patients are less likely to receive full-dose IP chemotherapy when the left colon is resected, but many of the patients studied never received their first cycle. Failures were often described as being caused by adhesions and complications of surgery. It is common practice to delay insertion of the IP catheter until a few days before the planned IP chemotherapy treatment. This allows further evaluation of the patient for surgical complications, such as peritonitis and anastomotic leak. The patient's recovery of bowel function after bowel resection and tolerance of a regular diet are reassuring and decrease the concern for infection and complications with IP chemotherapy. Delayed placement of an IP port may result in failure to place the

device at all, due to lack of enthusiasm of the patient and/or physician for a second surgical procedure so soon after the first.

Delayed insertion of an IP access device can be accomplished by the following three techniques: minilaparotomy, laparoscopy in the operating room, and interventional radiology using percutaneous methods in the radiology suite. Our preferred method is similar to the aforementioned open laparotomy technique. Access to the peritoneal cavity is made in a region where adhesions are not expected. The right lower quadrant is the preferred location, if the terminal ileum and cecum were not resected. The incision should be several centimeters below and lateral to the umbilicus to avoid the adhesions of the transverse colon to the anterior abdominal wall, which occur after omentectomy. The peritoneal cavity is identified, and free space (without bowel adhesions) must be found for safe introduction of the catheter. The technique can be adapted to the surgeon's preference; the catheter can be tunneled down from the port pocket above the costal margin before being placed into the peritoneal cavity under direct visualization using the tunneling device, or it can be brought up from the peritoneal cavity into the subcutaneous tissues and tunneled to the port pocket. The catheter is brought through the peritoneum, muscle, and fascia with a tunneling device or tonsil clamp to keep the perforation as small as the catheter. The catheter should **NOT** go through the minilaparotomy incision—the incision is only meant to guide the catheter without bowel injury through the abdominal wall. The incision should be closed to avoid kinking the catheter, and each layer should be separately closed carefully to prevent leakage of ascites or IP chemotherapy fluid. The port is sutured with 2-0 polypropylene in four corners to the fascia overlying the lower ribs. The port pocket is closed in two layers, subcutaneous and dermis, to minimize erosion of the port through the skin. The scar of the wound should not be immediately over the port access site. The port is flushed with 10 cc–20 cc of heparinized saline (100 units/cc). The remainder of the procedure is similar to that described. Chemotherapy administration is delayed at least 24 h.

3. LAPAROSCOPIC TECHNIQUE

Laparoscopic technique was developed for the purpose of combining the second-look laparotomy with catheter placement. Extensive lysis of adhesions may lead to bowel injury and is unlikely to enhance long-term fluid distribution, as the adhesions will likely reform. Laparoscopy is ideal when the surgeon placing the catheter is not the same as the one performing the original surgery. This allows reevaluation of the anatomy, disease status, and site selection for catheter placement. The catheter has been placed by two techniques. One is drawing the catheter into the peritoneal cavity through the 5-mm trocar site. In cases where the peritoneal orifice is larger than the catheter, an Endoclose®

(Ethicon, Inc.) device or Carter-Thomason subcutaneous tissue closure device (CloseSure® System; Inlet Medical, Inc., Eden Prairie, MN) can help with closing the peritoneum and fascia around the catheter. Alternatively, the catheter can be similarly introduced to a venous access device placement. Needle localization of the peritoneal cavity is the first step, under laparoscopic guidance, followed by a guide wire placement and removal of the needle. A dilator and pull-away sheath is placed over the guide wire. The wire and dilator are removed, the catheter is placed through the sheath, and the sheath is removed, leaving the catheter in the peritoneal cavity at least 10 cm long. The catheter is then tunneled from the peritoneal entrance site, through the subcutaneous tissues overlying the fascia, to the port pocket location and attached. The port is sutured in four corners with 2-0 polypropylene to the fascia overlying the inferior ribs at the midclavicular line. The subcutaneous tissues are closed with running 3-0 polyglactin 310 (Vicryl® Ethicon Inc, Somerville, NJ), and 4-0 polyglactin 310 (Vicryl® Ethicon Inc, Somerville, NJ) is used to close skin. The incision should not be located over the port access dome for easier Huber needle access. Care must be taken not to allow kinking of the catheter at the port connection site or at the peritoneal entrance site. The port should be accessed with the Huber needle and 10–20 cc of heparin; 100 units/cc is used to flush the port and the catheter, as well as to document flow and keep the catheter patent.

The interventional radiologist can place the IP catheter using ultrasound guidance for identification of the peritoneal space, or using computed tomography (CT) scan localization techniques. Ascites improves the identification of free peritoneal space. The use of contrast injection confirms the appropriate location of the needle. The remainder of the procedure is similar to that described above under laparoscopy. A wire is passed down the needle with fluoroscopy, followed by the dilator and pull-away sheath to assist with passage of the catheter into the peritoneal cavity. Fluoroscopy is used to document and visualize good catheter placement in place of laparoscopy. Free flow of fluid into the peritoneal cavity is observed by fluoroscopy. The tunneling and port placement is otherwise the same for laparoscopy.

Port-site locations have been described on the anterior superior iliac spine, inguinal ligament, and anterior ribs along the lower costal margin. It is difficult to access the port buried in the abdominal wall without a firm structure to support it. Allowing the chemotherapy nurses easy access to the port prevents injury to the catheter by multiple failed attempts to insert the Huber needle into the port diaphragm. The usual choice is the ribs, but there are reports of discomfort with each site chosen. Discussion of site selection with the patient will allow the surgeon to learn if a patient sleeps in a certain position, or wears undergarments that will rub in the area selected. With advanced communication, it may be possible to avoid some of the discomforts with port placement.

4. CHOICE OF DEVICE

Current evidence supports the use of a silicone catheter attached to an implantable port. There is debate whether the fenestrated peritoneal catheter or the venous access 9.6-Fr silicone catheter is preferred. The fenestrations allow fibrin sheath and plug formation in the polyurethane catheters. This appears not to be the case with the silicone peritoneal catheter BardPort #0602870 (Bard Access Systems, Salt Lake City, UT) (Fig. 5). Memorial Sloan-Kettering Cancer Center physicians have had recent success with peritoneal access since abandoning the polyurethane catheter and avoiding placement during bowel resection procedures where peritoneal contamination is of concern. At the University of Oklahoma we use only the 9.6-Fr silicone venous access catheter attached to the BardPort. These catheters are not associated with fibrin plugs, fibrinous sheaths, or adhesions, and do not get encased by bowel loops. These authors recommend BardPort because of the silicone catheter, and they do not use the Port-A-Cath or the Tenckhoff catheters (Fig. 6) because of adhesion formations. It is thought to be the switch to the silicone catheter that decreases complications, as well as avoids a contaminated peritoneal cavity. Inadequate research in this arena prevents any firm conclusions. There are other manufacturers of silicone catheters attached to ports, and generic brands are likely to perform

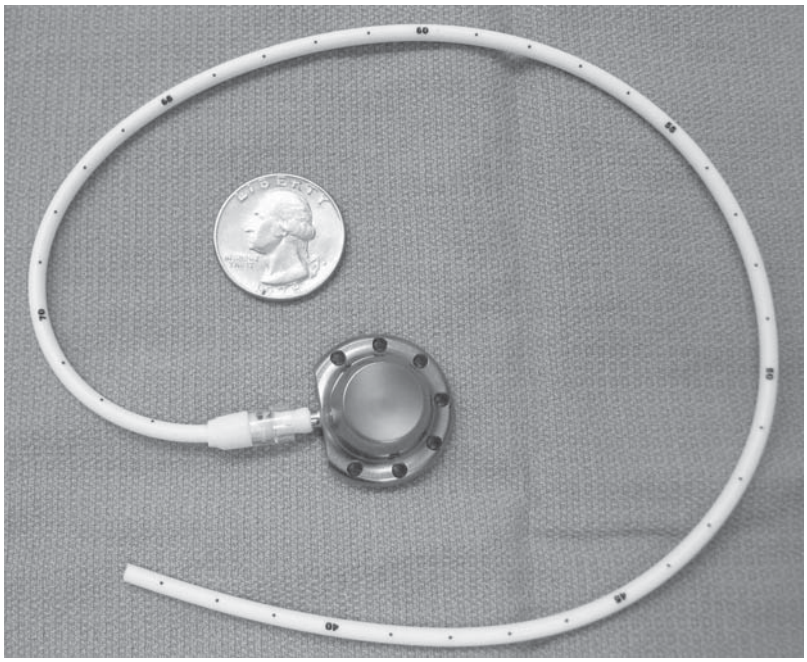

Fig. 5. The 9.6-Fr silastic BardPort #0602870 with attachable catheter (Pre-attached #0602660).

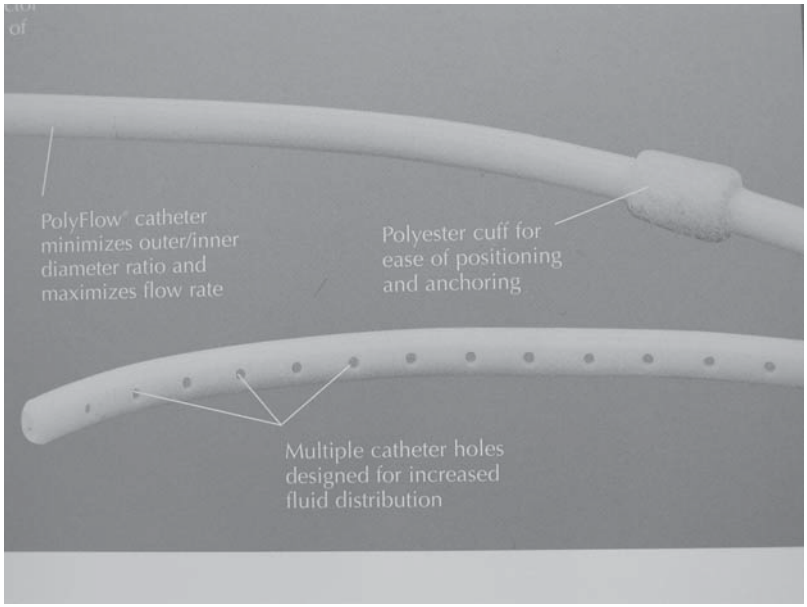

Fig. 6. An example of a multi-holed catheter, with cuff

similarly. The size and type of port depends somewhat on the physical size and depth of adipose tissue of the individual patient. The historical perspective provided later in this chapter, as well as the multiple reports on the high rates of complications of previous catheters, support the choice of the silicone venous access catheter.

The most important challenge today is to develop the commitment of the patients and physicians to this challenging treatment modality. Interventional radiologists are going to be unfamiliar with these treatment programs, and are likely to refuse to place these catheters. An institutional commitment and training program that includes chemotherapy nurses, gynecologic oncologists, and interventional radiologists improves the likelihood of successful treatment. The patient must also be accepting of more inconvenience and abdominal pain for the potential survival advantage. One of the most common causes of first-cycle failure of IP chemotherapy is not ever placing the access device because of either physician or patient reluctance to an additional surgical procedure. This is overcome by education and by placing the device at the first surgery.

5. PREVENTION OF COMPLICATIONS

Access problems are avoided by using a large enough port secured to the ribs with permanent suture such as polypropylene (Prolene®; Ethicon, Inc.). A large port is more easily palpated for introduction of the Huber needle. Difficul-

ties in accessing the port can lead to damage to the catheter by the Huber needle. The catheter chosen cannot be too flexible or too small, for this allows kinking in the subcutaneous tunnel, at the junction of the catheter to the port, or at the turn through the fascia and into the peritoneal cavity. Avoid the smaller diameter 6-Fr catheters to reduce the likelihood of kinking problems. The 9.6-Fr silicone catheter has the proper strength to avoid kinking, but will not harm the IP contents.

The retrograde flow of ascites or IP chemotherapy fluid into the subcutaneous tunnel or port pocket occurs when the catheter insertion site through the peritoneum is too large or if distal obstruction to flow occurs. There is also concern for tumor implanting in the port pocket or tunnel, especially when laparoscopic placement is chosen. To avoid tumor implantation, chemotherapy needs to be administered soon after laparoscopic procedures in ovarian cancer with gross tumor or ascites present. The obstruction of flow occurs from multiple etiologies. Kinking of the catheter can be seen on fluoroscopy, with contrast dye injection. The formation of a sheath around the catheter is evident when the contrast dye injected flows down to the tip of the catheter, then turns around and runs back up the outside of the catheter track. Peritoneal adhesions will cause the filling of a peritoneal pocket before retrograde flow occurs. The leakage of chemotherapy out the wound, vagina, or into the bowel should be avoidable. The simplest leakage is caused by the Huber needle being outside of the port. The port can be accessed, and then movement of the patient can dislodge the needle. It is critical to lay the patient supine and not allow her to sit upright in a chair during peritoneal infusion. The flexing at the waist constricts the abdominal volume and also can dislodge the needle. Vaginal leakage can be avoided by performance of a supracervical hysterectomy, which is feasible in many cases, when removal of the cervix is not required to complete an adequate surgical debulking. When the cervix is removed, a careful running and locking polyglactin 310 (Vicryl®; Ethicon, Inc.) suture is needed. A watertight closure of the vagina is necessary when IP chemotherapy is planned. Abdominal wall closure is also performed with care to avoid leakage. Bowel resections may require delay of chemotherapy to allow for wound healing, especially with the modern use of paclitaxel. Subclinical leaks, which are walled off with bowel adhesions and an inflammatory response, can be exposed and create peritonitis when IP chemotherapy is administered, which may be especially true when paclitaxel is utilized. There are multiple reports of bowel perforation associated with paclitaxel. Diarrhea after IP chemotherapy may be caused by intraluminal administration of IP chemotherapy or infection with *Clostridia difficile* causing enterocolitis. It is important to consider these possibilities in the evaluation of these patients. Fluoroscopy of the catheter will determine the catheter location, and where the contrast is being delivered.

Abdominal pain with infusion is often the result of poor distribution of the fluid into the abdomen, and stretching of the bowel adhesions surrounding the fluid pocket. If the discomfort requires discontinuation of IP chemotherapy, decisions can be assisted with fluoroscopy. Fluoroscopy of the catheter may help determine whether replacement of the catheter would be feasible, or if IP chemotherapy should be abandoned. Catheter replacements are rarely successful, unless specific problems such as rotation of the port or kinking of the catheter are the problem. Bowel adhesions will not usually respond to lysis of adhesions or repositioning of the catheter. Peritonitis is of concern when a patient has abdominal pain with peritoneal signs, fever, and an elevated white blood count. The differential diagnosis is challenging to evaluate because abdominal pain is common with IP chemotherapy. The pain should improve with time if it is only caused by stretching of the abdominal cavity with fluid infusion. Chemical peritonitis does occur, with cultures of the port and the peritoneal fluid remaining negative. This is a diagnosis of exclusion, and an infectious source should be initially assumed. Antegrade infection of the port, catheter, or peritoneal cavity by skin organisms is likely related to surgical site infection at placement, or contamination at the time of access. Vancomycin may be required to cover gram-positive cocci until organisms and their sensitivities are identified. Peritonitis with enteric organisms must make bowel injury likely on the differential diagnosis, and broad-spectrum antibiotics are required. Cultures of the peritoneum can sometimes be obtained by irrigation of the port with normal saline and withdrawal of fluid for culture. CT scanning with contrast should assist with this diagnosis, and even irrigation of the port with contrast may assist with the diagnosis. Free air under the diaphragm could theoretically have been introduced through the peritoneal port, but bowel perforation should be ruled out. The catheter should be removed if it is located in the lumen of the bowel, or if antibiotics fail to clear the infection. If an infection is found without injury or abscess, it may be treated with antibiotics, without removal of the device.

Cellulitis around a port pocket with fluctuance and pain is unlikely to respond to antibiotics alone, and it usually indicates an abscess in the port pocket. Antibiotics coupled with removal of the port will usually resolve the infection if peritoneal signs are not evident. Prevention of this complication may be improved by careful attention to antiseptic techniques at the time of port access *(1)*.

6. HISTORICAL PERSPECTIVE

In 1978, Dedrick proposed the potential benefit of IP administration of chemotherapy for peritoneal carcinomatosis caused by ovarian cancer *(2)*. Since this report, attempts have been made to infuse chemotherapy into the peritoneal cavity for the treatment of ovarian cancer. The report recommended that the

chemotherapy agent be administered in large volumes of fluid for adequate distribution, to ensure contact of chemotherapy agent with all tumors on peritoneal surfaces. The standard infusion volume has remained 2 L, using normal saline to dilute the cisplatin for consistent pharmacokinetic results. Abdominal pain may interfere with the successful delivery of the entire two liters of fluid. The current compromise standard orders are to mix the chemotherapy in one liter of normal saline, and infuse a second liter of normal saline into the abdominal cavity, if tolerated, to aid in distribution.

Infusion of chemotherapy into the peritoneal cavity requires access for infusion, and current protocols require multiple infusions at regular intervals. A temporary single-use device, or a semipermanent implantable device, was originally chosen for this procedure. Access to the peritoneal cavity can be obtained percutaneously, but in a cancer patient or a postoperative situation adhesions of small or large bowel to the anterior abdominal wall may complicate the procedure. The Veress needle was developed for safe access to the peritoneal cavity, and is a familiar instrument to all physicians trained in gynecologic laparoscopy. This device was intended to prevent injury to the bowel, vessels, or other organs during the access procedure (paracentesis or laparoscopy). Obtaining access to the peritoneal cavity continues to cause most of the complications in laparoscopic procedures today. This is a similar problem for IP chemotherapy because access problems are interfering with the universal acceptance of IP chemotherapy for ovarian cancer.

Pfeiffer reported on the use of the Veress needle for repeated access to the peritoneal cavity for delivery of chemotherapy *(3)*. This report was written secondary to the frustration with the totally implantable access devices in 11 patients, where they had difficulty with completion of six cycles of chemotherapy. Their technique is similar to the laparoscopic pneumoperitoneum method. The Veress needle was inserted through the inferior fold of the umbilicus with local anesthesia in the clinic, and 22 chemotherapy infusions were delivered in 7 patients with only minor side effects.

Oncologists utilized the guidance of the peritoneal dialysis literature to develop IP chemotherapy because the surgery literature had techniques developed in the 1960s for placement of dialysis catheters for infusion of dialysate into the peritoneal cavity *(4)*. Tenckhoff catheters were initially used, and complications were reported frequently, as the abdominal cavity of an ovarian cancer patient is very different from that of a renal failure patient *(5)*. The dialysis literature reported infections in 30%, hernias in 30%, drainage failure in 28%, leak in 24%, cuff extrusions in 10%, and bleeding. The Tenckhoff catheter implanted in the ovarian cancer patient caused peritonitis, inflow obstruction, leakage of fluid, bowel obstructions, and pain. Only 48% of the cases reported by Myers completed their treatment plan, and 59% suffered complications *(6)*. Runowicz used single-use catheters and preferred them to

Tenckhoff catheters *(7)*. Others believed that because accessing the peritoneal cavity was the likely time of patient injury, implantable catheters that could be repeatedly used would be safer *(8)*. Waggoner reported on 27 Groshong venous catheters placed in 24 patients at the time of laparotomy *(9)*. These silicone catheters were tunneled and exteriorized similar to a venous access Groshong. Infection was uncommon and ease of removal was a desirable finding, as many patients did not enroll on IP treatment protocols postoperatively.

Skin flora infections were common when catheters that had exteriorized tubing were used. There were Dacron cuffs surrounding the catheter to allow for fibroblasts to fix the catheters in place, which prevented accidental pulling and dislodgement. The Dacron cuffs were known to erode into the peritoneal cavity and adhere to bowel. There is no need for the Dacron cuffs on the completely implanted port systems because they are not subject to dislodgement. The elimination of the Dacron cuff also eliminates the complication of erosion of the cuff into the peritoneal cavity.

Braly reported on the use of Tenckhoff semipermanent dialysis catheters in their first 8 patients, followed by the use of Port-A-Cath IP catheters in the next 33 cases *(10)*. Two cases had the catheter placed at the time of laparoscopy. Laparotomy was needed in 12 of the cases, and others had concomitant cancer surgery, including 4 bowel resections. Catheter related complications were peritonitis (5 cases), cellulitis (2 cases), infusional pain (7 cases), catheter revision required (2 cases), infiltration (1 case), bowel obstruction (1 case), and bowel perforation (1 case). At the time of catheter removal, dense fibrinous sheaths and loculations of bowel were surrounding the peritoneal catheter. Braly successfully delivered 211 courses of chemotherapy to 41 patients with these techniques. Pfeifle used the Port-A-Cath in 54 patients, and no bowel perforations were identified *(1)*. Peritonitis *(3)* and fibrin deposits impeded bidirectional flow, but the system was generally used for 22 weeks with reasonable success.

Ultrasound guidance for peritoneal access, usually with the assistance of ascites creating an ultrasound "window," can be used by interventional radiology. Malmstrom reports on 125 patients receiving 465 courses of chemotherapy using the Port-A-Cath *(11)*. Complications were seen in 21.6% of patients. Catheter problems caused discontinuation of treatment in 7%, and in 12% treatment was discontinued because of drug toxicity. This catheter is made of polyurethane and has a Dacron cuff. Abdominal pain was observed in 9.6%, the catheter disconnected in 8%, inflow obstruction was observed in 4.8%, infection was observed in 4%, and rotation of the port preventing access was observed in 2.4%. These authors were very explicit about the importance of training, and the contribution of surgical techniques contributing to catheter disconnection and port rotation problems. They also reported plugs of fibrin within the catheter, and extensive adhesions entangling loops of bowel sur-

rounding the catheter. They, like others, describe a fibrinous sheath surrounding the catheter. Rubin reported on 136 catheters in 130 patients delivering 629 chemotherapy cycles using the Port-A-Cath peritoneal catheter *(12)*. Infections caused catheter removal in 5.1%, and inflow obstruction caused removal, which was associated with fibrinous sheath formation and bowel adhesions surrounding and encasing the catheter, in 5.1% of patients.

Orsi *(13)* reports on 15 successful placements, using a percutaneous approach, in 19 patients (79%); 4 were not completed because of adhesions preventing free peritoneal flow *(13)*. The procedure was accomplished in 45 min. Using ultrasound guidance under local anesthesia, a 16-gauge needle was used to access the peritoneal cavity in a lower abdominal quadrant. A guide wire was threaded through the needle, and a peel-away sheath and dilating cannula were advanced with the assistance of fluoroscopy. The wire and cannula were removed, and the 9.6-Fr open-ended silastic venous catheter was advanced down the peel-away sheath. Contrast was injected to verify peritoneal flow and distribution. The catheter was tunneled to the port site location (anterior superior iliac spine) and attached to the port in a subcutaneous pocket and sutured to fascia. The Huber needle was inserted at the end of the procedure, verifying function. The port and catheter were heparinized monthly. The catheters were used, on average, for 2.1 cycles per patient. No procedure-related complications were noted. One system was removed because of pain. No peritonitis was seen. Interventional radiology would therefore be able to introduce an implantable system into the peritoneal cavity using ultrasound guidance in a patient with ascites, without complications.

Intraoperative placement at debulking surgery is standard in Japan, where an Infuse-A-Port or Port-A-Cath is utilized *(14)*. At second-look laparotomy, 21.8% of the patients were found to have extensive adhesions. Some 16.7% complained of pain and redness around the port. Three had an abscess of the port pocket. Inflow obstruction was encountered in 6.4% of catheters. Three patients required laparotomy for major complications including ileus, perforation of vagina, and perforation of small intestine. Seventeen (22%) of the 78 patients discontinued treatment prematurely.

Makhija *(15)* reports on the change at their institution from polyurethane Port-A-Cath system as reported by Davidson *(16)*, to a silicone BardPort peritoneal catheter. The avoidance of catheter placement at the time of bowel resections was also believed to decrease their complications. Of 301 patients, 10% had catheter-related complications and 93% completed all of the prescribed chemotherapy. Malfunction of the catheter occurred in 6.3%, and infection in 3.7% of cases. Five patients had catheter repairs or replacement to complete their treatment. Some 69.6% of catheters were placed at laparotomy and 19.5% at laparoscopy, and 10.9% were placed at a separate procedure. This was considered a dramatic improvement from the Davidson report because

there were no major bowel injuries, and the complications were easily managed, and caused little disruption of treatment.

Walker describes the switch to BardPort 9.6-Fr Silicone single-lumen venous catheter Bard Access Systems, Salt Lake City, Utah *(17)*. The port is the same as described in the previous paragraphs, with a choice of a reliable attachment technology or preattached (order numbers 06026870 and 0602660). The silicone catheter does not adhere to the bowel or the peritoneal adhesions like the polyurethane catheter. The port can be removed in the office under local anesthesia, and the catheter slides out of the peritoneal cavity, and there are no adhesions or Dacron cuffs to impede removal.

Anaf describes peritoneal catheter placement using laparoscopy at the time of second-look laparoscopy *(18)*. Access to the peritoneal cavity was obtained in the left upper quadrant under the ninth rib at the midclavicular line. An open trocar insertion technique was used, but blind entry with Veress needle in left upper quadrant is described. Lysis of adhesions of bowel from abdominal wall is then performed to allow additional ports to be placed. A polyurethane catheter (which could be substituted for a silicone catheter) was brought through the 5-mm trocar, and while holding the catheter in the abdomen the trocar was removed. The catheter is then tunneled to the port pocket created overlying the lower costal margin at the midclavicular line. The chemotherapy was delivered on day two, and bowel function returned at that time as well. No tumor implants were seen in the catheter track or port pocket, and they hypothesize that this was because of rapid infusion of chemotherapy postoperatively. Others have reported laparoscopic tumor implants within weeks of a procedure *(19)*. Arts also demonstrated the use of laparoscopic guidance for placement of IP catheters *(20)*.

The literature on operative technique for the delivery device for IP chemotherapy is inadequate to yield firm conclusions. The author of this chapter has initiated prospective studies of operative technique and complications to improve catheter-related toxicities. The recommendations in this chapter are based on expert opinion because there is inadequate literature on the subject. There are patients who will not be able to tolerate IP chemotherapy, but this chapter should allow oncologists the information needed to treat most women successfully with 10–15% complication rates, which can be managed, are not life threatening, and do not affect survival.

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6 Hyperthermia and Chemotherapy: The Science

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Summary

Cancer ranks second only to heart disease as the greatest cause of mortality in the United States. Despite significant strides in diagnosis and therapeutics, clinical treatment of metastatic cancer still yields a poor prognosis. Basic science research is increasing our knowledge of the mechanisms by which chemotherapeutic and hyperthermic modalities exert their antitumor activity. Herein, we describe the current state of knowledge of these treatment modalities and the basic science behind their clinical usefulness. Moreover, we identify gaps in our understanding of the basic science of these treatments. Basic science is primed to exert a substantial role in extending our therapeutic options through the clarification of current therapeutic mechanisms, as well as the generation of novel treatments.

Key Words: Cancer; neoplasia; metastasis; chemotherapy; hyperthermia.

Those diseases that medicines do not cure, are cured by the knife and those that the knife cannot cure are cured by fire. And those that fire does not cure are to be reckoned wholly incurable.

Adams, F. *The Genuine Works of Hippocrates.*
New York: William Wood & Co., 1886:273

1. INTRODUCTION

Cancer continues to exact a heavy toll in terms of both human life and economic resources. The American Cancer Society estimated that in 2007, 559,650 Americans will die of cancer; this amounts to 22.8% of all deaths, second only to heart disease in mortality figures. Most cancer deaths in men (51%) are expected to be from cancers of the lung and bronchus, prostate, and colon

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and rectum. Among women, cancers of the lung and bronchus, breast, colon, and rectum are expected to account for more than half of all cancer deaths (52%).

Despite highly publicized improvements in cancer therapeutics, the long-term prognosis for patients with metastases is still dismal. Additionally, although significant strides have been made in lowering the mortality rates of many other diseases afflicting Americans (e.g., heart disease), the mortality rate for cancer has not significantly changed over a period from 1950–2004. These data indicate that despite advances in therapeutics, surveillance, and public awareness, there still exists a large need for improvement in these areas. One potentially new area of therapeutic advances, although controversial, is the application of exogenously induced heat (hyperthermia) to combat neoplasia and metastases. This method has attained a measure of success in the treatment of tumors, although it is clear that more investigation is needed before this method becomes firmly established in the treatment of cancer *(1–3)*.

2. PART I

2.1. Fundamentals of Hyperthermia

In humans, there are three major temperature ranges. An elevated body temperature <41.8°C is defined as fever and is recognized as a basic physiologic function contributing to survival. It is conserved across evolution and ubiquitous in the animal kingdom. Fever appears to have a beneficial role in enhancing defense of the body because it has a very high metabolic cost and would otherwise have been selected against *(4)*. Research has shown that for each 1C° = one centigrade degree rise in temperature the metabolic rate increases by 10% *(5)*. Sustained body temperatures above 44°C for durations >60 min have been shown to lead to protein denaturation, culminating in cell death. This is particularly important in neurons, which will undergo apoptosis *(6)*. The temperature range between "beneficial" fever and "deleterious" hyperthermia (41°C –44°C) is the temperature range where clinical hyperthermia therapy may exert a beneficial role (defined as destruction of the target tissue with minimal to no effect on the normal tissue) if malignant tissue is more thermosensitive than normal tissue *(7,8)* (Fig. 1). In fact, hyperthermia has been defined as a core body temperature >41°C for >60 min *(1,2,9)*.

Before discussion of the therapeutic utility of hyperthermia, the general concepts of thermosensitivity, thermoresistance, and thermotolerance need clarification. Thermosensitivity refers to the temperature threshold at which a tissue will be destroyed by a specific amount of heat. Thermoresistance is the initial innate ability of a cell to survive an acutely elevated temperature *(10,11)*. Thermotolerance is the transient ability of cells subjected to high temperatures to survive subsequent exposure to lethally elevated temperatures *(12)*. The cellular mechanisms responsible for this differential in sensitivity have not been

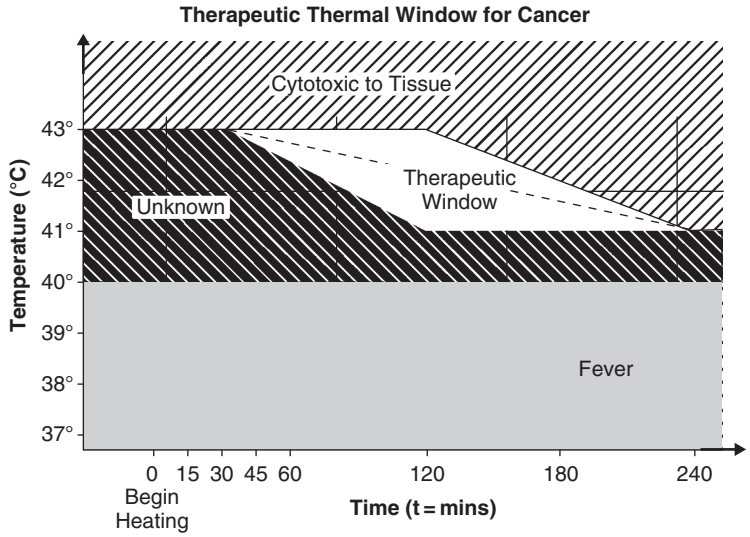

Fig. 1. The therapeutic window has four borders that have been substantiated by many studies. The lower boundary occurs at a point very near the upper reaches of physiologic fever (~40.8°C). At this temperature, it takes much longer for a cytotoxic effect to become manifest. The upper boundary occurs at a temperature where continued exposure or an elevated exposure damages normal tissue (43°C). At this temperature, the exposure time is significantly reduced. The dashed line in the window indicates the thermal iso-effect line, which is defined as the time/temperature interval that results in equivalent cell kill. (Adapted from Vertrees RA. Pathology of thermal stress in normal, transformed and malignant lung cells. University of Texas Medical Branch, Dissertation, May 1999).

clearly identified; however, it has been proposed that all of these mechanisms are dependent on the protection offered the cells by a group of constitutive and inducible proteins—heat shock proteins (HSPs). Attaining this knowledge is critical before the clinical usefulness of hyperthermia can be exploited as a therapeutic modality.

2.2. Historical Perspective

Historically, there are both anecdotal and specific reports indicating a potential beneficial role of therapeutic hyperthermia in the treatment of cancer. Busch reported observations of the spontaneous disappearance of a histologically diagnosed sarcoma after high fever associated with a *Streptococcus erysipelas* infection *(13)*. Following up on these observations, Coley intentionally infected patients with *S. erysipelas* and reported "curative effects" associated with the induced fever on humans with cancer *(14–16)*. In 1955, Nauts et al., *(17)* repeated these experiments with febrile therapy and realized a significant therapeutic advantage in patients with tumors; the therapy was abandoned, however, because of the side effects of the inoculations *(3)*.

The use of clinical hyperthermia in the treatment of cancer has currently morphed into four distinct areas defined by the presentation of the cancer involved: localized, isolated organ, regional, and systemic. Localized treatment, aimed at increasing temperatures in the tumors only, is applied to cancers that are confined to specific locations without signs of metastasis. These treatments produce heat that is directly transferred to the tumor by various means, including external, intraluminal, or interstitial methods *(18,19)*.

Isolated organ treatments generally use a perfusion device that delivers heat from an external source to the target via heated blood. Targeted tissues have been specific diseased organs, such as the liver affected by metastasized ocular melanoma *(20)* or limbs affected by malignant melanomas *(21–23)*. These treatments isolate the organ from the rest of the body and perfuse it with a combination of heat and chemotherapeutic agents, thus, allowing for a much higher concentration to be delivered to the target tissue *(23–25)*. In most cases, oxygenation of the perfusing blood is necessary.

Regional hyperthermia treatments, again, use an external heating source and deliver the heat energy plus a high concentration of a selected chemotherapeutic agent to the affected area using a heated bloodless perfusing solution. Currently, this technique is gaining favor in the treatment of locally advanced cancers that are confined to either the peritoneal or pleural cavities *(26–33)*.

Systemic hyperthermia treatments use an external heating source to treat patients with metastatic disease. Historically, many different techniques were used, including radiant heating *(34)*, dipping in hot wax *(35)*, wrapping the patient in plastic sheets *(36)*, encasing in a high flow perfusion suit *(37)*, and extracorporeal perfusion *(35,38,39)*. Today, this field has essentially congealed into two distinct camps. Pritchard et al., utilizes a heating tent, and induces hyperthermia to 39°C for up to 8 h *(40)*. During this time, chemotherapeutic agents are administered to the patient *(40–42)*. The other camp is represented by our work using extracorporeal perfusion, heating the patient to 42°C for 2 h without chemotherapy *(39,43,44)*. With our technique, the entire patient experiences the elevation of body temperature, not just a specific area or tissue, and the effect on the tumor is from the heat alone because chemotherapeutic agents are not used during the procedure *(34,45–55)*.

2.3. Fundamental Problems

The use of therapeutic hyperthermia for disseminated cancers (regional or systemic) is controversial and presents significant technical challenges. It is controversial because of the conflicting reports in the literature, with some attesting to a therapeutic usage and others showing no effect at all. These discrepancies are most likely caused by the current gap of knowledge correlating hyperthermia-related events at the cellular level to those at the more complex tissue level. This has happened because some very fundamental problems still

have not been adequately investigated. First, the concept of a "therapeutic range" has not been defined by experimentation. Second, there is currently no clear-cut and universally accepted definition of what constitutes a "dose" of "therapeutic heat". The third problem is thermometry; how, where, and what do we use to measure temperature changes in the body? In this section, we will discuss the fundamental problems concerning clinical hyperthermia and show how the lack of progress has become a major stumbling block in the implementation of hyperthermia as a treatment modality.

2.4. The Therapeutic Thermal Window

Ideally, a therapeutic thermal window would have both upper and lower boundaries defined by temperature and right and left borders defined by a time interval (Fig. 1). Within this window, hyperthermia will destroy the target tissues, while having little to no significant deleterious effect on normal surrounding tissue *(56)*. This appears plausible because Tomasovic et al., found that tumor burden generally decreased after induction of heat stress proteins and thermotolerance *(57)*.

Initially, we will define the upper boundary as existing at a temperature where hyperthermia destroys both normal and neoplastic tissue. In normal tissue, hyperthermia causes vasodilatation, which is a normal physiologic response to shift distribution of blood to peripheral tissue to shed heat through perspiration *(58–60)*. There is a documented increase in heart rate, cardiac output, urine production, and alteration in serum electrolytes *(61–63)*. Studies have further demonstrated that at the cellular level, hyperthermia causes an increase in cell wall fluidity and permeability, as well as an overall increase in cellular metabolism *(64)*. Pettigrew et al., showed that when core body temperature exceeded 42°C, the result was a significant deterioration of brain function, as well as liver damage *(35)*. In 1982, Hart et al., published a study that examined elderly patients that had suffered heat stroke (core temperature >41.8°C) *(65)*. Of these patients, 32% had adverse central nervous system symptoms. In 1994, Matsumi was able to demonstrate that, at least in monkeys, the safety limit for hyperthermia was a brain temperature ≤43°C for 60 min *(6)*. Similarly, Vertrees et al., documented that in swine, the safe upper limit was 43°C for 180 min *(66)*. Collectively, these data suggest that a safe upper boundary for normal tissue is approximately 42°C. To further clarify the upper boundary of the therapeutic window, we must also define a temperature that will exert deleterious effects on the neoplastic target tissue.

In some studies, cancer cells have shown an increase in programmed cell death, resulting from damage to DNA when temperatures exceed 42°C *(64)*. We conducted an experiment to test this boundary. The experiment was designed to investigate the effect of a broad range of hyperthermic temperatures on neoplastic and normal cell lines. In this experiment, colon cancer cells

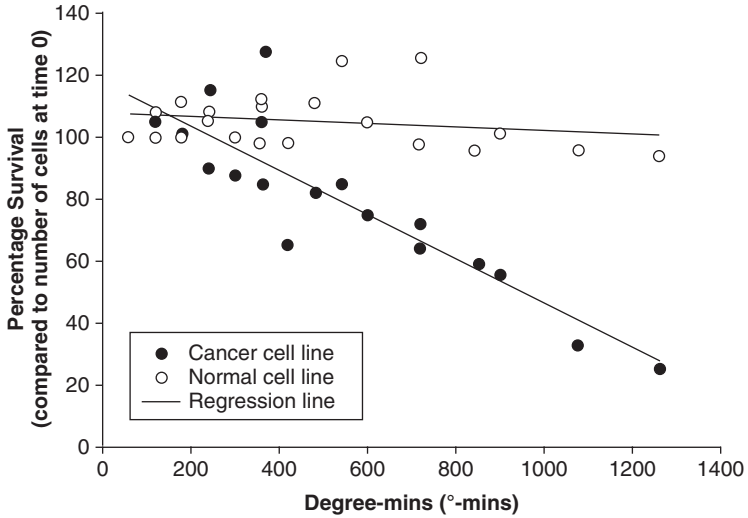

Fig. 2. The scattergram represents the results of experiments that determined the number of surviving cells at specific time x temperature combinations. As noted by the regression lines, these are two distinctly different plots, with the cancer cells showing much more susceptibility to the time x temperature combination.

(transformed) were subjected to temperatures varying from 37°C–44°C for 2 h, after which they were returned to 37°C for 3 h. At the conclusion of the experimental treatment, cells were enumerated and expressed as the percentage of viable cells obtained. As seen in Fig. 2, the effect of heat significantly ($p < 0.05$) reduced the number of cancer cells, compared to normal cells. In addition, the regression curves clearly depict two completely different responses. Data is expressed as Celsius-minutes (hyperthermic temperature = 37°C X minutes at elevated temperature) and suggests that neoplastic cells are more sensitive to the effects of hyperthermia than normal tissue *(67,68)*.

The lower hyperthermia boundary is defined as that temperature where the deleterious effect of heat on the target neoplastic tissue is minimal. A study has shown that the systemic effects of hyperthermia (temperature > 41°C) in cancer tissue can lead to activation of immune surveillance caused by the expression of the major histocompatibility complex protein *(69)*. Additionally, an increase in cell wall fluidity and permeability, as well as an increase in cellular metabolism, are seen *(64)*. These data suggest that the lower boundary is set at a point very near the upper reaches of a normal fever, which is approximately 41.8°C. In our study, there were no deleterious effects of hyperthermia if it did not equal or exceed 42°C *(67,68)*.

The width of the therapeutic window is the length of time that the tissues can be exposed with the desired result (i.e., survival for normal tissue and death for neoplastic tissue). All mammalian cells respond to heat-stress by rapid

induction and synthesis of evolutionarily highly conserved proteins known as HSPs, while the synthesis of other proteins is dramatically reduced *(70)*. Synthesis of HSPs is correlated with increased cell survival *(70–72)*, and resistance to apoptosis *(73)*. When HSPs are defective or absent, cell death occurs after heat exposure *(74,75)*. During heat shock, HSPs move from the cytoplasm to the nucleus, concentrating in the nucleolus very quickly; they then return to the cytoplasm upon cell recovery *(76)*. This rate of translocation is markedly faster in heat-tolerant cells *(77)*. The major role of HSPs under non–heat-stress conditions is in the translocation and folding of nascent polypeptides and the reconstitution of denatured ones *(76)*. Therefore, HSPs play an important role in modulating cellular responses to heat shock *(74)*. Fig. 3 illustrates the results obtained in another study comparing the response of heat shock protein 70 (HSP70) between an immortalized (noncancerous) and a transformed (cancerous) lung cell line *(78)*. Both cells lines were exposed to 43°C hyperthermia for 2 h, and then returned to 37°C. Aliquots of cells were harvested and enumerated on an hourly basis for 24 h. These data demonstrate that there is significantly less HSP70 initially available in the cancer cells; it took nearly 90 min to martial a response by the HSP in the cancerous cells, whereas the heat shock response is virtually immediate in the normal cells. HSP70 reaches its high

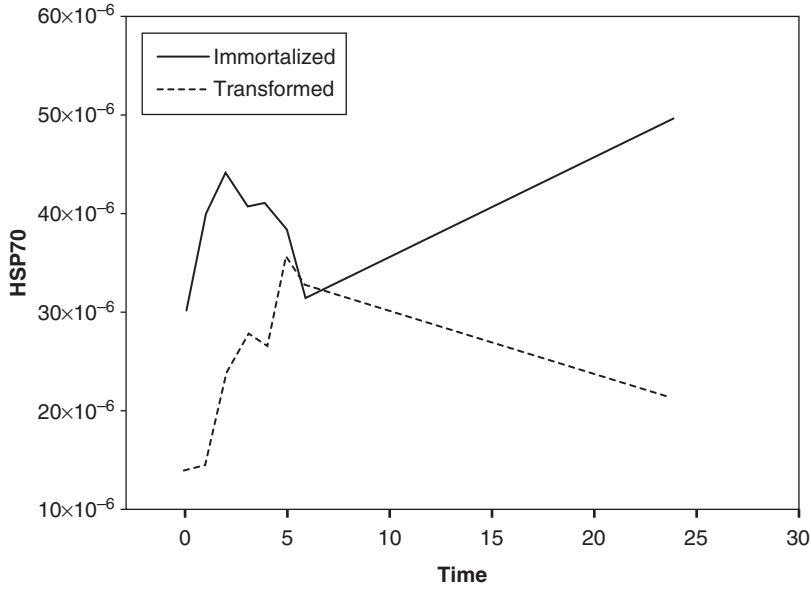

Fig. 3. This plot compares the amount of HSP70 present in the cells at each time point. Note that the amount of HSP70 is significantly less at the start, reaches a maximum only after heat is removed, and declines significantly after 24 h. (Adapted from Vertrees RA. Pathology of thermal stress in normal, transformed and malignant lung cells. University of Texas Medical Branch, Dissertation, May 1999).

point in the normal cells after 2 h of heating, whereas in the cancer cell line it peaks 2 h after the removal of cell from the heat stress. The resting level of HSP70 in normal cells at 24 h is much higher than in the cancer cell line *(78)*. An interesting point from this study implied that if the target tissue is heated too slowly, the therapeutic utility of the hyperthermia treatment could be significantly reduced in cancerous tissue because of the observation that the cell's heat shock response, despite being less than that of normal tissue, would be present. To study this hypothesis, the numbers of cells existing after varied rates of heating were compared. Vertrees determined that the various rates of heating had no discriminatory effect on normal or immortalized cells; however, there was a high negative correlation between cell survival and rate of heating in the transformed and cancerous cell line *(68)*. It still has not been clearly elucidated whether a rate of heating exists which may be deleterious to the patient. Current perfusion literature suggests that this is not the case, as long as the gradient in temperature between the hottest blood temperature in the patient and the patient's body temperature does not exceed 10C° = ten centigrade degree *(79,80)*. From these data, we were able to determine that the width of the window is between 120 and 180 min.

The heat-stress response may afford a therapeutic advantage if this response exhibits an appreciable difference between malignant and normal cells. We tested this hypothesis in a study where we obtained various cell lines and subjected them to hyperthermia at 43°C for 3 h, and then returned them to 37°C for 3 h (Fig. 4). After treatment, cells were harvested, counted, and expressed as a percentage of the original number of cells. Results show that all cell lines studied, with the exception of two, showed a significant reduction in the number of cells after exposure to hyperthermia. The two cell lines that did not show a reduction in number were a normal ovarian and normal lung cell line; all other cell lines showed a 50%–60% reduction in the number of cells and all were various cancer cell lines.

Through the collection of data we have obtained in our laboratory, as described above, we have determined the thermal therapeutic window for non–small-cell lung cancer cell lines, as well as *in vivo* in swine and humans. The thermal therapeutic window appears as in Fig. 1. Currently, we do not know what the thermal window is for other types of cancers.

2.5. What is a "Dose" of Heat?

Determining the "thermal dose" required to kill cancer cells, even given the aforementioned thermal window concept, is elusive and controversial. More fundamental than determining the thermal dose needed, is what constitutes a thermal dose. There are two significant problems to defining a thermal dose. The initial problem is one of thermometry; the closer the tissue is to the heat source, the more effective dose it receives. This issue will be dealt with in more

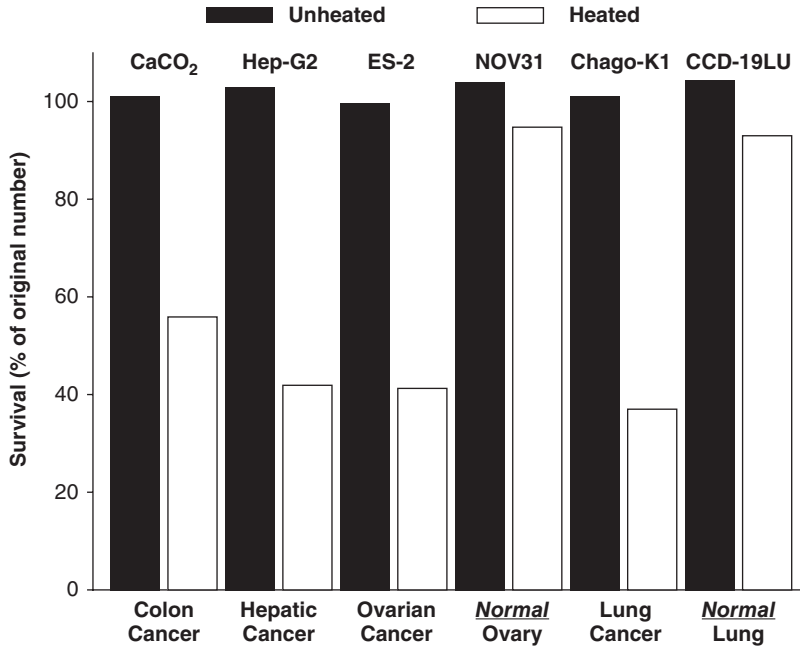

Fig. 4. The bar graph compares the effect of heat on many different cell lines. Each pair represents the number of cells before and after heating. Note that the heat exposure significantly reduced the number of cells in all cell lines except those that were normal (noncancerous).

detail in the next section, which is on thermometry. The second problem occurs because the effect of hyperthermia on tissues is cumulative throughout the exposure period. That is, there is a greater effect of the same hyperthermic temperature at 30 min than at 15 min. This is a critical issue because this holds for both malignant target tissue and normal tissue and could easily propel one outside the therapeutic window limits and damage normal tissue. It is important to find a precise definition of thermal dose because, when identified, it will give us a method of characterizing thermal treatments with significant correlations to outcome.

Many studies have shown that differences exist between cells in respect to their thermosensitivity, which is influenced by cell type and local environment *(56,81,82)*. Treatment at temperatures between 40°C and 44°C is cytotoxic for cells in an environment with a low pO_2 and low pH, conditions that are found specifically within tumor tissue because of insufficient blood perfusion *(83)*. The simplest method of measuring a thermal dose is to simply integrate the time the target tissue was at the specified hyperthermic temperature. This results in a time–temperature relationship. However accurate, this method does not

take into account the variance in thermal sensitivity at different temperatures in different tissue.

A lethal heat–dose response curve can be developed for most cell lines by determining the percentage of cells that survive a given time at a given temperature. From these data, a family of curves may be generated, yielding the survival curve. The survival curve reveals two important pieces of information: (1) the number of heat-resistant cells and (2) the exposure time required to reduce the survival to 37% of its initial value *(84)*. These data then allow for the ultimate expression of an Arrhenius plot *(85)*. An Arrhenius plot allows us to determine the ΔG (change in Gibbs free energy), ΔS (change in entropy), and ΔH (change in inactivation enthalpy). An interesting observation has been that there is an inflection point near 43°C. The ΔH and ΔS are different above and below this inflection point and imply that larger energies are needed at lower temperatures to produce cell killing *(86–88)*. The final data extrapolated from these studies is the equivalent time the cell needs to be heated to 43°C for an estimated 90% cell kill *(89)*. However, in all of these studies, the direct correlation between hyperthermic cell kill in the laboratory to that in the patient simply does not exist because it is not possible to do a lethal dose response curve in the clinical environment.

An early attempt to address this problem was offered by Sapareto et al., where they developed a mathematical description of the time–temperature relationship *(90)*. They selected a reference temperature of 43°C and mathematically converted all thermal exposures to "equivalent minutes" at this temperature. They developed the following relationship:

$$EM_{43} = \sum_{t=0}^{t=\text{final}} \Delta t R^{(T_1 - 43)}$$

In this relationship, EM_{43} is the equivalent minutes at 43°C, T is the temperature, t is the time interval of exposure, and R, which is 2 for temperatures >43°C and 4 for temperatures between 39°C and 43°C, is the heat sensitivity isoeffect *(89)*. The EM_{43} has direct relevance to the clinical situation, where this formula is used to determine the thermal dose delivered to tumor, as well as normal tissue, and it is the method we currently use *(67)*.

2.6. Thermometry

As previously stated, where, how, and when to measure temperature is of critical importance when using hyperthermia as a therapy for disseminated cancers *(91)*. Distribution of heat in tissues is not uniform between tissues and is dependent on proximity to the heating source. Thermal gradients exist within the core of homeotherms because of unequal distribution of heat *(92)*. Various organs and tissues heat at different rates because of differences in metabolism

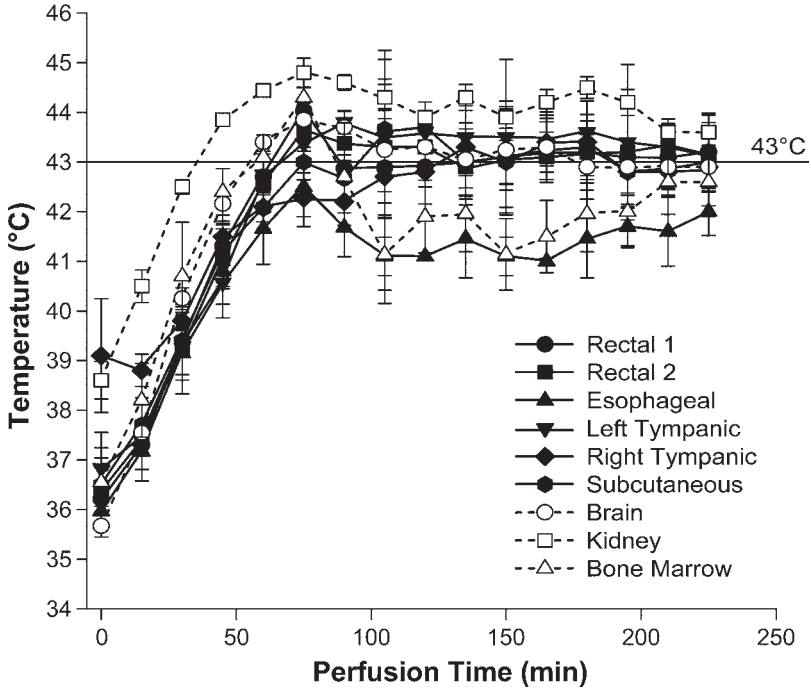

Fig. 5. We measured nine different temperatures continuously during the treatment period. It is interesting to note that although all sites heated at nearly the same rate, the bone marrow and esophageal temperatures did not reach the target temperature and kidney and tympanic exceeded the target temperature. (With permission from Vertrees RA, Leeth A, Girouard M, et al. Whole-body hyperthermia: a review of theory, design and application. *Perfusion* 2002 17:279–290).

and vascularity. The perfusion literature is replete with studies showing that gradients exist between tissues in regard to temperature changes *(80,93–97)*. These gradients result in areas within the body where a thorough heating becomes more difficult, thus, creating a site that could be considered as protected from heat, or heat privileged. One such site is the bone marrow, and another is subcutaneous tissue (Fig. 5). To have an optimal therapeutic effect in disseminated and malignant disease, all parts of the body must be heated to a uniform temperature. Once the body is uniformly heated, other problems arise. Tumors, as opposed to normal tissue, are mostly avascular up to a growth stage of 10^6 cells, where nutrients and oxygen are primarily supplied by diffusion. Further proliferation of the tumor is made possible by neovascularization originating in the host tissue, which becomes inadequate with increasing tumor growth. Consequently, the metabolism of the tumor tissue becomes inadequate; the result is an increase in hypoxia and tissue acidosis *(98)*. When heat is applied, tumor vasculature breaks down at about half the thermal dose that is

required for the disruption of normal vasculature *(99,100)*. Reduction in tissue blood flow limits the capacity of tissue to dissipate locally deposited heat and may permit selective tumor heating *(100)*. In addition, alteration in blood flow will adversely affect the tissue microenvironment *(81,101,102)*.

Vertrees and colleagues have designed a perfusion-based hyperthermia delivery system that has been shown to heat the body in a uniform manner *(44,63,66)*. In this system, heated blood is returned through a cannula that allows the blood to mix with the patient's blood return to the heart. This heated blood is perfused throughout the body by the cardiac output, which in hyperthermic patients is greatly increased. Interestingly, a patient enrolled in our phase I clinical trial presented with a suprasternal mass where tumor-temperature monitoring was possible. Zwischenberger et al., demonstrated that this mass received the highest thermal dose of any of the measured sites *(39,43)*.

Studies in mice show a response to hyperthermia as manifested by a decreased number of involved cancerous nodes and sites of metastasis. Studies in our recently developed mouse model reveal that heating human lung cancer cells before implantation rendered them incapable of forming tumors, probably because of sublethal damage *(103)*. Despite these significant effects, the response to heat of the cancer cell in tumors varies from survival to death—possibly affected by additional factors not yet elucidated.

3. PART II

3.1. Mechanisms of Hyperthermia-Induced Cancer Cell Death

By the early 1980s, basic science research had begun to elucidate mechanisms of hyperthermia-induced cell death. Cavaliere et al., *(104)* had confirmed the tumoricidal effects of heat through biochemical studies, Dickson et al., *(92)* had extrapolated the first thermal-dose time curves for heat killing, Giovanella *(105)* had demonstrated tumor cell thermosensitivity, and Dewey et al., *(106)* reported that heat prevented repair of radiation injury. In the 1980s and 1990s, relevant observations showed that in cancer cells, heat (1) selectively kills cells exponentially as a function of thermal dose (duration of exposure X degree of temperature elevation), (2) selectively kills S phase and other radio-resistant cells, and (3) partially inhibits DNA repair mechanisms *(107)*.

Cancer is a disease process where a genetic alteration has occurred within the cell that results in the cell being no longer under control of the host. Although many genes have been identified as contributing to cancer, three major groups encompass most of these genes: growth-promoting protooncogenes, growth-inhibiting cancer suppressor genes (antioncogenes), and anti-apoptotic (host-regulated cell elimination) genes. Each of these classes facilitates cancer development in different ways. Protooncogenes, when expressed, result

in the formation of cancer cells. Antioncogenes, when expressed, do not allow cancer cells to develop; however, once this type of gene is mutated, cancer cells may form without control. Proapoptotic genes will eliminate cells where an abnormality occurs; when these genes are mutated, cancer cells, once formed, are not eliminated. The result of each of these mutations is a malignant cell and cancer.

Many oncogenes will form cancer in various tissues. For instance, mutation of the oncogene *ras* in lung cells will lead to lung cancer, in colon cells will lead to colon cancer, and in pancreatic cells will lead to pancreatic cancer. The following discussion is limited only to the *ras* gene. Other genes act through other mechanisms, and space does not permit an exhaustive discussion. There is some evidence that heat has deleterious effects on malignant phenotypes *(108–110)*. Ras is a 21-kD GTPase that functions as a molecular switch, transducing signals from the plasma membrane through protein pathways to the nucleus. To transform a cell to the malignant phenotype, *ras* is mutated to the constitutively active form. The dominant oncogene present in lung, colon, and pancreatic cancers is *ras*, which has been documented to induce thermosensitivity in lung cancer cells. To transform cells, *ras* may down-regulate heat shock genes, and, in addition, may negatively regulate certain transcription factors. Engelberg et al., *(108)* concluded that the attenuated induction of *hsp* genes in cells with defective *ras* expression can explain their heat-sensitive phenotype, and that *ras* controls transcription of the heat shock genes.

It is conceivable that HSPs could act in response to heat in some manner to regulate *ras*, and protect important cellular proteins in a cell that is normal. Studies have also shown that diverse apoptotic stimuli cause caspase-mediated cleavage of RasGAP early in apoptosis *(111)*. *ras* is known to be a regulator of two distinct pathways *(112)*: (1) mitogen-activated protein kinase (MAPK), which results in proliferation *(113)*, and (2) stress-activated protein kinase, which results in apoptosis *(114,115)*. Studies have revealed a relationship between *ras*-mediated signaling pathways and HSPs *(108)*. Mivechi and Giaccia *(116)* documented that MAPK acts as a negative regulator of HSPs, in that as the expression of MAPK increased, HSP expression decreased and cellular proliferation continued. Selective down-regulation of HSP70 induces cell death in lung cancer, but not in normal lung cells *(117)*. Deficiency in HSP70 results in activation of c-Jun N-terminal kinase, extracellular signal-regulated kinase, and caspase-3 in hyperosmolarity-induced apoptosis *(118)*. Vertrees et al., documented that the presence of oncogenic *ras* results in defective thermoprotection in lung cancer cells, which is a different response than that seen in normal lung cells, lending further credence to the idea of hyperthermia as a useful adjunct therapy in cancer patients *(78)*.

If, however, *ras* is defective (either absent or mutated), then the amount/type of the HSP may be inadequate, and the cell's proteins will not be protected

during heat shock. This is a phenomenon we observed in our culture studies *in vitro (78)*, and which also needs to be investigated in cancer cells *in vivo*. Recently, Shi et al., reported that hyperthermia enhances cytotoxic T-lymphocytes (CTLs) cross-priming by increased expression of HSP70 and increased transcription of several tumor antigen–associated antigens, including MAGE-B3, -B4, -A8, and -A10 *(119)*. Induction of CTL by cross-priming is a critical mechanism for inducing antitumor immunity in patients. This observation, taken together with the aforementioned data on the role of HSPs in tumor death, suggests that HSPs play multiple roles to kill tumors *in vivo*.

Apoptosis (cell suicide) is the result of death forces from within *(120)*, the stimulus for which can originate with either the intrinsic or extrinsic pathways *(121)*. The intrinsic pathway consists of intracellular proteins and can be stimulated by such proteins as *myc, ras*, etc. *(122–124)*. The extrinsic pathway consists of intracellular proteins stimulated by cell surface receptors, such as tumor necrosis factor α–related apoptosis-inducing ligand (TRAIL), tumor necrosis factor α (TNF-α), etc. *(125–129)*. Each of these pathways has its own effectors, which are caspase-8 and -9 for intrinsic and extrinsic pathways, respectively. These effectors then activate caspase-3, which is responsible for activation of the nuclear signal for apoptosis—poly ADP-ribose polymerase (PARP) *(130,131)*.

Many investigators have documented that hyperthermia, generally, within the therapeutic range induces apoptotic cell death *(132,133)*. Barry et al., *(134)* was able to document that DNA digestion resulting in apoptosis was induced within 30 min by hyperthermia *(135–137)*. Tomasovic et al., *(138)* conclude that both types of DNA fragmentation (regular and irregular) are operant in some cell lines exhibiting a cytotoxic response to heat treatments, and that increased fragmentation reflects the greatly enhanced cytotoxic interactions seen with treatments in those cells.

Additional research by our group helped to elucidate the relationship between hyperthermia and apoptosis. Data demonstrated that hyperthermia induces apoptosis in transformed cells, and that apoptosis is mediated by caspase-3 as a result of activation of cell-death membrane receptors of the TNF family *(139)*. In this study, we examined the protein expression of both intrinsic and extrinsic stimuli; apoptosis effectors 3, 8, and 9; nuclear signal PARP; and early, middle, and late morphological features associated with apoptosis. Results show that after hyperthermia, only in cancerous cells as opposed to immortalized cells (lung), was there an increase in the expression of TRAIL, cleaved caspase-9, cleaved caspase-3, and degraded PARP. An Annexin-V (which translocates to outer leaflet in early apoptosis) stain that is positive, the presence of condensed chromatin, exposed 3′ OH ends of DNA, and DNA laddering are all hallmarks of apoptosis *(139)*.

4. PART III

4.1. Hyperthermia and Chemotherapy

In recent years, the understanding of the biology of cancer has dramatically increased, leading to renewed interest in developing screening and early detection methods as well as providing new therapeutic targets. In parallel, the discovery of several new chemotherapeutic agents with novel mechanisms of action and promising activity against various types of cancers have renewed interest in combined therapies. Many would argue that chemotherapy for advanced metastatic disease should not be offered because of the relative ineffectiveness of even the best regimens. However, this leaves a large number of patients with only supportive therapy for their disease—an unacceptable situation.

The combination of two therapies into one therapy, such as the combination of hyperthermic treatment with standard chemotherapeutics, can produce a wide spectrum of results, ranging from enhanced cell kill to stimulated cellular growth. Combination therapies can result in subtractive, zero, individual, additive, and synergistic effects. When the therapies are administered simultaneously, the possibility exists for immediate interactions that can render both interventions worthless (zero effect). For example, it is conceivable that a drug can stimulate sufficient HSP up-regulation that all cells will become refractory to the coincident heat therapy, resulting in a very limited cell death (subtractive). On the other hand, heat could possibly alter the structure of a drug, making it nontoxic. The sequential application of therapies will decrease the likelihood of unacceptable interactions; however, interactions are still possible. Should a drug therapy follow hyperthermia, it is possible that the induced inherent thermoprotection will shield the cell from the effects of the pharmaceutical and vice versa. However, it is also conceivable that in this mode cell death could be present from both interventions (individual). The most salubrious effect is that of synergism. This would occur when both therapies resulted in a cell kill that exceeds the sum of both individual therapies. An example would be if a drug synchronizes all cells of a tumor to enter a specific phase of the cell cycle then a subsequent therapy is timed to destroy all cells in that phase of the cell cycle. Such an interaction is very desirable in its effect on tumor cells. However, if this circumstance occurs it is quite possible that an increased amount of damage will also occur to normal host cells as well—an undesirable situation.

Historically, hyperthermia was administered with a few select drugs where efficiency was studied. In an interesting study treating dogs with spontaneous malignant melanoma, Page et al., concluded that melphalan combined with whole-body hyperthermia can be safely administered, although a reduction in

dose is necessary *(51)*. In a corollary to these results, Orlandi et al., determined that thermal enhancement of melphalan cytotoxicity could be mediated at least in part by an inhibition of p34cdc2 kinase activity, which prevents cell progression into mitosis *(140)*.

Furthermore, it has been shown that greater tumor cell killing, tumor growth delay, and prolonged survival are produced by a combination of radiation, thermosensitive liposome-entrapped melphalan, and hyperthermia compared with animals receiving single-modality or bimodality treatments. Chelvi and Ralhan concluded that this multimodality approach will be potentially useful for more effective management of melanoma *(141)*. Averill et al., showed that increased melphalan cytotoxicity in multidrug-resistant (MDR) cells was accompanied by changes in membrane permeability to the drug *(142)*. Cyclosporine A caused an increase in melphalan uptake in MDR cells and a decrease in melphalan efflux out of cells leading to an overall increase in intracellular drug accumulation, and that hyperthermia caused marked enhancement of melphalan cytotoxicity when cyclosporine A was present. Larrivee and Averill determined that heat alone increased both melphalan uptake and drug efflux in cells and suggested that the combination of cyclosporine A and hyperthermia could be very useful in overcoming melphalan resistance by increasing intracellular drug accumulation in MDR cells *(143)*. Turcotte and Averill-Bates discovered that a major advantage arising from the use of regional hyperthermia is the ability to target drug cytotoxicity to the tumor volume *(144)*. A useful finding is that ethacrynic acid, heat, and/or melphalan are also effective against MDR cells with overexpression of P-glycoprotein. Together, these aforementioned studies demonstrate that there is potentially great therapeutic benefit combining heat therapy with chemotherapeutics.

In clinical studies of melphalan and hyperthermia, we see varied responses. Robins et al., found that melphalan was well tolerated at 41.8°C, and that clinical results were consistent with preclinical predictions providing a foundation for further trials *(145)*. Hafstrom and Naredi reported rather disappointing results with the combination treatment, where 2 patients died within the first postoperative month, 5 patients were reoperated on owing to postoperative bleeding, and 3 of 6 patients with liver metastases from malignant melanoma or leiomyosarcoma, and none of 5 patients with liver metastases from colorectal cancer, showed a partial response *(146)*. In the Robins et al., follow-up study, combining TNF-α, melphalan, and whole-body hyperthermia (41.8°C for 60 min), responses included two complete remissions (malignant melanoma, TNF dose level I; breast cancer, TNF dose level II) and two disease stabilizations (both malignant melanoma, TNF dose level I) *(147)*. Hyperthermia affected the pharmacokinetics of intraperitoneal (IP) melphalan by decreasing the quantity of peritoneal fluid melphalan without increasing the plasma quantity, though it increased intraabdominal tissue concentrations *(148)*. Lindner et al.,

documented conflicting results when melphalan was used in conjunction with isolated hepatic perfusion and TNF-α, where they show considerable toxicity, and question the effectiveness in patients with colorectal liver metastasis *(149)*. Results in patients with melanoma and leiomyosarcoma were different and warrant further study. Libutti et al., treated these patients who had unresectable hepatic malignancies with a perfusion hyperthermia technique, TNF, and melphalan, with favorable results *(150)*. Pilati and colleagues show that under hyperthermic conditions, neither an increase in liver parenchyma toxicity nor changes in melphalan pharmacokinetics were observed, and suggested that these findings support the use of hyperthermia in the clinical environment *(151)*. Isolated limb perfusions with TNF-α and melphalan for recurrent melanomas resulted in a high complete response rate and a low limb-recurrence rate in patients at the cost of only mild toxicity *(152)*.

Another chemotherapeutic agent used in conjunction with hyperthermia for the treatment of cancers is mitomycin C. Mitomycin C exerts its mode of action as an alkalizing agent that, upon activation, binds to guanine and cytosine moieties of DNA, resulting in the inhibition of DNA synthesis. Herman et al., studied the combined effect of mitomycin C and hyperthermia and determined that a considerable potential therapeutic efficacy with the addition of hyperthermia to mitomycin C exists *(153)*. These results show that hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C is a safe and reliable treatment for peritoneal seedings in severely advanced gastrointestinal cancers and encourage us to proceed with this new therapeutic modality *(154)*. These outcomes indicate that the use of selected anticancer drugs with hyperthermia and radiation can produce highly cytotoxic interactions that markedly modify the effect of radiation *(155)*.

Sakaguchi et al., determined that the enhancement was prominent in cases of drugs and hyperthermia combined and speculated that hyperthermochemotherapy, using mitomycin C has a potential to attack selectively hypoxic cells present in a solid tumor *(156)*. Loggie et al., was an early proponent of HIPEC for advanced gastrointestinal and ovarian cancers *(26)*. In a laboratory study, Takeuchi et al., determined that increased antitumor response was achieved with the combination of mitomycin C, flavone acetic acid, and hyperthermia because of a decrease in blood flow to the tumor and subsequent hypoxic conditions *(157)*. Studying the combined effect on gastric cells, Shchepotin et al., determined that hyperthermia did not enhance the effect of mitomycin C and urged further investigation on gastric cancer *(158)*. In a clinical trial for peritoneal carcinomatosis, Gilly et al., determined that in 9 out of 10 patients with preoperative malignant ascites, it cleared after treatment *(159)*. One-year survival rate was 54.2%. They state that HIPEC with mitomycin C "is a safe and reliable treatment for peritoneal carcinomatosis in far advanced digestive cancers." Francois reported 42 cases of gastric cancer with peritoneal carcinosis

treated with HIPEC (10 mg/L mitomycin C at 46°C–49°C for 90 min) and suggests even in light of numerous complications that HIPEC with mitomycin C is a new treatment for carcinosis of gastric origin *(160)*. Paroni et al., demonstrated that local hyperthermia enhances the systemic absorption of mitomycin C during intravesical chemotherapy for bladder cancer *(161)*. For resectable gastric cancers with stage 1 and 2 carcinomatosis, 1-, 2-, and 3-yr actuarial survival rates were 80%, 61%, and 41%, respectively, and Sayag-Beaujard et al., concluded that HIPEC appears to be an interesting therapeutic option in patients with digestive cancers and small malignant peritoneal granulations *(162)*.

The latest generation of antineoplastic agents has produced significant advances in both understanding and survival from cancer and needs to be studied in relation to hyperthermia. Recent studies suggest that, irrespective of the primary site of action of a drug, cell death by most pharmacologic agents is mediated by activation of the signal transduction pathway for apoptosis. A study by Barry et al., emphasizes this point *(134)*. Their results suggest two signal pathways for apoptosis, one directly associated with drug action and a second that requires cell cycle–related events.

Gemcitabine (dFdC) is a deoxycytidine nucleoside analogue that has a marked effect on several enzymes involved in DNA synthesis and repair *(163)*. It requires intracellular activation by phosphorylation into its active triphosphate dFdCTP form, which is incorporated into DNA at the penultimate position and blocks further elongation of the DNA strand *(164)*. This drug inhibits cellular proliferation in S phase, which causes cells to accumulate at the G_1–S-phase boundary *(165)*. Gemcitabine can also be incorporated in RNA-inducing apoptosis *(166)*. This drug is active against human tumor xenograft models of lung, breast, and colon carcinoma *(167)*. Again, the combination should show at least an additive effect because gemcitabine halts cells in the S phase of the cell cycle, which is the most receptive phase for heat kill.

Latz et al., demonstrated that treatment of cells with gemcitabine immediately before irradiation eliminates, or at least greatly reduces, the variation in radioresistance during S phase *(168)*. This reversal of S-phase radioresistance could imply that gemcitabine interferes with the potentially lethal damage repair–fixation pathway, setting the stage for additional kill by another agent. They suggest that hyperthermia or densely ionizing radiation in combination with gemcitabine could prove of value in this situation.

Several investigators have coupled hyperthermia with gemcitabine in both lab and clinical studies with varied results. Haveman et al., showed that simultaneous application led to decreased cytotoxicity, whereas an interval of 20 h or 24 h between exposure to dFdCyd and hyperthermia led to enhanced cell killing *(169)*. Mohamed et al., showed that moderate hyperthermia (41.5°C for 30 min) increases the cytotoxicity of gemcitabine on mouse fibrosarcoma *(27)*.

van der Heijden et al., showed a synergistic interaction for hyperthermia and gemcitabine on human transitional cell carcinoma cell lines *(170)*. Hyperthermia alone did not cause decreased cell proliferation. Synergism was most prominent with low drug doses. In a clinical case report, 2-yr follow-up of a patient that received IP perfusion (saline heated to 42°C containing cisplatin, etoposide, and mitomycin C, followed by 24 courses of postoperative chemotherapy with gemcitabine) for pseudomyxoma peritonei to be in good condition with no signs of progression *(171)*. In a recent study, we report that the combined therapy is synergistic in effect because of hyperthermia-enhancing gemcitabine-induced apoptosis *(172)*. We support this conclusion by documenting that the cancer cell line had significantly more Hoechst-positive (apoptotic) cells, and that TUNEL, DNA fragmentation, and Annexin-V all corroborate the presence of apoptosis. Western blot comparing the effect of hyperthermia in cancer cells to normal cells revealed that TRAIL and FAS-L displayed significant increases (threefold and twofold, respectively); that caspase-3 showed a decrease in uncleaved form and an increase in cleaved form, and a 50-fold increase in activity effectively blocked with the caspase-3 inhibitor DEVD-fmk; that caspase-9 showed near depletion of uncleaved form; and that PARP degradation was clearly visible during heating. After hyperthermia, gene expression demonstrates a 5.7-fold increase in TRAIL and insignificant changes in TNF-α, FAS-L, and caspase-3, -8, and -9 in transformed cells *(172)*. Additionally, Vertrees et al., demonstrated that the combination of hyperthermia and gemcitabine, when given in a series of experiments, delayed further tumor development as long as the dual therapy was administered; however, when the therapy was withdrawn, normal tumor development resumed *(172)*.

The mechanism of action of taxanes (paclitaxel or docetaxel) is promotion of microtubule assembly and stabilization resulting in interference with mitosis. This drug has displayed antitumor activity against nude mouse xenografts of melanoma, breast, colon, lung, pancreas, and ovarian cancer cells. Hyperthermia should theoretically increase the cell kill when used with the taxanes because the cell after taxane exposure would be held in S phase, making it susceptible to heat-induced destruction. However, studies where paclitaxel and hyperthermia (41.8°C for 60 min) were administered together showed no thermal enhancement of cytotoxicity in human and murine cell lines. The authors did show that paclitaxel and docetaxel were heat stable at 41.8°C and 43°C *(173)*. Cividalli and colleagues demonstrate that hyperthermia had a superadditive effect on paclitaxel (45 mg/kg) combined with a hyperthermic treatment (43°C for 60 min) *(174)*. An additional study of the taxanes showed that paclitaxel cytotoxicity was not enhanced by hyperthermia (41.5°C for 30 min), but that docetaxel cytotoxicity was *(27)*. By way of explaining a possible mechanism for the observed phenomenon, Salah-Eldin and colleagues show that both treatments disturbed the heterodimerization of Bax with Bcl-2

(175). Hyperthermia, but not paclitaxel treatment, induced a gradual Bax translocation from the cytoplasm to the nucleus. Although both treatments induced a prominent cell cycle disturbance in the G_2M phase, paclitaxel treatment induced typical apoptosis, and hyperthermia hardly induced apoptosis at all. Their results suggest that the subcellular redistribution of Bax and the phosphorylation of Bcl-2 depend on the type of apoptosis inducers, such as hyperthermia and paclitaxel. The report by Zoul et al., in 7 patients treated for inoperable local recurrence of breast cancer after mastectomy, irradiation, and chemotherapy or hormonal therapy indicates that the combination of weekly paclitaxel (60 mg/m^2–80 mg/m^2) in 3-h infusions and hyperthermia (41°C–44°C for 45 min for 6–18 cycles) may be effective in the treatment of locally recurrent breast cancer after mastectomy *(176)*.

Irinotecan is a topoisomerase I inhibitor with a broad spectrum of clinical activity. Mohamed et al., demonstrated that the combination of moderate hyperthermia (41.5°C for 30 min) and irinotecan against a spontaneous murine fibrosarcoma results in increased cytotoxicity *(27)*. Sumiyoshi et al., hypothesized that an antiangiogenesis strategy combining fever-range whole-body hyperthermia (FR-WBH) and irinotecan hydrochloride could inhibit the development of metastatic disease with minimal toxicity in rats *(42)*. They found that both the group treated with FR-WBH alone and the combined FR-WBH + irinotecan hydrochloride group had delayed onset and reduced incidence of axillary lymph node metastases, reduced lung metastases, and longer survival compared to control. Elias et al., studied 39 patients with peritoneal carcinomatosis of either gastrointestinal or peritoneal origin who underwent complete cytoreductive surgery (CRS), followed by HIPEC with a stable dose of oxaliplatin (460 mg/m^2), plus 1 of 7 escalating doses of irinotecan (from 300 mg/m^2 to 700 mg/m^2) *(177)*. HIPEC was carried out with the abdomen open, for 30 min at 43°C, with 2 L/m^2 of a 5% dextrose instillation in a closed continuous circuit. Irinotecan concentration in tumoral tissue increased until 400 mg/m^2 and then remained stable despite dose escalations. It was 16–23 times higher than in non-bathed tissues. Intraperitoneal heated oxaliplatin (460 mg/m^2) plus irinotecan (400 mg/m^2) presented an advantageous PK profile and was tolerated by patients, despite a high hematological toxicity rate. In another clinical study, 25 patients (10 women and 15 men; mean age, 53 yr) were identified who had progressive liver metastases by carcinoembryonic antigen, imaging studies, or both after irinotecan. A 1-h hyperthermic isolated hepatic fusion (IHP) (mean hepatic temperature, 40.0°C) with 1.5 mg/kg melphalan (mean total dose, 100 mg) was administered via laparotomy. Perfusion with an oxygenated extracorporeal circuit was established with inflow via a cannula in the gastroduodenal artery and common hepatic artery inflow occlusion. Outflow was via a cannula in an isolated segment of the inferior vena cava. During IHP, portal and inferior vena cava flow were shunted to the axillary vein. Patients were assessed for

radiographical response, recurrence pattern, and survival. The median number of liver metastases before IHP was 10 (range, 1–50), and the median percentage of hepatic replacement by tumor was 25%. There was one complete response and 14 partial responses in 25 patients (60%), with a median duration of 12 mo (range, 5–35 mo). Disease progressed systemically in 13 out of 25 patients at a median of 5 mo (range, 3–16 mo). The median overall survival was 12 mo (range, 1–47 mo), and the 2-yr survival was 28%. The authors concluded that in patients with progressive CRC liver metastases after irinotecan, IHP had good efficacy in terms of response rate and duration, and suggest continued evaluation of IHP with melphalan as second-line therapy in this clinical setting *(178)*.

Carboplatin produces interstrand DNA cross-links rather than DNA-protein crosslinks. This effect is cell cycle nonspecific. The addition of heat to this drug could potentially enhance the numbers of cells killed during the heat-sensitive S phase. This drug has shown antitumor activity against breast, colon, lung, pancreas, and ovarian cancer cells. Several studies have assessed the efficiency of hyperthermia and carboplatin in both the lab and clinical venues. Robins et al., concluded from a clinical study that carboplatin with WBH (41.8°C for 60 min) is well tolerated, even at conventional carboplatin doses, and that results are consistent with preclinical predictions of an increased therapeutic index for this combination *(179)*.

5. CONCLUSION

Despite the lack of significant improvement in reducing cancer mortality rates over the past half-century, advances in basic medical science have increased our abilities to understand the molecular pathogenesis of cancer. This knowledge, in concert with technological advances, has allowed clinicians a foothold from which to combat cancer. Basic science has given clinicians the molecular tools to yield further information on their patients' plight; we now have the ability to genotype certain neoplasias, and with this information tailor chemotherapeutic treatment regimens to yield the most beneficial outcome. The presence or absence of estrogen sensitivity in breast cancer specimens is one such example of how molecular tools are helping to direct chemotherapeutic treatments. Additionally, the usefulness of hyperthermia as a potential treatment modality for cancer has been suggested for over a century. The lack of understanding of the scientific basis for this treatment, as well as gaps in the technology with which to administer the "dose" has played a role in keeping this therapy from the mainstream. Basic science research, however, has recently helped to clarify the actions by which hyperthermia is beneficial in a clinical setting to treat tumors and metastases. It has been demonstrated that this therapy has a twofold benefit, through both the induction of apoptosis of neoplasias and

the potential augmentation of the immune response to cancer through cross-presentation of tumor antigens.

The therapeutic usefulness of hyperthermia and chemotherapeutics are beginning to become clear. However, many questions still remain; the answers will surely expand our ability to treat cancer. Basic science is poised to play a significant role in advancing our therapeutic options through the generation of newer treatments, as well as through the clarification of actions of current treatments.

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7 Hyperthermic Intraperitoneal Chemotherapy in Nongynecologic Cancers

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Summary

Cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) has had a significant impact in the management of peritoneal surface malignancies of nongynecologic origin. It has improved the quality and quantity of life for these patients. Evidence of improved median survival has been observed independent of the origin of the carcinomatosis, and this treatment paradigm resulted in measurable 5-yr survival in diseases where it did not exist before the use of CRS + HIPEC.

Key Words: Peritoneal carcinomatosis; MPM; malignant peritoneal mesothelioma; hyperthermic intraperitoneal chemotherapy; CRS; gastrointestinal.

1. INTRODUCTION

The purpose of this chapter is to provide data that has defined the indications for the use of CRS + HIPEC in the treatment of nongynecologic malignancies. The history and background for using CRS with HIPEC in the treatment of patients with gastrointestinal (GI) tumors with peritoneal dissemination, as well as the current indications for HIPEC, are reviewed.

2. BACKGROUND

Dr. Brian Loggie's interest in the treatment of patients who have GI cancers with peritoneal carcinomatosis (PC) and malignant peritoneal mesothelioma (MPM) began in 1993. These patients commonly presented with symptomatic complaints of early satiety, abdominal pain, weight loss, and shortness of breath. No accepted treatment paradigm existed for this disease manifestation, which continues to be graded as

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M1 or stage IV disease. At that time, the only active systemic chemotherapy was 5-fluorouracil (5-FU) augmented by leucovorin, which had a clinical response rate of approximately 20% and few complete responses (<5%). This poor clinical response rate was in contrast to the activity of the chemotherapeutic agents used to treat ovarian cancer. Our medical oncologists at that time agreed that they had little to offer their patients with PC/MPM and nothing with the reasonable or consistent likelihood of prolonged survival. The overall survival and quality of life (QoL) for these patients was poor. Patients with symptomatic bowel obstruction or ascites typically did not survive a year. Asymptomatic patients presenting early with low-volume PC were unlikely to survive 2 yr.

Not only was chemotherapy ineffective, but so was surgery. In symptomatic patients, palliative surgical efforts were associated with high perioperative morbidity and mortality with short median survival. For example, Blair reported 63 patients with PC from nongynecologic cancer that underwent palliative surgery *(1)*. The complication rate was 44%, postoperative mortality was 15%, and median survival was only 90 d. Chu reported that the median survival for patients undergoing surgery for PC of gastric, small bowel, pancreatic, and colorectal origins treated by surgery alone was 1 mo, 1 mo, 0.7 mo, and 6 mo, respectively *(2)*. The presence of ascites and a poor performance status were unsatisfactory prognostic indicators independent of the tumor type. Yazdi and co-workers reported a retrospective study in patients undergoing palliative surgery for advanced peritoneal disease with ascites *(3)*. They also found a high operative mortality (41%) and median survival of only 2–4 wk, which is worse than those reported by Blair. Unlike the other reports, this study also included patients with ovarian malignancies and concluded that nonovarian tumors and advanced age were associated with an increased risk of mortality.

It could be argued that these series represent outcomes that are unfairly biased by more advanced disease and an earlier "era" of patient cases. A prospective nonrandomized multi-institutional European study was conducted to help address these issues and was reported in 2000 *(4)*. A uniform postoperative staging system, which had been proposed by Dr. Gilly in Lyon, France, was used. Patients underwent conventional surgical therapy and received standard systemic chemotherapy. Tumor debulking was performed, but neither IP chemotherapy nor HIPEC were given. The striking result of this study was that even the patient subset with complete removal of all gross disease (stage 0) and, subsequently, treated with the best available systemic therapy had no long-term survivors. A median survival of only 10 months was reported for this "best" group.

3. RATIONALE FOR HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

The underlying rationale for CRS + HIPEC evolved out of clinical observation and the recognition of the peritoneal-plasma barrier. Because single modal-

ity or metachronous therapy had clearly failed in the past, CRS + HIPEC was conceived as a form of combined modality therapy. As the first component, CRS was preparatory to and necessary for the second component, HIPEC, for several reasons. First, chemotherapeutic agents have limited penetration into tumor from the surface exposure. Lesions more than approximately 1 mm may not be infiltrated completely by local chemotherapeutic agents. Thus, it is clear why one of the most important conclusions in all contemporary studies on the application of CRS + HIPEC for tumors of GI origin is that the completeness of resection correlates significantly with overall survival. Second, surgery mobilizes all the adhesions, allowing exposure to recesses and pockets in the peritoneal cavity, which promotes more uniform drug distribution. Third, laparotomy (or laparoscopy) is the best staging method because computed tomography, magnetic resonance imaging, and positron emission tomography scans are often inaccurate in determining the extent of tumor involvement, and it is the key component of patient selection for CRS + HIPEC. Appropriate patient selection is equally important to good outcome of this technique (*see* Patient Selection).

The rationale for HIPEC was based on the perceived benefits described for IP therapy. These include high drug concentrations and limited systemic exposure. Our previous pharmacokinetic studies demonstrate that peritoneal concentrations of mitomycin C achieved during IPHC are approx 10 μg/mL, which is significantly greater than that obtained after systemic administration *(5)*. Hyperthermia was used as a synergistic agent to increase the intensity of therapy. Temperatures of 43°C–44°C alone can trigger apoptosis, whereas at higher temperatures of 45°C–47°C, necrosis predominates *(6)*. In vitro studies demonstrate that higher temperatures (43°C) increase the uptake of mitomycin C into tumor *(7)*. In addition, temperatures of 42.5°C can markedly increase the activity of DT-diaphorase, an enzyme that may activate mitomycin C intracellularly *(8)*. Hyperthermia increases local vascularity and may increase drug delivery. Cellular uptake and metabolism of drugs can be altered. Therefore, it is hoped that hyperthermia can augment the tumor-killing effects of IP chemotherapy perfusion, although this question has not been subjected to clinical trial.

The timing of HIPEC is also an important consideration for enhancing response. Tubes placed within the peritoneal cavity after surgical debulking are rapidly walled off by adhesions and prevent the complete bathing of peritoneal surfaces, causing nonuniform drug distribution. It has been reported that the catheter-associated complication at postoperative IP therapy significantly limited the completion rate in ovarian cancer patients *(9)*. Moreover, these tumors can sometimes regrow rapidly in the postoperative period. It would seem logical to introduce the IP chemotherapy as soon as possible. We perform HIPEC in the operating room immediately after tumor debulking, which is when tumor burden is at its lowest. Early dividing cells that have been exposed

to the IP chemotherapy agent will hopefully progress to cell death, rather than having time to repair.

The peritoneal-plasma barrier limits systemic absorption of these agents, which can be given at high concentrations in the peritoneum space. Nonetheless, there remains systemic uptake of chemotherapeutic agents that can result in chemotherapy-related complications, such as bone marrow suppression. Increased systemic uptake is associated with increased severity of chemotherapy-related complications. However, patients with higher systemic drug exposure had statistically significant improvements in long-term survival *(5,10)*. This was not entirely expected, but suggests that the systemic uptake may be an important part of HIPEC treatment and deserves further investigation.

4. PATIENT SELECTION

There are few absolute guidelines for patient selection. Contemporary body imaging is often unreliable. Patients may be selected for CRS + HIPEC with the goal of long-term clinical remission or with the primary goal of symptomatic palliation. It may not be apparent which category the patient will fall into until the time of surgical exploration. Ideally, an obvious but quite challenging goal is to avoid offering CRS + HIPEC to patients who would not benefit from it. Some guidelines will be discussed in the following paragraphs.

First, and the most important goal for selection, is that patients be able to successfully undergo complete removal of all visible disease. The following recommendations are based on our experience. Patients should have a good performance status (Eastern Cooperative Oncology Group 2 or greater) and no major co-morbidity precluding a major operative procedure. Major GI symptoms related to obstruction or ascites will often diminish PS and typically mitigate against complete CRS. We, and others, have noted that extensive involvement of small bowel surfaces or small bowel mesentery prohibited successful CRS. Thus, on scanning, there should be no evidence of gross, widespread disease in the mesentery or multiple sites of bowel obstruction. There should be no evidence of extraabdominal metastatic disease. We exclude patients with parenchymal metastatic liver disease (not surface metastatic disease). There will be a better chance for complete cytoreduction for patients with the following traits:

- Absence of a palpable fixed pelvic tumor shelf.
- Absence of biliary or ureteral obstruction.
- Absence of bulky disease in the gastrohepatic ligament, porta hepatis, and lesser sac areas.

In some circumstances, bulky disease alone does not prevent complete CRS. Conversely, some malignancies such as poorly differentiated (i.e. signet cell)

adenocarcinomas may be widespread and unresectable without much evidence of bulk disease. Sound clinical judgment is required. Findings at exploratory laparotomy typically reveal more disease than is depicted on scans, and will require intraoperative decisions about the extent, manner, or feasibility of surgical resections.

5. PALLIATIVE THERAPY

Patients undergoing incomplete CRS may benefit from HIPEC to treat or prevent MPM. HIPEC is typically not offered if it is anticipated that widespread bulky residual disease will remain after CRS. HIPEC can be a palliative option for patients with MPM. Associated mechanical GI obstruction is considered a contraindication when there is extensive mesenteric involvement or multiple areas of obstruction. High volume ascites creating early satiety and vomiting related to abdominal distention and pressure can be confused with obstruction, but these symptoms are relieved with paracentesis in patients with "pseudo-obstruction."

6. TECHNIQUES FOR CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Careful preoperative planning is needed to confirm relatively normal organ function and minimize operative risks *(10)*. If extensive pelvic dissection is anticipated, cystoscopy and temporary bilateral ureteral catheters will be placed immediately before laparotomy. This speeds up surgery by decreasing the need for mobilization, and also decreases possible tumor seeding and injury to ureters and facilitates bladder resection or repair. CRS requires mobilization and visualization of every abdominal organ. The liver is completely mobilized. This includes resection of the falciform ligament and median suspensory ligaments (often involved with tumor) and division of the right and left triangular ligaments. This is required to provide adequate exposure to the diaphragms (which are often involved with disease) and to permit free circulation of the perfusion fluid. All abdominopelvic recesses are explored and exposed for chemotherapy. This includes full mobilization of the stomach and resection or opening of the gastrohepatic ligament (with sparing of the vagus) to expose the lesser sac. Morrison's pouch and recesses in the porta hepatis are inspected and exposed. The bilateral abdominal gutters and pelvic recesses are inspected and exposed. The large and small bowel are mobilized and run completely with exposure of mesenteric surfaces.

Cytoreduction techniques include the use of the argon beam coagulator at high wattage (150 W), which can be used to ablate large numbers of tiny implants on the parietal peritoneum, mesentery, and liver surface. The Cavitron

ultrasonic surgical aspirator can be used to debulk tumor implants with high water content, such as mucinous implants in pseudomyxoma peritonei (PMP) or papillary epithelial mesothelioma implants. Peritonectomy procedures are especially useful for diseases involving diaphragms and pelvis. Diaphragmatic disease may require en bloc removal by stripping the peritoneum away (peritonectomy) and may also occasionally require partial full-thickness resection and primary repair of the diaphragm. Bulky invasive tumor in any of the sites mentioned, but especially at the base of the mesentery, presents a challenge that may prohibit successful cytoreduction. Stapling techniques for bowel anastomosis reduce the surgical time and have been reliably used in these operations. This includes EEA stapling for low colorectal anastomoses. We have seen no obvious increase in postoperative fistulae with HIPEC.

Both open and closed methods have been described for HIPEC (*see* Chapter 11). We do not use the open technique because of safety concerns. Our closed methods will be briefly described here. Swan-Ganz monitoring was done for pilot trials, but is never used now. In general, aggressive temperature control is not needed because mild-to-moderate temperatures are used for inflow. Patients are not cooled during the CRS. Passive measures are implemented during HIPEC, which include not warming airway gases and intravenous solutions. During the perfusion, some active cooling measures can include using room temperature air in the patient's air warming system. Circulating-water cooling blankets are not used. We have never had to stop a perfusion for systemic temperature increases, even with inflow temperatures of 42°C. An increase of core temperatures to fever ranges is seen and rapidly reverses after HIPEC. A temperature of 38.5°C is typical. Peritoneal perfusion catheters are placed in the abdomen after CRS. Two inflow catheters (22-F) are directed beneath the respective hemidiaphragms and outflow catheters (32-F) are directed toward the pelvis. These catheters are connected to inflow and outflow tubing, respectively, with Y connectors. The tubes are brought out through the midline incision. Temperature probes are placed on the inflow and outflow catheters. The abdominal skin incision is closed temporarily with a running suture to prevent leakage. A perfusion circuit is then established through a filter, a roller pump, and heat exchanger. For this purpose, we use a commercial device that is FDA-approved for abdominopelvic perfusion. This device permits use of continuous variable perfusion rates and perfusion temperatures. For GI malignancies, mitomycin C is the agent used at our center. Approx 3 L of Ringer's lactate is used as the perfusate and is circulated at 600–1,200 mL/min. With higher flow rates, higher outflow temperatures are obtained, but more heat is absorbed systemically. Once inflow temperature exceeds 38.5°C, 30 mg of mitomycin C is added to the perfusate. At 60 min, an additional 10 mg of mitomycin C is added to keep mitomycin concentrations elevated. The maximum inflow temperature that we use off-protocol is typically 40.5°C–41°C at inflow, which is mild

hyperthermia. The perfusion is run with this drug routinely for 120 min. The abdomen is gently massaged and shaken throughout the perfusion to improve drug distribution. After the perfusion, a washout with 2 L Ringer's lactate is done. When there are concerns about potential drug toxicity, such as in patients treated extensively with systemic chemotherapy, either the dose of mitomycin C is reduced (to 30 mg) and/or the perfusion time (to 60–90 min) is reduced. Currently, carboplatin perfusions are being investigated under protocol at our institution for patients with mesothelioma. This drug is dosed at 800 mg/m^2, which is added to 4 L of Ringer's lactate perfusate and circulated for a 90-min perfusion at 41°C–42°C. We have opted not to use inflow temperatures greater than 42°C off-protocol because of concerns for hyperthermia-related toxicity. The lower temperatures were used in our previous clinical trials with good clinical safety and good effect *(10)*. To our knowledge, different temperatures have not been assessed for long-term differences. In our view, temperatures >43°C are probably too toxic. Given the combination of surgery, chemotherapy, and heat, it is difficult to know which is responsible for some postoperative problems. It is our clinical impression that ileus after HIPEC is more likely than with surgery alone and that mitomycin is worse in this regard than carboplatin (unpublished data). We also recognize elevations of serum amylase and lipase in some patients who may or may not manifest symptoms of pancreatitis (unpublished data). These cases are treated with parenteral or enteral nutritional support until enzymes normalize. Falling white blood cell and absolute neutrophil counts in a worrisome context (such as extensively before chemotherapy) are treated with growth factor support. The perioperative use of autologous blood transfusions limits transfusion needs. Hepatic, pulmonary, renal function, and wound healing could also be affected by HIPEC *(11)*.

7. RESULTS FOR CYTOREDUCTIVE SURGERY + HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy has been proven effective for the treatment of PC from PMP, appendiceal, and colorectal sources. It has been used increasingly in the treatment for PC from gastric cancer, small bowel tumor, and mesothelioma with encouraging results. The largest amount of data on HIPEC has been in the management of PMP, a rare entity that typically arises from a low-grade mucinous tumor of the appendix that has different biology from other appendiceal or intestinal cancers. CRS + HIPEC is becoming a standard therapy in the management of this disease. Many studies have justified its use in carcinomatosis from colorectal cancer.

7.1. Appendiceal Cancer (Including Pseudomyxoma Peritonei)

Primary appendiceal cancer is rare, and is divided into several major categories, including carcinoid, mucinous neoplasms, and adenocarcinoma, as well as rarer types such as adenocarcinoid, goblet cell, and signet cell type. Altogether, they account for 0.5% of all GI malignancies *(12–14)*. The most common metastatic location for these tumors is to spread to the peritoneal cavity, causing PC. Historically, this was considered a fatal situation. The 5-yr survival rate before using CRS + HIPEC was dismal for all appendiceal patients with peritoneal metastasis, even with CS. Gough reported only 5% of patients surviving disease-free for longer than 5 yr after treatment by surgery alone *(15)*. Aggressive CRS and IP chemotherapy has significantly changed the dismal picture of PC from appendiceal cancer. In a series of phase II studies, appendiceal tumors with peritoneal seeding treated with CRS + HIPEC validated the theoretical benefit of this technique with an 85% long-term survival in selected patients *(16)*. This specific subset of patients has the best median and overall survival for PC arising from a GI disease site.

Adenocarcinoma of the appendix with PC is considered a high-grade lesion with extremely poor prognosis. Sugarbaker first reported the successful use of CRS and administered IP normothermic mitomycin C (day 1 postoperatively) and 5-FU (days 2–5 postoperatively) in appendiceal cancer *(17)*. These patients had a 3-yr survival rate of 38% and 35% in 31 patients with adenocarcinoma or cystadenocarcinoma, respectively. With the CRS + HIPEC technique described earlier in this chapter, Loggie reported a 3-yr survival of 52% from 22 cases with PC from appendiceal origin (excluding PMP patients) *(10)*.

The peritoneal spreading of mucinous tumor is called pseudomyoxme peritone (PMP). The primary tumor in the appendix can arise as a benign mucocele that eventually ruptures, or can be malignant, invading through the appendiceal wall. In both situations, mucus-producing adenomatous epithelial cells are disseminated throughout the abdomen and pelvis. This results in extensive accumulation of mucinous tumor at characteristic sites within the peritoneal cavity. PMP can arise from non-appendiceal sites, but this is rare, occurring in <1%–2% of the cases we have seen.

The experience with 385 PMP patients treated over a 15-yr time span with CRS and IP chemotherapy showed the survival of all patients was approximately 50% *(18)*. The completeness of cytoreduction, the histopathological characteristics, and the extent of previous surgical interventions were found to be related prognostic factors in a multivariate analysis. Patients with a complete cytoreduction and adenomucinosis by pathology had a 5-yr survival of 86%, whereas for patients with mucinous adenocarcinoma pathology the survival at 5 yr was 50%. Incomplete cytoreduction lead to a 5-yr survival of 20%. A recent series of 110 patients with peritoneal dissemination from appendiceal cancer

(mostly PMP) confirmed these results *(19)*. In that study, CRS + HIPEC was used as described earlier in this chapter, and survival was stratified by histological characters. Disseminated peritoneal adenomucinosis and intermediate tumors (peritoneal mucinous carcinomatosis I [PMCA-I]) were associated with a better 3-yr survival rate at 80%, whereas PMCA pathology resulted in only 35% 3-yr survival. As noted, the R0/R1 resection rate in this study was 44% in comparison to 65% achieved in the first study, which implies these patients had more advanced disease and therefore survival was lower. The inability to perform complete cytoreduction compromises overall survival in this disease.

Carcinoid tumor is the most common appendiceal tumor (about two thirds of all cases) with most being early lesions and incidental findings from appendectomy specimens. It is rare for these tumors to develop PC. In a report of 37 cases of PC caused by carcinoid tumors, the appendix was the primary site for 5 cases, whereas most cases were ileal in origin *(20)*. Overall, a 66% 5-yr survival was achieved if complete CRS followed by HIPEC was performed, and 41% 5-yr survival if incomplete CRS was done.

Adenocarcinoid, which is an aggressive intermediate between carcinoid and adenocarcinoma, is rare. In one report, 20% of adenocarcinoid caused PC *(21)*. Debulking alone may result in a small benefit for this tumor subtype. Butler reported a median survival of 7 mo in 4 patients after debulking without IP chemotherapy *(22)*. With CRS and IP chemotherapy, Mahteme reported much better median survival of 18.5 mo, with 5-yr survival rate of 25% in 22 cases *(23)*.

For signet cell adenocarcinomas of the appendix, we have used CRS + HIPEC in conjunction with systemic chemotherapy. Currently, we are using a variation of the FOLFOX regimen, but avoid the use of bevacizumab in the preoperative period. It is too early to comment on long-term survival for patients treated with this rare and aggressive tumor type.

Recently, more results are emerging from different groups that support the role of CRS combined with HIPEC in the management of PC *(24–28)*. These large bodies of phase II single-institution trials and level 2 data have all illustrated the benefit of CRS combined with HIPEC. Clearly, minimally invasive mucinous neoplasms treated with this modality experience a 20-yr survival approaching 70%, which is a significant improvement when compared to treatment before HIPEC. In the absence of a phase III study, this new combined treatment should be regarded as the standard of care for epithelial appendiceal neoplasms and PMP syndrome *(29)*.

7.2. Colorectal Cancer

PC is present in approx 5%–10% of patients with colorectal cancer at the time of first diagnosis and in approximately 25% of patients with recurrent disease *(26,30)*. This form of carcinomatosis is more common than PMP and

has long been considered a terminal condition with median survival ranging from 5 mo to 7 mo *(2,4,26)*. For many of these patients, the peritoneum is the only site of disease without hematogenous spread to other distant sites, and they succumb to intestinal obstruction or starvation. Because of these parallels in tumor behavior to PMP, there has been increased interest in using CRS + HIPEC strategies to treat selected patients with this disease.

Over the last decade, approximately 10 phase II trials and 1 phase III randomized trial were published that used combined CRS and perioperative IP chemotherapy for patients with PC from colorectal cancer *(10,31–35)*. These results showed improved median survival ranging from 15 mo to 39 mo compared with historical control of 3 mo to 7 mo. Importantly, a 20%–30% long-term survival rate (5 yr) was reported, which is quite similar to the survival for surgically treated liver metastasis from colorectal cancer. Dr. Zoetmulder's chapter on colorectal cancer (*see* Chapter 8) presents his randomized trial data on this topic. The surgical options in the management of peritoneal surface malignancies of colonic origin were reviewed and discussed by an international group of surgical oncologists experienced in CRS + HIPEC at the First International Symposium on Regional Cancer Therapies, which was held in Snowmass, Colorado in January 2006. A consensus statement was developed for the treatment of patients with colon cancer with peritoneal involvement, which was based on published phase II and phase III trials (*see* Fig. 1).

7.3. Gastric Cancer

PC is a common cause of death in patients with gastric carcinoma. Advanced disease is often present at the time the primary tumor is diagnosed. Peritoneal recurrence develops in nearly 50% of patients, even after curative gastrectomy is performed. The median survival in this patient population ranges from 2.2 mo to 8.8 mo, with a 5-yr survival of 0% *(37–39)*. Resection *(40,41)*, with or without systemic chemotherapy *(37,42)*, has been shown to yield poor outcomes for patients with advanced gastric cancer.

With encouragement from the results of PC of appendiceal and colorectal cancer, Hall *(43)* recently reported that 34 cases of PC caused by gastric carcinoma underwent gastric resection with CRS, followed by HIPEC with mitomycin C. An historical control group consisted of 40 contemporaneous patients who underwent radical gastrectomy without extended nodal resection (so-called D1 dissection). The median survival for patients undergoing CRS + HIPEC was 8 mo and showed no difference from the control group of 7.8 mo. However, the control group had much earlier stage disease. When examined for survival based on resection status, the CRS + HIPEC group compared to controls had longer median survival for the R0 resection group (microscopically negative margin) of 36 mo vs 23 mo. The median survival in the R1 resection group (macroscopically negative margin) was 11.2 mo vs 6.8 mo. However, for patients

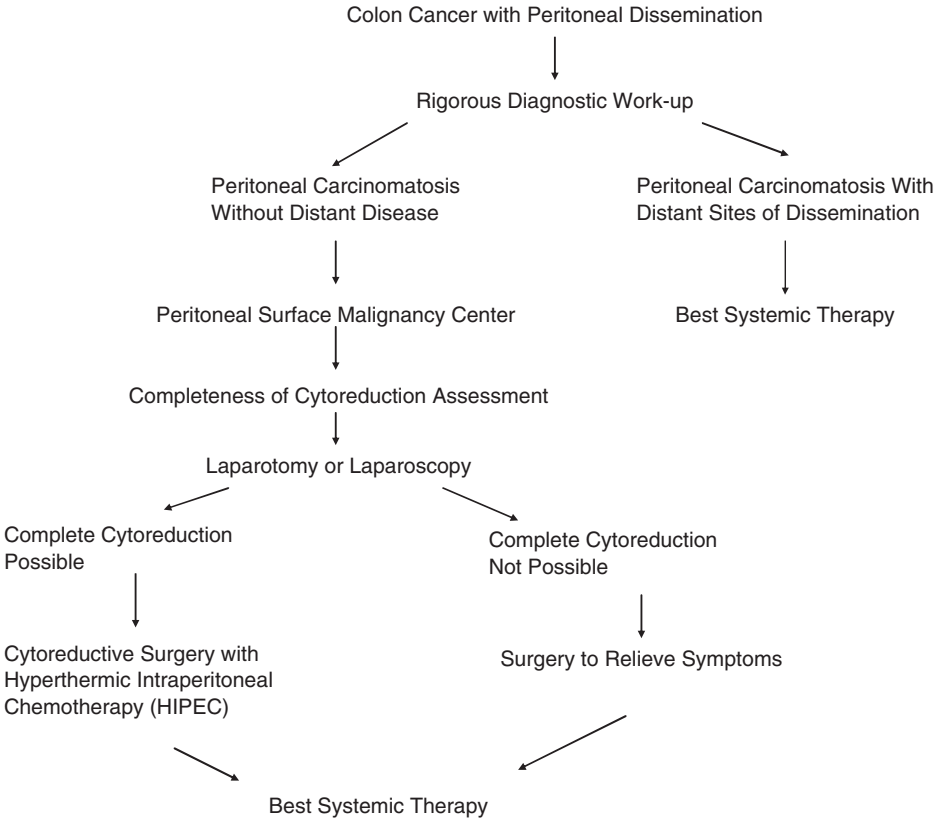

Fig. 1. Clinical pathway for the management of peritoneal surface malignancies of colonic origin: A Consensus Statement. *(36)*

with >2 cm gross disease, residual CRS + HIPEC did not confer any benefit, with median survivals of 3.3 mo vs 6.5 mo. The CRS + HIPEC group did have increased morbidity (35% vs 17.5%) caused by more extensive surgery (D2 resection) and toxic drug effects. It was concluded that careful patient selection for this procedure is paramount, and patients in whom an R0/R1 resection can be achieved are the best candidates. More studies are warranted.

Because the peritoneal cavity is a common site of disease recurrence in gastric cancer, the use of IP chemotherapy as an adjuvant therapy in the absence of gross carcinomatosis has been investigated. A favorable impact on survival has been demonstrated in patients with stage III gastric cancer. In a study by Yu *(39)*, the patients with stage III disease had 18% 5-yr survival with surgery alone vs 48% survival with gastrectomy plus early postoperative IP chemotherapy. More reports from Japan confirmed the advantage of adjuvant

treatment with perioperative IP chemotherapy in gastric cancer patients with potentially curative resection (negative margins of resection and an absence of disseminated disease) *(38)*.

7.4. Malignant Peritoneal Mesothelioma

Malignant peritoneal mesothelioma (MPM) is a rare disease. Like other peritoneal surface malignancies, it has been associated with a median survival of <1 yr *(44)*. Often, these patients present with intractable MPM unresponsive to systemic chemotherapy that rapidly becomes refractory to paracentesis. Unfortunately, these patients suffer from severe abdominal and respiratory symptoms that ultimately result in their death *(45,46)*.

The implementation of CRS + HIPEC in the management of MPM is yet another example of how this therapy has improved not only the QoL in these patients but also the overall survival in this rare peritoneal surface malignancy. Loggie *(45)* reported that 12 cases of MPM underwent CRS combined with HIPEC using mitomycin C. In this small series, 11 cases were male, and there were 11 cases with significant gross residual disease after resection (R2 resection). Despite this, a 34-mo median survival was achieved—a survival rate 3 times that of historical controls. Ascites were controlled in all patients, which significantly improved the QoL, even with positive residual disease left behind. Using cisplatin as the HIPEC agent and a single postoperative dose of 5-FU and paclitaxel, Alexander's group at the National Cancer Institute reported 17-mo progression-free median survival and 92-mo overall survival, with estimated 5-yr survival of 59% *(46)*. These encouraging results were further confirmed by other groups with significant long-term survival *(47–49)*.

It is very difficult to completely resect all gross disease in many patients with MPM. Some may benefit from second-look CRS and repeat HIPEC. The benefits of systemic therapy before and after CRS + HIPEC remain an open question. The current encouraging phase II clinical results have led many peritoneal surface malignancy groups to use CRS + HIPEC as a standard of care for MPM in the USA and abroad. The pursuit of better chemotherapeutic agents, biologic agents, or drug enhancers is worthy of further laboratory and clinical study *(50,51)*. Although prospective randomized trials of this approach are theoretically attractive, the rarity of MPM, which is truly an "orphan disease," makes accrual to appropriately powered trials unlikely *(45)*.

8. MORBIDITY AND MORTALITY AND QOL

Good long-term results can be achieved in selected patients with PC by a combination of CRS + HIPEC. These operations can require major surgical resections and extensive dissection of vital structures. Therefore, in patients with extensive disease, but considered resectable, these operations can take many

hours, and have the inherent risk for significant blood loss, fluid shifts, and time-related complications. Morbidity rates as high as 54%, and surgical mortality rates as high as 9% have been reported with aggressive CRS. *(28,31,33,35,52–55)*. The morbidity and mortality events in these cases are a direct reflection of the extent of surgery required to achieve complete cytoreduction in these patients, but the hyperthermia and chemotherapeutic agents can exacerbate these events. Because the completeness of cytoreduction has proven to be the most critical component in achieving long-term disease remission, and also is the major determinant in postsurgical complications, balancing this variable for these patients is the most challenging aspect of their management *(56,57)*. The judicious use of growth factor agents that stimulate red and white cell populations can reduce transfusion requirements and prevent grade 3–4 neutropenia.

In appropriately selected patients, a reasonable morbidity and mortality can be achieved with good long-term outcome and QoL. McQuellon first studied the issue of QoL in this particular population of patients using the Functional Assessment of Cancer Therapy-Colon (FACT-C) scale *(58)*. Initially, the overall QoL decreased significantly from baseline to the postsurgery period, but rebounded to greater than baseline at 3 mo and improved over a year. For patients with ascites, their QoL increased immediately postoperatively and improved continuously at 3 mo and 6 mo. They did report considerable distress in the form of depressive symptoms preoperatively. This decreased over the course of time, reflecting that the patients who were treated successfully gained a new sense of hope and experienced fewer physical symptoms. In a follow-up study on long-term survivors by the same group, good QoL was reported in 17 patients who survived from 3 yr to 8 yr after CRS + HIPEC. The majority of patients (62.5%) described their health as excellent or very good, and no limitations on moderate activity were reported in 94% of cases *(59)*.

9. CONCLUSION

Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy has had a significant impact in the management of peritoneal surface malignancies of non-gynecological origin. It has dramatically improved the quality and quantity of life for these patients. Evidence of improved median survival has been observed independent of the origin of the carcinomatosis, and this treatment paradigm resulted in measurable 5-year survival in diseases where it did not exist prior to the use of CRS + HIPEC.

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8 Peritoneal Carcinomatosis of Colorectal Origin

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Key Words: Peritoneal carcinomatosis; colorectal cancer; cytoreductive surgery; HIPEC

1. PERITONEAL CARCINOMATOSIS OF COLORECTAL CANCER

Second to liver, the peritoneum is the most frequent site of metastases in colorectal cancer. In approximately 10% of patients, peritoneal carcinomatosis (PC) is already present at the time of initial diagnosis *(1)*. PC is found in 30% of patients with recurrent colorectal cancer, either as part of more generalized metastases or as the only site. PC is the only site of tumor activity in 40% of cases *(2)*. This means that approximately 8% of all colorectal cancer patients will have PC as their only site of cancer activity at some stage of their disease. PC is generally considered to represent distant metastasis and is staged as M1. Accordingly, until recently, treatment has been limited to palliative surgery, such as enterostomy or bypass to relieve obstruction, and systemic chemotherapy. There are few studies specifically reporting on the outcome of this approach in PC *(3)*. Most studies on chemotherapy in metastatic colorectal cancer include all sites of metastases, with a dominance of liver metastases. Although some reports suggest that colorectal cancers recurring as PC are less likely to respond to systemic chemotherapy, there is little evidence for this. However, there is no doubt that PC patients have a shorter life expectancy than do patients with other metastatic sites, such as liver. This is probably explained by the difficulty in visualizing PC on scans, leading to relatively late diagnosis and the early development of bowel obstruction, even on relatively small tumor volumes. In our series at the Netherlands Cancer Institute, the diagnosis of PC in recurrent cases was made in 80% of patients during laparotomy for bowel obstruction. As a result, many patients will have either a (high output) ileostomy or a relative

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obstruction, making optimal chemotherapeutic treatment more difficult. In this circumstance, median survival is reported to be between 4 mo and 12 mo *(4)*.

2. CURATIVE TREATMENT OF PC OF COLORECTAL ORIGIN

Paul Sugarbaker has greatly contributed to a better understanding of the fact that PC is regional tumor spread, comparable to lymph node metastases and limited liver metastasis. He has pioneered a curative approach based on complete surgical removal of all peritoneal tumor, combined with hyperthermic intraperitoneal chemotherapy (HIPEC) *(5–8)*.

3. COMPLETE CYTOREDUCTION

The aim of cytoreduction is to leave no macroscopic tumor residue behind. Because peritoneal metastases of colorectal cancer usually present as true surface tumors, with little in-depth infiltration, it is often surprisingly easy to remove peritoneal seedings by lifting the peritoneum off the subperitoneal loose connective tissue layer. This approach to peritonectomies is very effective in the removal of PC localized on the parietal peritoneum of the abdominal wall, the small pelvis and bladder, and the peritoneal covering of the diaphragm, which is located above the liver and the spleen. Involvement of the visceral peritoneum on stomach, small bowel, and colon presents more difficulties. Resection of the affected bowel sections is usually the only solution. Extensive involvement of the small bowel and its mesentery makes patients inoperable. Also, extensive involvement of the hepatic hilum and the omental bursa presents technical problems. Because this type of surgery causes very large wound surfaces, meticulous hemostasis is essential. This means extensive use of electrosurgery.

4. HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Even the most extensive surgery for PC does not succeed in removal of every cancer cell. Microscopic foci will always remain. It is also important to realize that during surgery in PC a large number of free cancer cells are present, and they find an easy seeding bed in all the fresh wound surfaces. Additional treatment is needed to prevent early recurrence from these residual tumor cells *(9)*.

During HIPEC, the abdomen is used as a basin, perfused with a drug containing solution, at a chosen temperature, in our case usually between 40°C and 41°C (Fig. 1). Because the perfusion is performed during the same operative session as the cytoreduction, there is no problem of adhesions, and full exposure of the risk-bearing surfaces can be guaranteed. Some centers use an open perfusion technique, which allows the surgeon to manipulate bowel during the perfusion and correct any unequal distribution *(10)*. Others close the abdominal skin and manipulate the abdomen from the outside during the perfusion to achieve

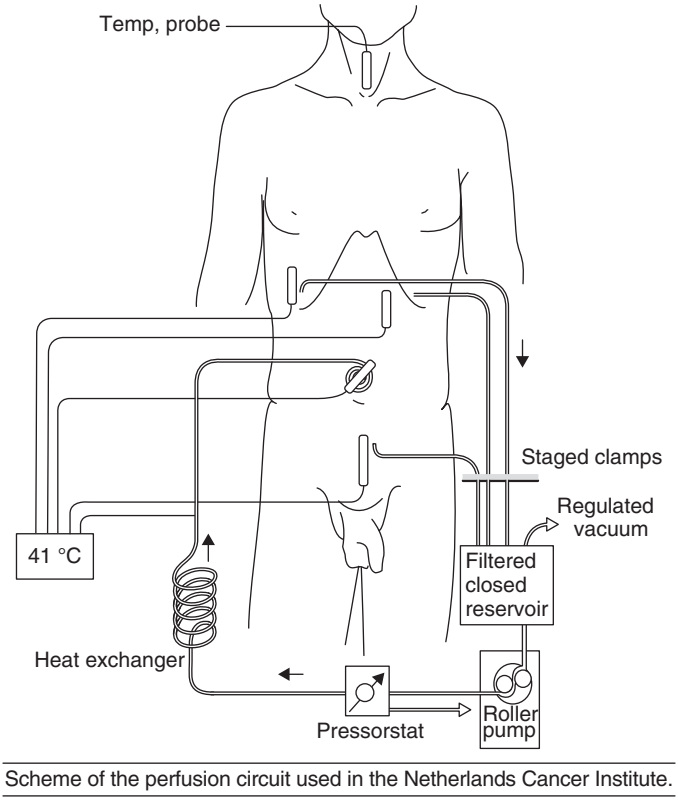

Fig. 1. Scheme of HIPEC of the abdominal cavity.

equal distribution—the so-called "shake and bake" technique *(11)*. There is no evidence that either technique is superior.

The advantage of HIPEC is that it brings cytotoxic drugs in direct contact with the tumor cells on the surface of the peritoneum, with only limited drug movement toward the systemic compartment. Because of this, the IP time-dose exposure (area under the curve [AUC]) can be very high, whereas exposure of sensitive organs like the bone marrow is limited *(12)*. An additional advantage is the possibility to manipulate temperature. Many cytotoxic drugs show an increased cytotoxic activity at higher temperatures. For mitomycin C (MMC), this effect starts at 39°C and appears to be optimal between 40°C and 41°C. At temperatures exceeding 42°C, normal tissue toxicity, especially of small bowel, becomes a problem. The temperature gradient from the surface is steep, adding to the selective action of HIPEC, saving the deeper layers from toxicity *(13)*.

Most HIPEC work in PC of colorectal origin has been done with MMC because it is active against colorectal cancer, both in cell lines and in systemic treatment in patients. There is a strong dose–response relation in cell lines.

Mitomycin C has direct cytotoxic activity, which makes it suitable for treatment of limited duration. Cytotoxic effect increases with temperatures over 39°C. In a dose-finding study, the maximal tolerated dose was established at 40 mg/m^2, at a temperature of 40°C–41°C and a duration of 90 min *(14)*. At the NKI we use a dose of 35 mg/m^2, with half of that dose being given at the start, followed by a quarter dose after 30 min and again after 60 min. Pharmacokinetic studies show that 80% of the drug is absorbed. The AUC in the perfusate is 12–20 times that in plasma. Many groups use considerably lower doses of MMC. The main toxicity of IP MMC is mild leukocytopenia with nadir 10 d after HIPEC.

More recently, Elias has published encouraging results using HIPEC oxaliplatin concurrent with intravenous 5 fluorouracil (5-FU) and leucovorin, hoping to utilize the synergistic activity of these drugs *(15,16)*.

5. SYSTEMIC CHEMOTHERAPY

Systemic chemotherapy has improved during recent years *(17,18)*. The addition of oxaliplatin or irinotecan to 5-FU and leucovorin has increased the response rate and the median survival in metastatic colorectal cancer. The addition of angiogenesis and epidermal growth factor receptor blockers further improves the effect, and median survival in the region of 24 mo has been reported. For reasons previously mentioned, survival in PC patients is probably somewhat shorter. In colorectal cancer, the cancer volume treated by chemotherapy strongly influences the long-term outcome. In the adjuvant setting in Dukes C colon cancer, when only very small amounts of residual cancer have to be treated, even simple regimens such as 5-FU/leucovorin can cure one third of patients. The same schedule never cures any patients with macroscopic disease. This provides the rationale for reduction of tumor load in PC patients by CRS and HIPEC, followed by systemic chemotherapy for the minimal residue. In most studies on HIPEC during the 1990s, 5-FU/leucovorin was used. Today, capecitabine combined with oxaliplatin for 6 mo is commonly used. Whether the sequence of treatment could also be reversed, treating with systemic chemotherapy first and reserving the cytoreduction/HIPEC therapy until the maximum response, is open to further study. However, it seems clear that the common practice of treating first with systemic chemotherapy and only referring patients for HIPEC once they have recurred denies patients the curative opportunities of well-planned combination therapy. In a multicenter series, Glehen found that previous systemic chemotherapy was a poor prognostic feature in PC patients being treated with HIPEC *(19)*.

6. STAGING AND SELECTION OF PATIENTS

Cytoreduction and HIPEC is a regional therapy. There is a consensus that it should, in general, be restricted to patients who have only cancer in the

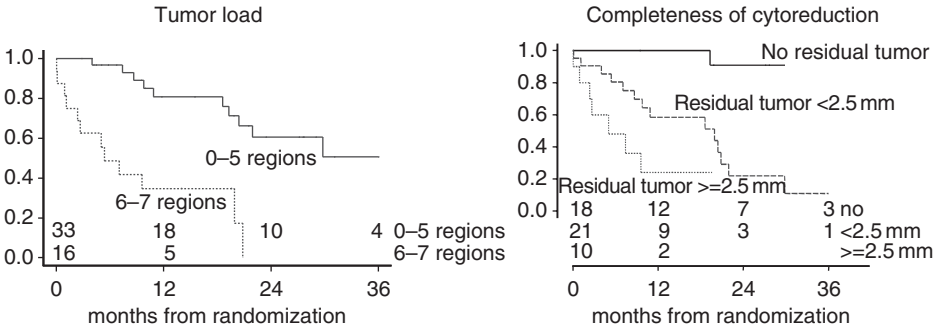

Fig. 2. Impact of extent of PC and completeness of cytoreduction on survival. (Verwaal et al., 2003, with permission).

peritoneal cavity, excluding patients with liver and lung metastases, although some long-term survivors have been reported after HIPEC and resection of limited liver metastases *(20)*.

All studies on CRS and HIPEC for PC of colorectal origin show that prognosis is strongly related to the extent of PC and to the completeness of the cytoreduction (Fig. 2). To categorize the extent of PC, several systems are in use. Gilly published a simple 4-stage system: localized-low volume, localized-high volume, generalized-low volume, and generalized-high volume *(21)*. Sugarbaker proposes a rather complex Peritoneal Cancer Index (PCI), in which the abdomen is divided into 13 regions, in which the presence of PC is registered as: 0 = none, 1 = <1 cm, 2 = 1–5 cm, and 3 = >5 cm *(22)*. This results in a PCI between 1 and 39. At the Netherlands Cancer Institute, we use a simplified PCI (SPCI), dividing the abdomen into 7 anatomical regions:

1. pelvis/sigmoid
2. ileocecal
3. small bowel
4. omentum/transverse colon
5. perigastric/subhepatic
6. right diaphragm
7. left diaphragm/spleen

Again, registering the size of the PC involvement between 0 and 3, this results in a SPCI between 1 and 21 *(23)*. All systems demonstrate that higher scores (more tumor) correspond to poorer prognosis. However, the difficulty is to define a clear cutoff point, beyond which HIPEC should not be performed. This is, in part, because of the different impact of the regions and of the size. For instance, low-volume diffuse involvement of the small bowel makes the prog-

nosis very poor, even in the absence of other lesions, whereas even very large ovarian metastases are almost always easily resected and hardly influence survival in a negative sense. In the Netherlands Cancer Institute series, the predictive value of the number of involved regions is stronger then the predictive value of the SPCI or PCI *(24)*. We now restrict CRS and HIPEC to patients with no more than 5 regions involved. Another way to look at the selection problem is the possibility to resect all macroscopic PC. Completeness of cytoreduction is the strongest predictor for long-term survival, with hardly any survivors at 1 yr after grossly incomplete resections, median survival of approximately 2 yr for small residue patients, and up to 35% 5-yr survival for patients after complete cytoreduction. This seems to clarify the belief that patients in whom it is technically impossible to resect all PC, or nearly all, should not undergo this treatment. These patients include those with diffuse involvement of small bowel or its mesentery, and those with diffuse involvement of the hilum of the liver and the omental bursa.

Ideally, staging should lead to selection or rejection of patients before laparotomy. This remains difficult because of the poor visualization of PC on CT scans or other imaging techniques *(24,25)*. The best information is still the observation of the surgeon during laparotomy. The opportunity is present because many of these patients are diagnosed during laparotomy for their primary or for obstructive recurrences. It is, however, disappointing that few surgeons report the extent of PC in a reliable way. Educating our colleagues to make the effort to look around in the abdomen and accurately register the involved areas would greatly improve selection.

If doubt about the extent or resectability of PC remains, laparoscopy can be a very informative procedure. However, in patients who have undergone repeated laparotomies there are often blind areas. At present, we exclude approximately 10% of referred PC patients after preoperative workup and approximately 10% during laparotomy.

7. RESULTS OF NONRANDOMIZED STUDIES

Small series of PC patients treated with cytoreduction and HIPEC have been published since the late 1980s. These series have in common small numbers, unknown selection criteria, and variations in the actual treatment. This notwithstanding, they show that by this locoregional approach truly long term survival is possible in a disease that was deemed incurable by any other means *(26,27)*. Since the 1990s, some larger series have been published with a more consistent treatment strategy (Table 1). In these series, median survival is reported to be approximately 2 yr, with 5 yr survival at 20%–25% *(28–33)*. Glehen published a large multicenter series in which these results were confirmed *(19)*. Many enthusiasts for the HIPEC approach found these results so convincing that they

Table 1
Literature Review of Most Recent Updates on CRS and HIPEC in the Management of PC of Colonic Origin

Chief Investigator	*Center*	*Design*	*Year*	*Patient*	*HIPEC (n)*	*Follow-up (mo)*	*Median (mo)*	*Survival (%)*				
								1-yr	**2-yr**	**3-yr**	**4-yr**	**5-yr**
Verwaal *(34)*	Amsterdam	Phase III	2004	54	MMC Arm	22	22	67	44	–	–	–
				51	Control Arm		13	56	22	–	–	–
Cavaliere *(29)*	Padova	Phase II	2003	46	MMC + cis-platin	15	18	68	31	–	–	–
Di Filippo *(35)*	SITILO	Phase II	2003	69	MMC	–	–	–	–	27	–	–
Levine	Winston-Salem	Phase II	2004	77	MMC	15	16	56	–	25	–	17
Gilly *(21)*	Lyon	Phase II	2004	53	MMC	60	13	55	–	32	–	11
Glehen *(19)*	Multicenters	Phase II	2004	506	MMC/LOHP	53	19	72	–	39	–	19
Morris	Sydney	Phase II	2005	30	MMC	12	30	71	62	–	–	–
Kecmanovic *(31)*	Belgrade	Phase II	2005	18	MMC	21	15	–	–	–	–	–
Elias *(36)*	Villejuif	Phase II	2005	30	LOHP	55	60	97	73	53	49	–
Zoetmulder	Amsterdam	Phase II	2005	117	MMC	46	22	75	–	28	–	19
Sugarbaker *(33)*	Washington	Phase II	2005	70	MMC	47	33	88	–	44	–	32

adopted HIPEC as standard therapy for PC of colorectal origin. However, it is clear that selection bias can be very strong in these patients, which is the reason why many medical oncologists remained unconvinced of the real benefits.

8. RANDOMIZED STUDY

There is only one randomized study comparing the HIPEC approach with conventional treatment of PC of colorectal origin *(34)*. In this study from the Netherlands Cancer Institute, patients with proven PC were randomized either to undergo limited palliative surgery, followed by systemic treatment with 5-FU/leucovorin, or to undergo CRS and HIPEC, followed by the same systemic chemotherapy. In a 3-yr period, 105 patients were randomized: 51 in the standard arm and 54 in the experimental arm. Only 44 patients in the standard arm started their chemotherapy. Two patients refused the result of the randomization and went abroad to undergo HIPEC treatment. The other patients did not start, mainly because of early progression.

In the experimental arm, 5 patients did not get their HIPEC therapy. One patient died while on the waiting list, one patient refused at the last minute, and 3 patients developed distant metastases between randomization and the planned operation date. Thirty-five patients started their systemic chemotherapy after recovery from the HIPEC treatment. The main reason for not starting was complicated postoperative period. Detailed information on the extent of PC was only available in the patients undergoing HIPEC. Many patients had very extensive PC, with 54% having 5 or more out of 7 abdominal regions involved and >30% having 6 or 7 regions involved.

It was possible to resect all macroscopic PC in 38% of patients. In 43% of patients, small residues (<2.5 mm) were left behind, while in 19% larger residues remained. To achieve this level of cytoreduction, a multitude of surgical resections had to be done, including omentectomy and multiple bowel resections in most patients. In accordance with this extensive surgery, complications have been frequent, the most common of which were infections related to small bowel leakage. In 17 patients, mild leukopenia occurred, with a nadir on day 10. Regardless, 30-d mortality was only 2% and the mean hospital stay 26 d. However, 8 patients died within 3 mo, most often because of long-term postoperative complications and early cancer recurrence. All early deaths, and the majority of complications, occurred in patients with extensive PC (6 or 7 regions involved).

All patients were analyzed according to the "intention to treat" principle. Survival data showed that patients in the HIPEC arm lived significantly longer than patients undergoing conventional therapy (Fig. 3). The median survival almost doubled from 12 mo to 22 mo. Also in this study, a survival plateau developed at 20%, with no additional death after 5 yr.

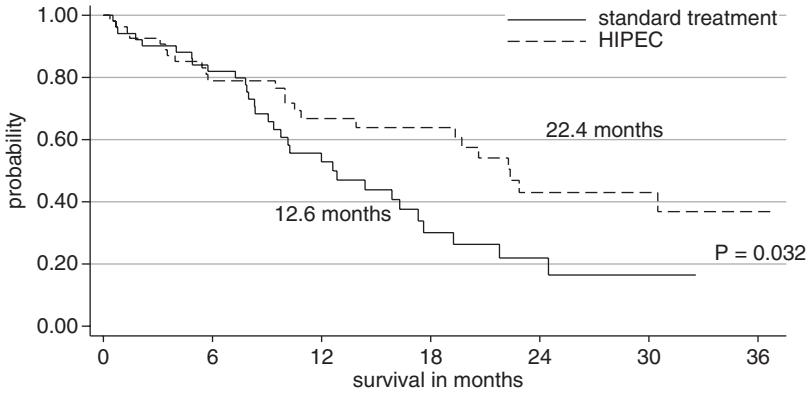

Fig. 3. Survival in 105 patients randomized to either undergo standard therapy or CRS + HIPEC (Vervaal et al., 2003).

Cost comparison between the two treatment arms showed that in the Netherlands setting, HIPEC treatment costs 17,284 euros per life-year gained. Quality of life (QoL) comparison showed some reduction in the QoL score 3 mo after HIPEC treatment, but QoL scores were equal in both arms after 6 mo.

9. THE LEARNING CURVE

Over the past 10 yr, the treatment of PC of colorectal origin with CRS and HIPEC has gradually improved at our Institute. Better understanding of the factors determining survival has lead to stricter selection, based on extent of disease and on the possibility to achieve complete cytoreduction. Gradual diffusion of the encouraging results of our PC treatment among our surgical and medical colleagues has resulted in many early referrals, avoiding the end of the road cases we were confronted with before. We have also learned valuable lessons concerning the limits of what can be done, and what should not be. As a consequence, the percentage of patients recovering from HIPEC without any complications has risen to 73%, with no treatment-related death during the past 3 yr. Simultaneously, the percentage of complete cytoreductions has risen to 71% and the median survival to over 27 mo (Fig. 4). In patients with complete cytoreductions, the 5-yr survival is now >40%.

10. FUTURE PROSPECTS

Cytoreductive surgery and HIPEC can successfully eliminate PC of colorectal cancer, or reduce the tumor load to levels that can be cured with systemic

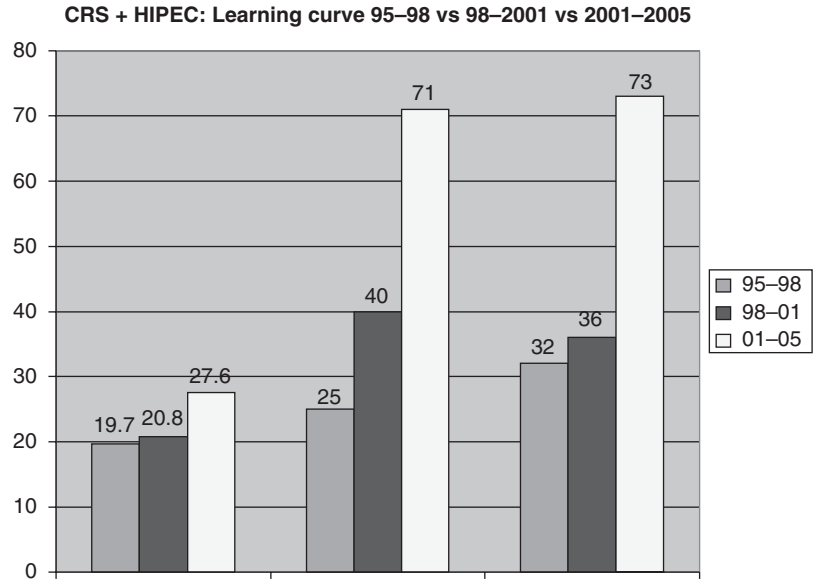

Fig. 4. Learning curve, influence on completeness of cytoreduction, complication rate and median survival.

chemotherapy. The improvement of systemic chemotherapy for colorectal cancer, as we are witnessing today, gives hope that a cure will be possible for more patients. How best to incorporate these newer drugs into the combined modality treatment of PC will be the challenging subject for research in coming years.

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9 Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Ovarian Cancer: Experience in France

Olivier Glehen, MD, PhD, and Francois-Noel Gilly, MD, PhD

Summary

Epithelial ovarian cancers (EOC) represent 80%–90% of all ovarian malignancies, and they are the most common cause of death for all gynecological tumors in the Western world *(1)*. The majority of patients have an advanced Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease at presentation, but the disease is often confined to the peritoneal cavity *(2)*. Current standard treatments of these patients consist of initial cytoreductive surgery (CRS) to <1-cm residual nodules, followed by combination systemic chemotherapy with a taxane and platinum analogue, either carboplatin or cisplatin.

Our experience in France with a phase II prospective single-center study shows that the population is inhomogeneous, and >58% of patients underwent CRS and HIPEC after >2 prior recurrences and >2 laparotomies. Because of these multiple recurrences before inclusion, it was not possible to calculate the progression-free interval (PFI). In the literature, most of the series evaluating CRS alone are dedicated to secondary CRS, meaning that the patients are experiencing their first recurrence. The only feasible comparison between secondary CRS alone and this study could be on the completeness of cytoreduction, which appears as the most important prognostic factor. The present phase II study clearly underlines that combined salvage therapy can achieve long-term survival in some patients with second, third, or fourth locoregional recurrence from ovarian cancer.

Key Words: Advanced ovarian cancer; peritoneal carcinomatosis; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy.

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1. INTRODUCTION

For advanced EOC, even optimal CRS and optimal systemic chemotherapy may result in cancer recurrences in 30%–50% of cases *(3)*. Although the concept of CRS with a goal of leaving residual tumor masses <1 cm in diameter was first introduced in 1975 *(4)*, maximal initial CRS was found to be the most powerful determinant of survival in a recent meta-analysis *(3)*.

Although primary treatment for advanced EOC is now consensual, two clinical settings remain controversial: (1) patients undergoing a second-look laparotomy with persistent large macroscopic disease on the peritoneum (chemoresistant patients), and (2) patients who develop intraabdominal recurrent disease >6 mo after a complete response to standard primary therapy. Other systemic chemotherapy courses (switching from paclitaxel/platinum to other drugs) or "repeated-CRS" could be proposed in these 2 clinical settings. The impact of "repeated CRS" (second-, third-, fourth-look, etc.) for chemoresistant patients and for those with recurrent disease is still controversial.

Considering the fact that recurrent advanced ovarian cancer is mainly a locoregional disease involving the peritoneum and the adjacent intraabdominal organs, we designed a prospective phase II study to evaluate repeated CRS combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The rationale for combining CRS and HIPEC is based on, first, the reported results of secondary CRS in EOC *(5)*; second, the reported results of CRS combined with HIPEC for PC arising from digestive cancers *(6)*; third, the theoretical advantage of combining hyperthermia and chemotherapy through the IP route; and fourth, the pharmacokinetic advantage of IP cisplatin *(7)*.

2. METHODS AND PATIENTS

Our experience in France with a phase II prospective single-center study is described here. Inclusion criteria were as follows:

1. patients between 18 yr and 75 yr of age,
2. patients with advanced EOC cancer who were found to have large macroscopic residual intraabdominal masses at the second-look surgery,
3. patients with advanced recurrent epithelial cancer after a PFI of at least 6 mo,
4. patients with advanced re-recurrent epithelial cancer after >3 surgical looks and/or >3 systemic chemotherapy lines,
5. patients with no extraabdominal metastases on preinclusion thoracic and cerebral CT scan,
6. patients with a World Health Organization index of <2,
7. patients with satisfactory cardiorespiratory and renal status,
8. and informed consent.

Exclusion criteria were as follows:

1. patients receiving systemic chemotherapy during the month before inclusion,
2. patients who received abdominal radiotherapy,
3. and patients with renal or myocardial failures.

3. SURGICAL PROTOCOL AND INTRAOPERATIVE STAGING SYSTEMS

Under general anesthesia with endotracheal intubation, the abdomen was opened through a midline incision and a laparotomy was performed to explore the whole abdominal cavity and obtain cytologic and pathologic samples. A precise description of the size and extent of disease was noted on a dedicated form, using the Gilly Peritoneal Carcinomatosis (PC) staging system *(8)* (Table 1) and the Sugarbaker Peritoneal Cancer Index (Fig. 1) *(9)*. Complete resection of tumor masses (including digestive organ resection if necessary) and peritonectomy were performed whenever possible to maximally reduce tumor volume, according to Sugarbaker's surgical guidelines *(10)*. The anatomical sites of peritonectomy were recorded on a specific form.

The assessment of the completeness of cancer resection (CCR) by CRS was performed by the surgeon at the end of the procedure using three categories:

1. CCR-0 (no macroscopic residual cancer),
2. CCR-1 (no residual nodule >5 mm in diameter),
3. and CCR-2 (at least one residual nodule >5 mm in diameter).

The HIPEC protocol was designed according to our previously reported experience *(8)* using a closed sterile circuit. At the end of the surgical procedure, each patient underwent HIPEC infusion under general anesthesia and general hypothermia (32°C maintained throughout the peritonectomy procedure using cold wraps on both lower extremities and an ice hat) to avoid the risk of

Table 1
Gilly PC Staging

Stage	*PC Description*
0	No macroscopic disease.
1	Malignant tumor nodules <5 mm in diameter. Localized in one part of the abdomen.
2	Tumor nodules <5 mm in diameter. Diffuse to the whole abdomen.
3	Tumor nodules 5 mm–2 cm in diameter.
4	Large (>2 cm diameter) tumor deposits.

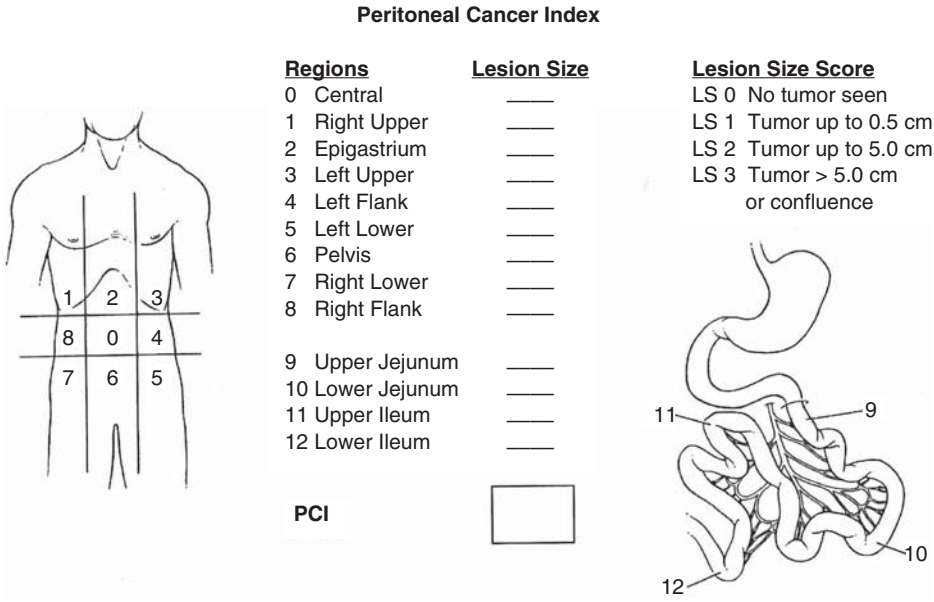

Fig. 1. PC Index (PCI Score 9).

core hyperthermia during the HIPEC. Before closure of the laparotomy, two inflow drains were inserted under the left and right diaphragmatic cupula (30-Fr silicone drain; William Harvey, Bard Cardiopulmonary Division, Haverhill, MA) and a third drain (outflow; 32-Fr) was inserted in the pouch of Douglas. Temperature probes were also inserted into the abdominal cavity, behind the liver pedicle and near the first jejunal loop. Other temperature probes were set up outside the abdominal cavity, on the inflow and outflow drains 8 cm from the skin, and inside the bladder within a Foley catheter. The laparotomy incision was then closed, and the inflow and outflow drains were connected to a closed sterile circuit in which a 4–6 L perfusate (Travenol, Norfolk, UK) was circulated at a flow rate of 500 mL/min, using a dedicated apparatus (Cavitherm, EFS Electronics, Millery, France). The perfusate contained 20 mg/m^2/L cisplatin, whereas the maximal total dose admitted was 80 mg. Intra- and extraabdominal temperatures, as well as intraabdominal pressures, were automatically recorded and controlled every 4 s through the Cavitherm computer system. HIPEC was performed for 90 min, with monitoring of respiratory and hemodynamic parameters at inflow temperatures ranging between 44°C and 46°C (Fig. 2). The same 2 senior surgeons and the same senior anesthesiologist performed all surgical and anesthetic procedures. All patients were observed in the intensive care unit for 24 h postoperatively. Pre- and postoperative hyperhydration was conducted for 4 d. Adjuvant postoperative chemotherapy was given in some patients. The patients were seen for follow-up every 3 mo for clinical examination, which

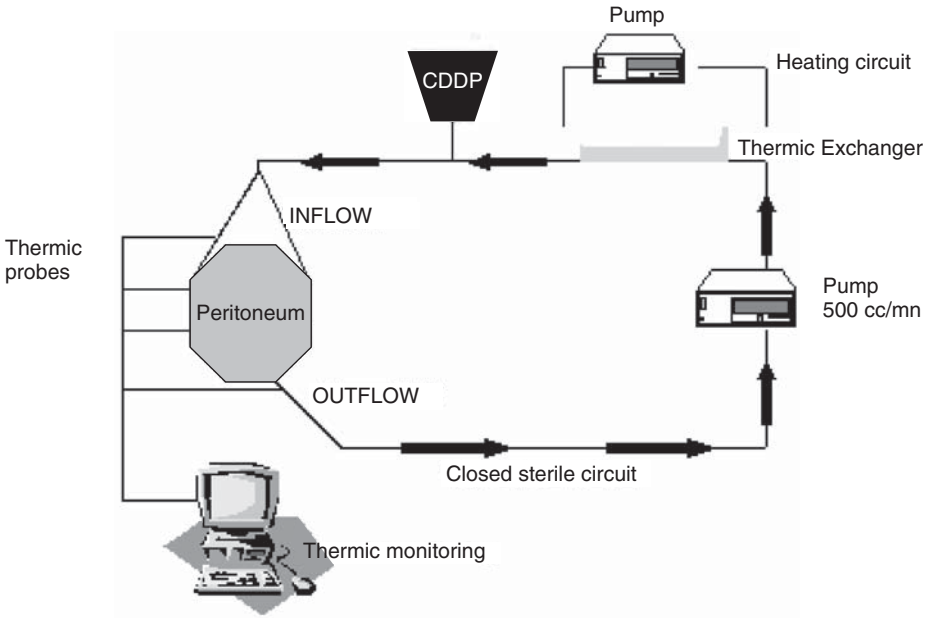

Fig. 2. Closed-abdomen HIPEC device.

consisted of CA 125 screening with CT scan (at 3 mo, 6 mo, 9 mo, 12 mo, 18 mo, 24 mo, 26 mo, and 32 mo).

4. PATIENTS

From 1990 to 2004, 81 patients with mean age of 54.3 yr (range from 30 yr to 75 yr) were treated. Initial FIGO staging was Ia ($n = 1$), Ic ($n = 4$), IIa ($n = 2$), IIIa ($n = 2$), IIIb ($n = 14$), IIIc ($n = 55$), and IV ($n = 3$). Primary tumors were well or moderately differentiated ($n = 32$), poorly differentiated ($n = 49$), pN0 ($n = 31$), pN+ ($n = 17$), and pNx ($n = 33$). Forty-nine patients were included <2 yr after the initial diagnosis. Four had large residual tumor after the first line of chemotherapy, 12 had a first recurrence with a PFI of 6 mo, 8 patients had a first recurrence with a PFI of 6 mo–18 mo, and 25 patients were included after the second or third recurrence. Thirty-two patients were included for advanced recurrent disease occurring >2 yr after the initial diagnosis (14 re-recurrences occurred between 2 and 3 yr, 10 occurred between 3 and 4 yr and represented the third or fourth recurrence after the primary treatment, and 8 occurred >4 yr after the primary treatment and represented the fifth or more recurrence). Thirty-four patients were included for second-look surgery, 31 for third-look, 13 for fourth-look, 1 for fifth-look, 1 for sixth-look, and 1 for eighth-look. Using

Gilly staging, the extents of the PC were 1 ($n = 12$), 2 ($n = 15$), 3 ($n = 16$), and 4 ($n = 38$). The mean PCI was 11.5 (range from 1 to 30).

5. STATISTICAL ANALYSIS

Data were recorded prospectively, and no patients were lost to follow-up. The cut-off date of this analysis was September 1, 2005. Median follow-up was 47.1 mo (range from 9.0 mo to 203.7 mo). Postoperative complications were recorded from the operation date up to the 30th postoperative day, and registrations were limited to grade 3 and 4 complications. Data were recorded and analyzed using a commercially available computer program (Statview 4.5; Abacus, Inc., Berkeley, CA) and are expressed as mean and range. A Kaplan–Meier survival curve was fitted to the data, and the log-rank test was used to identify differences between curves. Logistic regression was used for multiple analyses to discriminate among various effects on survival. $p < 0.05$ was considered statistically significant.

6. RESULTS

6.1. Perioperative Results

Details from surgical resection and peritonectomy procedures are presented in Table 2. Cytologic examination of peritoneal liquid lavage revealed free malignant cells in 39 patients. Mean number of bowel anastomoses performed was 0.6 (range from 0 to 4). Mean duration of CRS (excluding HIPEC duration) was 4.3 h (range from 2 h to 8 h). A complete macroscopic resection (CCR-0) was achieved in 45 patients, whereas CCR-1 was achieved in 20 and CCR-2 in 16.

6.2. Postoperative Mortality

Two patients died postoperatively (2.5%). A 59-yr-old woman presenting with a recurrent IIIc EOC 1 yr after the primary treatment underwent a CRS with small bowel resection, peritonectomies, and HIPEC, but died from peritonitis (anastomotic leakage) and acute renal insufficiency on the 12th postoperative day. A 71-yr-old woman operated on for a second-look surgery was found with a PC stage 4 and underwent a low anterior resection with complete pouch of Douglas peritonectomy and HIPEC, and died from myocardial infarction on the 5th postoperative day.

6.3. Postoperative Morbidity

Eleven major complications occurred in 10 patients (13.6%). Three patients experienced a postoperative anastomotic leakage with colonic fistula on the 8th, 9th, and 10th postoperative day, respectively (2 were reoperated and 1 was

Table 2
Surgical Resection and Peritonectomy Procedures Performed in 81 Patients

Exeresis	*Location*	*Number*
Colectomy	Right	9
	Left	4
	Subtotal	5
Low anterior resection		6
Small bowel resection		10
Splenectomy		6
Cholecystectomy		13
Diaphragm resection		2
Ureter resection		2
Partial bladder resection		2
Total gastrectomy		1
Peritonectomy	Right cupula	20
	Left cupula	10
	Right colon gutter	18
	Left colon gutter	10
	Pouch of Douglas	32
	Lesser omentum	3
	Omental bursae	1
	Glisson exeresis	12
	Anterior peritoneum	11
	Posterior peritoneum	19

medically treated by external drainage). One patient experienced a postoperative pancreatic fistula on the 26th postoperative day. One patient experienced a small bowel fistula on the 12th postoperative day that was medically treated. Three patients were treated with pleural drainage for right pleural effusion occurring after peritonectomy of the right diaphragm during CRS. One patient had a prolonged postoperative ileus up to the 15th postoperative day. Two patients experienced grade 3 leukopenia and 1 temporary renal insufficiency. Mean duration of hospital stay was 17.1 d (range from 6 d to 41 d).

6.4. Postoperative Complementary Treatments

Forty-three patients received at least one course of postoperative adjuvant systemic chemotherapy, as follows: platinum alone ($n = 4$), paclitaxel alone ($n = 5$), paclitaxel and platinum ($n = 10$), gemcitabine ($n = 3$), liposomal doxorubicin ($n = 13$), topotecan ($n = 3$), and cyclophosphamide ($n = 5$).

6.5. Survival

Mean follow-up was 68.1 mo (range from 9.0 mo to 203.7 mo). Thirty-nine patients (48.1%) had died (2 died in the early postoperative period and were mentioned as postoperative mortality, 36 died from disease recurrence, and 1 died from a myelodysplasia). Among these, 36 patients died from recurrence, 25 died with PC, 7 with PC and liver metastases, 1 with PC and malignant effusions, and 3 with liver metastases alone. Overall median survival and disease-free survival were 28.4 mo and 19.2 mo, respectively. For CCR-0 patients, overall and disease-free survival were 54.9 mo and 26.9 mo, respectively. For CCR-1 and -2 patients, overall median survival was 17.0 mo and 5.1 mo, respectively. Univariate analyses were used to evaluate the impact of different factors on overall survival and disease-free survival and are underlined in Table 3. Gilly staging and

Table 3
Variables Influencing Overall and Disease-Free Survival

Variable		*Overall Survival*	*p Value*	*DF Survival*	*p Value*
Initial staging	pN0	24.3	0.22	17.0	0.94
	pN+	26.0		21.1	
Initial tumor differentiation	Well and moderately	47.8	0.62	16.9	0.25
	Poorly	27.5		19.4	
Time interval between primary treatment and CRS and HIPEC	<2 yr	27.5	0.22	19.2	0.32
	<2 yr	28.4		20.8	
Surgical look	>2	24.3	0.91	19.2	0.90
	<2	28.4		19.4	
PCI score	>12	37.6	0.002	12.8	0.001
	<12	13.1		2.4	
Gilly staging	1 and 2	40.0	0.02	19.2	0.006
	3 and 4	17.0		7.3	
Peritoneal cytology	Negative	33.3	0.16	13.8	0.19
	Positive	17.0		4.0	
Completeness of cytoreduction	CCR-0	54.9	0.0001	47.8	
	CCR-1	17.0			
	CCR-2	5.1			
Post CRS systemic chemotherapy	No	28.4	0.60	20.6	0.97
	Yes	33.3		19.2	

PCI, peritoneal cancer index; DF, disease free.

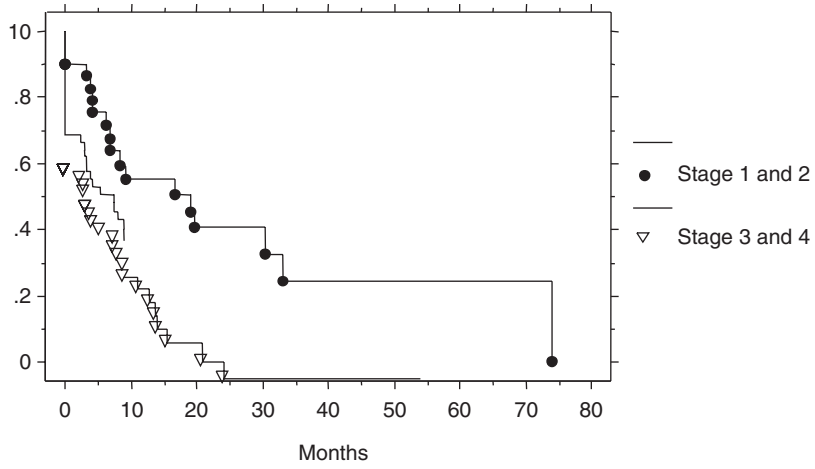

Fig. 3. Disease-free survival according to preoperative PC staging. (Gilly)

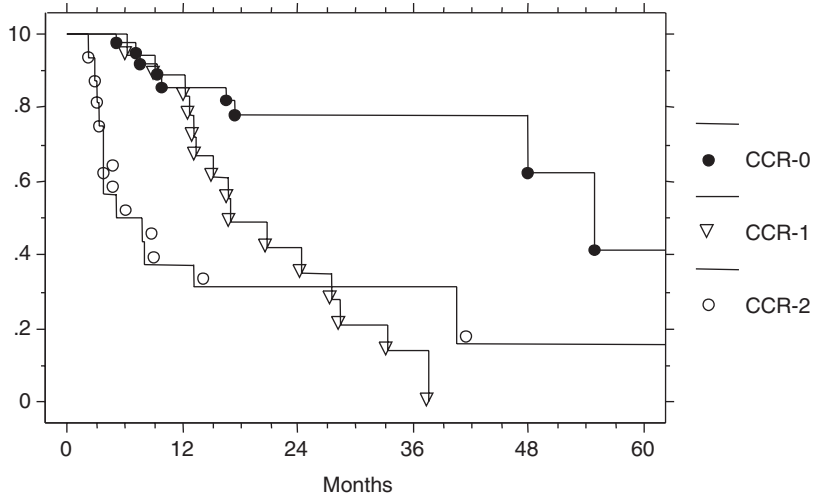

Fig. 4. Overall survival according to completeness of cytoreduction.

PCI score, as well as completeness of cytoreduction (CCR-0 and -1), significantly influenced the overall survival, as well as disease-free survival (Figs. 3 and 4). By multivariate analysis, only 2 variables were found to be independent significant prognostic indicators for overall survival: Gilly PC staging and completeness of cytoreduction.

7. DISCUSSION

After first-line cisplatin-based chemotherapy for advanced ovarian cancers, approx 60%–80% of patients will develop persistent or recurrent disease. The

literature reports numerous studies evaluating innovative forms of second-line or salvage therapy, such as new drugs, high-dose chemotherapy, or IP chemotherapy; the response rates to these salvage therapies do not exceed 22%, and reported median survival ranges from 8.8 mo to 15 mo *(11)*. Evaluation of secondary CRS has also been reported for chemoresistant or recurrent advanced ovarian cancers; despite a general acceptance during primary treatment, its role is still to be defined in persistent or recurrent disease. Many phase II studies report secondary CRS as an essential component of combined therapies when tumoral volume is optimally reduced, and the benefit of secondary CRS correlates with residual tumor volume *(3,5,12)*.

Since the 1980s, new therapeutic approaches to the treatment of PC have been reported with combinations of CRS and HIPEC, mainly to treat peritoneal dissemination of colorectal cancer or pseudomyxoma peritonei *(6)*. The rationale for these aggressive and combined new approaches is to optimally reduce tumor volume with CRS, whereas HIPEC could treat residual microscopic disease.

This study, which was carried out in a center with 16 yr of experience with CRS and HIPEC in colorectal cancer and pseudomyxoma peritonei, aimed to evaluate mortality and morbidity rates, as well as survival, in resistant or recurrent advanced ovarian cancers. The combination of extensive surgery with IP chemotherapy is associated with up to 10% mortality and 0%–30% morbidity rates (Table 4). However, mortality and major morbidity rates decreased with experience as a consequence of the learning curve and the strict selection of patients *(6)*. Anastomotic leakages represent an important part of postoperative morbidity, whatever the HIPEC technique used (open- or closed-abdomen HIPEC), whereas postoperative right pleural effusions, probably induced by right diaphragmatic peritonectomy, can be treated with postoperative pleural drainage *(20–22)*. Performing HIPEC during the same operation time as a major CRS could be the reason for morbidity. However, mortality and morbidity rates of secondary CRS alone seem to be similar, as shown in Table 5. To limit mortality and major morbidity rates, strict selection criteria are needed for the patients (good general status, satisfactory myocardial and renal functions, correct preoperative white blood cell count, and no systemic chemotherapy during the month before CRS and HIPEC), as well as the routine use of temporary stomas to protect bowel anastomoses.

Survival results achieved in the present study were similar to the literature (Table 4) and were mainly affected by the completeness of cytoreduction. Performing a CCR-0, i.e., a complete macroscopic resection within the peritoneal cavity, resulted in a 54.9-mo median survival. The results achieved with combined CRS and HIPEC must be compared to those obtained from secondary CRS alone, as well as from salvage (second-line or higher) systemic chemotherapy. Munkarah and Coleman, in a recent review of the English literature

Table 4
CRS Combined with HIPEC for Resistant or Recurrent Advanced Ovarian Cancer

Author	*IP drug*	*Number of patients*	*Number of CCR-0 and -1 patients*	*Mortality %*	*Morbidity %*	*Overall median survival for CCR-0 and -1*
Zoetmulder *(19)*	cisplatin	5	5	0	0	
de Bree *(20)*	docetaxel	19		10	10	39.0
Sugarbaker *(15)*	cisplatin and doxorubicin HIPEC or EPIC	28	25	0	11	45.8
Deraco *(13)*	mitomycin C and cisplatin	27	19	3	11	28.0
Plaisant *(21)*	paclitaxel	13	9	7.7		25.5
Zanon *(22)*	cisplatin	32	23	2.5	16.7	37.8
Piso *(14)*	mitoxantrone	19	9	5	28	33.0
Our series	cisplatin	81	65	2.5	13.6	54.9 CCR-0

EPIC, Early postoperative intraperitoneal chemotherapy.

Table 5
Secondary CRS Without HIPEC for Resistant or Recurrent Ovarian Cancer

Author	*No.*	*PFI Interval (mo)*	*Optimal CRS (No.)*	*Mortality (%)*	*Major Morbidity (%)*	*Overall Median Survival (mo)*	*CCR-0 Median Survival (mo)*	*CCR-0 and -1 Median Survival (mo)*	*CCR-2 Median Survival (mo)*
Vacarello *(23)*	38		14	0	2.6	19.0			
Cormio *(24)*	21	25	14	0	11	29.0	32.0		9.0
Gadducci *(25)*	30	>6	17			21.0	37.0		19.0
Eisenkop *(26)*	106	>6	87	2.3	18.4	34.4	44.4		19.3
Zang *(27)*	106		46	2.2	13.0			20.0	8.0
Scarabelli *(28)*	149	>7							
Tay *(29)*	46	>12	19	2.0	8.7	22.5	38.0		11.0
Onda *(12)*	44	>6	26				47.0		20.0
Rose *(5)*	201	>1.5							

on the topic *(16)*, found that CRS alone was able to achieve a 44 mo–60 mo median survival in CCR-0 patients. In 2002, Barakat reported a 39.6-mo median survival using IP chemotherapy as a salvage therapy for patients with recurrent disease *(17)*. The advantage of using the IP route for chemotherapy was recently confirmed in a randomized study for primary treatment of advanced epithelial cancer *(18)*. As usual, comparison between these different phase II studies is difficult; numerous variables may be involved in whether there is improvement in survival results, such as PFI between primary treatment and recurrence, use of systemic chemotherapy before the secondary CRS, size of the IP lesions, and, last but not least, the exact quality of completeness of cytoreduction, which could be differently estimated by surgeons.

In the present series, the population is inhomogeneous, and >58% of patients underwent CRS and HIPEC after at least 2 recurrences and >2 laparotomies for recurrent ovarian carcinoma. Because of these multiple recurrences before inclusion, it was not possible to calculate the PFI. In the literature, most of the series evaluating CRS alone are dedicated to secondary CRS, meaning that the patients are experiencing their first recurrence. The only feasible comparison between secondary CRS alone and this study could be the completeness of cytoreduction, which appears as the most important prognostic factor.

Undoubtedly, designing a prospective control study will be useful to clearly evaluate the respective roles of IP chemotherapy and of CRS in recurrent advanced ovarian cancer. The present phase II study clearly underlines that combined salvage therapy can achieve long-term survival in some patients with second, third, or fourth locoregional recurrence from ovarian cancer; the key point is the strict selection of patients, whereas CRS and HIPEC represent a hopeful, but aggressive, therapy.

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10 Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Ovarian Cancer: World Experience

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Summary

Research into the incorporation of hyperthermic intraperitoneal chemotherapy into treatment regimens for women with ovarian carcinoma has lagged behind that of other cancers causing peritoneal carcinomatosis despite the fact that ovarian cancer represents an excellent target for this modality of treatment. This chapter reviews experience with this technique from around the world, with the exception of France, and discusses future developments.

Key Words: Ovarian cancer; intraperitoneal cytotoxic drug delivery; intraperitoneal hyperthermic chemotherapy; hyperthermia.

1. INTRODUCTION

In 1979, John Spratt, a surgeon at the University of Louisville, was the first to use a device that he had helped design to deliver hyperthermic intraperitoneal chemotherapy (HIPEC) in humans (1). His first patient was a 35-yr-old male with pseudomyxoma peritonei who received thiotepa at a temperature of 42°C, followed by early postoperative hyperthermic chemotherapy.

After this milestone, it was surgical oncologists who investigated the use of HIPEC for peritoneal carcinomatosis arising from cancers for which standard chemotherapy was relatively ineffective and prognosis notoriously dismal. These included gastric *(2)*, colorectal *(3)*, and mesothelioma *(4)*, as well as appendiceal carcinoma *(5)*.

In 2001, a landmark paper from Dr. Zoetmulder's group at the Netherlands Cancer Institute in Amsterdam reported a randomized phase III trial in patients

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with peritoneal carcinomatosis from colorectal cancer (*see* Chapter 8). Patients were randomized to receive either HIPEC after radical debulking surgery or traditional intravenous chemotherapy and palliative care. The patients treated with radical debulking surgery with HIPEC had a statistically significant prolongation of life over patients treated on the control arm *(3)*.

During the last quarter of the twentieth century, ovarian cancer (EOC) specialists were establishing the role of primary cytoreductive surgery (CRS) and postoperative chemotherapy with platinum analogues and, later, taxanes. Unlike gastrointestinal malignancies, EOC was more sensitive to chemotherapy with response rates of approximately 70% on initial exposure *(6–9)*. Despite this, approximately two-thirds of patients recur, and the overall survival is only about 50%.

Hyperthermic intraperitoneal chemotherapy involves three modalities of treatment: chemotherapy, heat, and IP delivery. As Drs. Markman and Jaaback describe in Chapters 2 and 3, IP delivery of normothermic chemotherapy in EOC has proven its efficacy as a front-line treatment. Three large, randomized controlled studies in the United States investigating the IP delivery of cisplatin, carboplatin, or paclitaxel in combination with intravenous delivery have shown a survival advantage for the IP approach *(10–12)*, and a Cochrane Collaboration *(13)* review of all randomized trials of IP therapy in ovarian cancer confirms this advantage. (*See* Chapters 2 and 3)

The evidence for a role of hyperthermia in the management of ovarian cancer comes mainly from preclinical studies, but the case for its use is strong (*see* Chapter 7). Hyperthermia, on its own, has been demonstrated to be tumoricidal *(14)*. It increases the cytotoxicity of cisplatin and other chemotherapeutic agents in both human cell culture and animal models *(15–19)*, and it may reverse cisplatin resistance *(20)*. Investigations of the cellular effects of the combination have demonstrated increased DNA cross-linking and increased DNA adduct formation *(16,21)*. It has also been shown that cisplatin penetrates deeper into peritoneal tumor implants when delivered intraperitoneally with hyperthermia *(21)*. However, the precise underlying molecular mechanisms of these effects are still unknown.

2. CLINICAL EXPERIENCE

The investigation of the role of HIPEC in ovarian cancer began in the United States and was soon taken up by researchers in other countries. The published literature (Tables 1 and 2) currently includes only nonrandomized series from individual institutions, which "en masse" are comprised of heterogeneous study populations and varied treatment and data-reporting methods. Extracting meaningful comparisons from these reports is difficult, but in the absence of randomized controlled trials, they are the best information available. The HYPER-O Registry (discussed later in this chapter) is designed to help address this

Table 1
Literature on HIPEC in Ovarian Cancer

Author	*City*	*Country*	*Year*	*Inclusion*
Loggie *(22)*	Winston-Salem, NC	USA	1994	advanced
Steller *(23)*	Bethesda, MD	USA	1999	front-line
van der Vange *(24)*	Amsterdam	Holland	2000	recurrent/persistent
Cavalieri *(25)*	Rome	Italy	2000	recurrent/persistent
Deraco *(26)*	Milan	Italy	2001	recurrent/persistent
Panteix *(27)*	Lyon	France	2002	recurrent
Ajisaka *(28)*	Kanazawa	Japan	2002	front-line (case report only)
de Bree *(29)*	Herakleion	Greece	2003	recurrent/persistent/ second look
Zanon *(30)*	Torino	Italy	2004	recurrent/persistent
Look *(31)*	Washington, DC	USA	2004	front-line, recurrent/persistent
Piso *(32)*	Hanover	Germany	2004	primary/recurrent
Ryu *(33)*	Seoul	South Korea	2004	interval debulking/second look
Gori *(34)*	Buenos Aires	Argentina	2005	second look
Reichman *(35)*	Newark, NJ	USA	2005	recurrent/at interval debulking
Yoshida *(36)*	Fukui	Japan	2005	front-line interval debulking second look
Helm *(37)*	Louisville	USA	2007	recurrent /persistent

situation. In this chapter, the current information will be briefly described and discussed (Fig. 1).

Brian Loggie reported the first case of HIPEC use in a woman with advanced EOC amongst a series of 6 patients with peritoneal carcinomatosis that was mainly caused by gastrointestinal malignancies *(22)*. In this phase I study, a patient with EOC received 30 mg of IP mitomycin C at a temperature of 39°C–40.5°C for 2 hr.

Steller and a research team at the National Cancer Institute in Bethesda, MD *(23)* reported the first series of HIPEC as front-line treatment for ovarian carcinoma. A phase 1 study was performed to examine the feasibility, toxicity, and pharmacokinetics of carboplatin given to 6 patients, 5 who had small-volume residual disease after optimal CRS; the sixth patient appears to have

Table 2
Literature on HIPEC in Ovarian Cancer: Technique

Author	*Type*	*n*	*HIPEC agent*	*Dose*	*Time (min)*	*Temp °C*
Loggie *(22)*	pilot	1	MMC	30 mg	120	39–40.5
Steller *(23)*	pilot	5	carboplatin	800–1200 mg/m^2	90	41–43
van der Vange *(24)*	pilot	5	cisplatin	50/75 mg/m^2	90	40
Cavalieri *(25)*	retrospective	20	cisplatin	25 mg/m^2/L	90	41.5–42.5
Deraco *(26)*	phase II	27	cisplatin	25 mg/m^2/L	60	42.5
Panteix *(27)*	pharmacokinetic	16	cisplatin	60/80/100 mg	90	41–43
Ajisaka *(28)*	case report	1	cisplatin mitomycin etoposide	240 mg 40 mg 80 mg	60	41–43
de Bree *(29)*	prospective	19	docetaxel	75 mg/m^2	120	41–43
Zanon *(30)*	phase II	30	cisplatin	100/150 mg/m^2	60	41.5–42.5
Look *(31)*	retrospective	12*	cisplatin MMC	not stated not stated		
Piso *(32)*	retrospective	19*	cisplatin or mitoxantrone	75 mg/m^2 15 mg/m^2	90	41.5
Ryu *(33)*	retrospective	57	carboplatin interferon-α	350 mg/m^2 5×10^6 IU/m^2	90	43–44
Gori *(34)*	retrospective	32	cisplatin	100 mg/m^2	60	41–43
Reichman *(35)*	retrospective	13	cisplatin	50 mg/m^2	90	40
Yoshida *(36)*	retrospective	10	cisplatin MMC etoposide	100 mg 20 mg 100 mg	50	41–44.5
Helm *(37)*	retrospective	18	cisplatin or MMC	100 mg/m^2 40 mg	90	42–43

*Included patients receiving early postoperative intraperitoneal chemotherapy.

Fig. 1. Logo of the HYPER-O Registry.

been the first case of HIPEC at the time of interval debulking after front-line chemotherapy.

Further developments came from European centers. In 2000, van der Vange *(24)* and collaborators at the Netherlands Cancer Institute published a study of 5 heavily pretreated patients with advanced intraabdominal EOC debulked to <5 mm disease. In this feasibility study, patients were exposed to IP cisplatin. Although not a primary endpoint, survival data is given and 4 patients were dead at 3 mo, 4 mo, 12 mo, and 24 mo after treatment. One was alive and free of disease a surprising 43 mo later after adjuvant cisplatin and cyclophosphamide.

Cavaliere *(25)* at the Regina Elena National Cancer Institute in Rome, Italy treated a mixed series of 40 patients with peritoneal carcinomatosis of ovarian, colorectal, appendiceal, and mesothelial origin. There were 20 patients with ovarian cancer who underwent surgical cytoreduction and HIPEC with cisplatin. All had been previously treated with surgery and/or chemotherapy and were no longer responsive to conventional therapies. Only a proportion of the patients received HIPEC, and because separate data on this group is not given, it is not possible to assess specific outcomes with HIPEC treatment.

Marcello Deraco *(26)*, of the Instituto Tumori in Milan, Italy, reported 27 patients with surgical cytoreduction followed by HIPEC with cisplatin, and published his experience in 2001. Twenty-six patients had received prior surgery, 23 had received systemic chemotherapy, 2 had received salvage IP chemotherapy, 1 had received immunotherapy, and 1 had received radiation.

Of those receiving chemotherapy, 48% were given a paclitaxel/cisplatin combination, 7% a paclitaxel-based regimen without platinum, and 30% a platinum-based regimen. Of these patients, 37% (10/27) had either localized pelvic peritoneal involvement or slight dissemination into remote peritoneum, and only 67% (18/27) underwent CRS. At the end of cytoreduction, 70% had disease of <2.5 mm. Deraco reported a 2-yr overall survival of 55%, with 21% of patients being progression free at 2 yr, and 44% locally progression free. The median time to progression was 21.8 mo.

Panteix *(27)* carried out a pharmacokinetics study of HIPEC cisplatin on 16 patients with metastatic EOC at progression. All had been treated with prior chemotherapy, but only 11 had undergone prior surgery. At 3 yr, 37.5% were alive; 12.5% were alive at 7 yr.

In 2003, de Bree *(29)*, of the Medical School of Crete, Herakleion, Greece, reported on patients with EOC treated with HIPEC with docetaxel. Eligibility included those with recurrence ≤6 mo after completion of systemic chemotherapy or persistent peritoneal carcinomatosis after primary systemic chemotherapy. Twelve patients with ovarian cancer were treated for refractory/persistent disease or early IP recurrence, and five additional patients were found to have persistent disease at second-look laparotomy after front-line therapy. After cytoreduction, 75% had ≤5 mm as the largest residual lesion size. Eight were alive and without disease at 2 mo–72 mo, 3 were alive with disease at 17 mo–79 mo, 3 died of cancer at 36 mo, 54 mo, and 78 mo, respectively, and 3 died without obvious ovarian cancer, one at 30 mo and 2 perioperatively.

Zanon *(30)* performed a prospective phase II study of patients <75-yr-old with ovarian carcinoma who had completed at least a first-line platinum-based regimen. Surgical cytoreduction was performed, and at the end of the procedure HIPEC with cisplatin was given. Seventy-seven percent were cytoreduced to <2.5 mm residual disease. Two-year survival was reported as 60%. After median follow-up of 18.9 mo, the median regional relapse-free survival was 17.1 mo, with median survival of 28.1 mo.

Look and colleagues *(31)* reported on 28 patients treated with advanced and recurrent ovarian carcinoma. Four of the 28 were treated front-line, and only 16 of the 28 had prior chemotherapy. Patients were treated with either early postoperative IP normothermic chemotherapy or HIPEC, but were not separately analyzed. Sixty-six percent were cytoreduced to <2.5 mm disease.

In 2004, Piso *(32)* described 19 patients with primary or recurrent disease treated with either HIPEC cisplatin or mitoxantrone, with 11 going on to receive early postoperative normothermic chemotherapy. Eleven patients were treated front-line, and 8 were treated for recurrent disease, with 50% having a complete cytoreduction. Mean survival for the entire group was 33 mo, and 5-yr survival was 15%. Interestingly, there was no significant survival difference between patients with primary and recurrent cancer (29 mo vs 30 mo).

In 2005, Reichman *(35)* treated 12 patients with advanced or recurrent EOC. Nine had recurred after initial maximal CRS followed by systemic chemotherapy, and it is assumed that the remaining 3 had initially presented with advanced disease and responded to systemic chemotherapy. One patient was treated for a mixed mesodermal sarcoma of the ovary and the analysis of outcome includes this patient. All patients received HIPEC with cisplatin. After a median follow-up of 13.7 mo, the overall 3-yr survival was reported as 55%, with a median disease-free survival of 15.4 mo and a 3-yr disease-free survival of 11%.

Two relatively large studies have focused on HIPEC as consolidation therapy and will be discussed in more detail later in this chapter, in the Consolidation section. In Seoul, South Korea, Ryu *(33)* reported on 57 women who underwent HIPEC at the time of either interval debulking or second-look surgery after front-line therapy. Gori *(34)* reported on 51 patients who underwent primary surgery with optimal cytoreduction to <2 cm, followed by chemotherapy with intravenous cisplatin and cyclophosphamide. Yoshida *(36)* reported on 10 patients at various times front-line, at interval debulking, and at second-look laparotomy.

At the University of Louisville, we have initially focused on the role of HIPEC in patients with recurrent/persistent EOC. *(37)* Our experience has included 18 heavily pretreated patients with recurrent/persistent carcinoma of the ovary with >6 mo follow-up. Eighty-three percent were cytoreduced to ≤2 mm residual, and >80% of the patients received EOC cisplatin, with the remainder receiving mitomycin. Median overall survival is currently 31 mo, with 43% of patients experiencing 2-yr survival.

3. ADVERSE EVENTS ASSOCIATED WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Much of the data on the toxicity of HIPEC has come from reports of its use in association with major surgery that is, itself, associated with significant morbidity. In his report of the use of HIPEC in 29 patients at the time of second-look surgery, Gori *(34)* found no intraoperative toxicity and a single postoperative complication of a deep fascial dehiscence. It appears that this may by the largest series of pure HIPEC because there was no macroscopic disease in any of the patients at the time of second-look after optimal front-line surgery.

4. MORTALITY

Where HIPEC alone, without early postoperative chemotherapy, has been reported for the treatment of EOC in association with surgery, the perioperative mortality is 3.7% (7/187 cases) *(22–25,26,29,30,33,34,36–38)*. The causes of

death included disseminated intravascular coagulation (1), pulmonary embolus (2), gram-negative sepsis (1), and intestinal leakage (3).

5. MORBIDITY

Postoperative morbidity has been reported in eight series *(23,24,26,29,30, 33,34,36)*. An overall assessment can be appreciated from series including patients with CRS and HIPEC: 11% "grade 2–3 toxicity" *(26)*, 16.5% postoperative "morbidity" *(30)*, and 28.3% "major complication rate" *(33)*. Including our experience, we can examine the complication rates for 184 patients (Table 3) *(23,24,26,29,33,36)*. Hematologic morbidity was rare. Excluding disseminated intravascular coagulation causing death in one patient, grade 3 leukopenia occurred in 6/184 (3.3%) and thrombocytopenia in 4/184 (2.2%). Significant renal toxicity was reported in 8 (4.3%) patients.

Table 3
Complications Associated with Surgery and Delivery of HIPEC*

Hematologic	**n**	**Surgical**	**n**
DIC	1	anastomotic leaks	2
leucopenia grade 3	6	intestinal perforation	5
thrombocytopenia	4	intra-abdominal bleeding	3
		bowel obstruction	7
Metabolic			
hypoalbuminemia	8		
raised liver enzymes	4		
renal toxicity	8	sepsis	9
renal failure	6	peritonitis	1
unknown grade	2	wound infection	11
		wound seroma	1
Pulmonary/and neck		pelvic abscess	1
embolus	3	dehiscence	2
pleural effusions	6	total	1
pneumonia	1	deep	1
central vein thrombosis	2	hernia	2

$n = 184$ patients. Other complications have included a hematoma from the inferior epigastric vessels, abdominal pain 4, temporary cutaneous fistula after removal of gastrostomy tube, transient hematuria, and a femoral nerve neuropathy thought to be related to retraction at surgery.
*Excluding grade 1 and 2 complications.
(Table adapted from *(23,24,26,29,30,33,34,36,38).*)

Surgical complications included anastomotic leaks (2,17), intestinal perforations (5) (2.7%), bowel obstruction (7) (3.8%), and intraabdominal bleeding/hematoma (3) (1.6%).

The incidence of anastomotic leaks appears low, but it is difficult to be sure of the exact percentage. Within the series from which the complications were reported, there was a minimum of 59 bowel anastomoses, with 6 patients receiving diversions *(23,24,26,29,30,37)*. Assuming that these diversions protected 9 anastomoses in total, then the leak rate would be 1 in 25 (4%), not an unreasonable figure when considering the extent of surgery. The occurrence of "spontaneous" intestinal perforations after HIPEC is concerning, and it may be related to the effect of heat and chemotherapy agents on bowel serosa traumatized even mildly during enterolysis.

The exact incidence of sepsis is difficult to define, but is of concern when perioperative chemotherapy is given. Septic complications were reported in 9 (4.9%) patients with wound infection in 11 (6%) and peritonitis in 1 and pelvic abscess in 1. Pulmonary effusions occurred in 6/184 patients (3.3%), pulmonary embolus in 3 (1.6%), wound dehiscence in 2 (1%), and hernia in 2 (1%).

Reoperation was performed at least 6 times for inferior epigastric hematoma, spontaneous ileal perforation, cholecystitis, total wound dehiscence, pelvic hematoma, anastomotic leak, fistula of ureterorectal stump, intraabdominal hematoma/small bowel obstruction, and tissue necrosis of the anterior abdominal wall thought to be caused by devascularization. This figure is probably an underestimate because Ryu reported the occurrence of 4 intestinal perforations, but did not confirm further surgeries for these patients (*33*).

In a review of secondary CRS without perioperative chemotherapy for recurrent ovarian carcinoma, the mortality rate was found to be 1.4% (0%–3.4%) out of 631 patients; the major perioperative morbidity rate was 11% (67/631). *(38)*. Although the complication rates associated with HIPEC and surgery are often attributed mainly to the surgical procedure itself, it is likely that the HIPEC does lead to a somewhat increased rate of morbidity.

6. OUTCOME

Assessing outcome within the series reported in the literature is not easy because of the heterogeneity of treatments and study populations. There are four main situations within the time course of ovarian cancer in which HIPEC may have a role:

1. recurrent/persistent disease,
2. front-line therapy,
3. as consolidation therapy after front-line therapy,
4. at the time of interval debulking.

The experience within each group will be considered separately.

6.1. Recurrent/Persistent Disease

Out of the series reported in Table 1, 5 include 92 patients with recurrent/persistent disease treated with HIPEC in whom outcome data are identifiable. Within these studies, the 2-yr survival is reported as 40% (24), 43%, 55% (26), and 60% (30). Three-year survival is reported by de Bree as 50% *(29)*. The median time to progression, when identifiable, was between 10 mo and 21.8 mo *(26,30,37)*. It is difficult to compare results from individual case series, but there is no doubt that although the majority of patients are not cured by surgery and HIPEC, some patients do appear to do much better than would otherwise be expected. The combination may be "resetting" the clock. When recurrence does occur, it is most commonly within the peritoneal cavity. Of 35 recurrences reported, 30 (86%) occurred within the peritoneal cavity *(24,26,29,37)*.

Prognostic factors are similar to those for ovarian cancer in general: the extent of residual disease after secondary debulking surgery, the age of the patients, the time from initial presentation to the time of the HIPEC surgery, and the peritoneal cancer index *(26,30,35)*.

The aforementioned review of outcomes for women with recurrent ovarian carcinoma treated with secondary surgical cytoreduction followed by miscellaneous and undetailed chemotherapy supports the role of surgery for recurrent disease *(38)*. The inclusion of HIPEC into this setting to further improve results is a logical research question to be addressed.

6.2. Front-line

Incorporation of HIPEC into front-line treatment of EOC makes considerable theoretical sense. The essence of treatment of EOC is maximal CRS followed by aggressive chemotherapy. However, the incorporation of normothermic IP chemotherapy in the recent Gynecologic Oncology Group protocol #172 only led to a complete pathologic response rate of 57% in the group of patients who underwent second-look laparotomy, and 65% of the patients recurred *(12)*. If HIPEC were to be performed at initial surgery, adhesions would have all been divided, any residual tumor would be at the smallest possible volume, and HIPEC could be given not only at an optimum time as far as peritoneal exposure is concerned, but many days before the usual time when postoperative chemotherapy is given.

Despite Steller's 1999 evaluation of carboplatin in the front-line setting (23), very little has been published on front-line HIPEC. In fact, there are reports of only 14 other patients treated in this fashion in 4 publications. Ajisaka *(28)* reported a single case of a 35-yr-old woman with primary papillary serous carcinoma of the peritoneum treated with HIPEC with cisplatin/mitomycin/

etoposide, followed by early postoperative normothermic chemotherapy with IP cisplatin and intravenous cisplatin, mitomycin, 5-fluorouracil, and etoposide. This regimen, not unexpectedly, caused severe bone marrow suppression, and only 3 cycles were possible. In a mixed series, Look used HIPEC at the time of initial debulking surgery or soon after in 4 patients *(31)*, Piso in 7 patients *(32)*, and Yoshida in 2 *(30)*. These numbers are too small to assess any meaningful effect, but the precedent for treatment at this time has been set and further study is needed.

6.3. Consolidation

Despite adequate front-line therapy, it is well established that even with a complete pathologic response confirmed at second-look laparotomy, 60% of patients will recur within 10 yr *(39)*. This emphasizes the need for methods of consolidating complete initial responses.

There have been no randomized studies investigating the role of HIPEC as consolidation therapy at second-look laparotomy, but some work has been reported in this setting.

de Bree *(29)* was the first to report the use of HIPEC at the time of positive second-look laparotomy in 5 patients. Although vital prognostic factor information is not detailed, two patients died of disease at 36 mo and 54 mo, and 3 were alive and free of disease at 9 mo, 19 mo, and 60 mo. Yoshida (36) treated four patients with negative second-look surgery with HIPEC; 2 recurred at 16 mo and 27 mo, respectively, and 2 were alive and well at 120 mo and 168 mo, respectively.

Ryu *(33)* reported on 117 patients: 57 who underwent front-line CRS, followed by intravenous chemotherapy and treatment with a second surgery with HIPEC; and a historical control group of 60 patients who underwent initial CRS, followed by intravenous chemotherapy only. In the experimental arm, some patients had their second surgery performed after 6–8 cycles of chemotherapy and some at an interval debulking procedure, provided there had been a partial response to 3–4 cycles of initial chemotherapy. HIPEC was given in the form of carboplatin 350 mg/m^2 and interferon-alpha at a temperature of 43°C–44°C. The disease-free survival was significantly better at 48.7 mo in the HIPEC arm versus 19.8 mo in the control arm. Overall survival was also significantly better, at 63.4 mo versus 52.8 mo. For patients with stage III disease, the median disease-free and overall survivals were 26.4 mo versus 6.1 mo and 60.9 mo versus 22.3 mo. For stage III patients with a residual lesion <1 cm at the second surgery (26/53), median disease-free survival was 40.6 mo versus 13.2 mo, and 5-yr overall survival was 65.6% versus 40.7%.

Despite the relatively large number of patients in this study, germ cell tumors were included in the data together with patients with early-stage disease. It is

not known how many had interval debulking surgery and what the initial surgery was in this group. Also, the number of patients with a complete pathologic response at the time of the second surgery is not stated. Outcome in the control arm of the stage III patients is poor, raising doubts about the meaning of the comparison results.

Gori *(34)* reported on 51 patients who underwent primary surgery with optimal cytoreduction to <2 cm, followed by chemotherapy with intravenous cisplatin and cyclophosphamide. Of this group, 32 patients underwent second-look laparotomy with HIPEC cisplatin and 19 who refused second-look laparotomy formed the control group.

At second-look laparotomy, there were no patients with macroscopic disease, but 4 had microscopic disease. Three patients in the HIPEC group were excluded from analysis because of problems with the perfusion temperature. Although not statistically significant, there was a trend to improved outcome in the HIPEC group. After a mean follow-up amongst survivors of 64.4 mo for the HIPEC and 60.1 mo for the control group, median survival was 64.4 mo and 46.4 mo, respectively ($p = 0.29$). Recurrence occurred in 20/29 (69.9%) of the HIPEC group and 12/19 (63.1%) of the control group. This was a nonrandomized study and the results are open to some questions, including the low rate of positive second-looks in the study group.

Now that second-look surgery can be performed laparoscopically, along with the delivery of HIPEC laparoscopically *(40)*, this would be a useful avenue of research.

6.4. Interval Debulking

Although the standard of care for patients presenting with ovarian cancer is CRS, this is not always possible. Many patients will respond to initial chemotherapy and become candidates for interval debulking surgery. This circumstance would also be a good situation for HIPEC treatment and would have the advantage of use at front-line surgery that would provide lead time to arrange for the perfusion team and equipment to be available. Several series have included patients treated with HIPEC at the time of interval debulking, but the numbers are too small for meaningful analysis and conclusions *(23,29,33,35,36)*.

7. CONCLUSIONS

Hyperthermic intraperitoneal chemotherapy has a theoretic role in the management of EOC, but practical application requires an enormous amount of additional research.

The modality could be incorporated at all stages of treatment, but might have the greatest effect if brought forward to the time of initial surgery, or for consolidation after completion of front-line therapy.

The gynecologic oncology specialty owes a considerable amount of appreciation to pioneering surgical oncologists who have played an important role in the development of HIPEC.

8. INTERNATIONAL REGISTRY FOR HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

This chapter demonstrates the relative dearth of information on HIPEC in EOC. Although the number of cases in the literature is low, we believe that surgeons have been applying this form of treatment to patients, but have not reported their experience. At the Brown Cancer Center, University of Louisville, we have established an internet registry called HYPER-O. The registry is designed to allow a wealth of information on patients with EOC treated with HIPEC to be collected in a uniform format that will enable accurate and meaningful analysis of techniques applied and outcomes such as disease-free interval, survival, and prognostic factors. Because many procedures have been performed by surgical oncologists, the database includes established scoring systems such as the peritoneal cancer index and the completeness of cytoreduction score. The registry is HIPAA-compliant and registration is open to all physicians treating ovarian cancer with HIPEC. The registry has been supported by Thermasolutions Inc. (Pittsburgh, PA). For further information please visit www.hyperoregistry.com.

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11 Techniques of Delivering Hyperthermic Intraperitoneal Chemotherapy

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Summary

Hyperthermic intraperitoneal chemotherapy (HIPEC) was first delivered to a human in 1979 by Dr. John Spratt at the University of Louisville when he treated a male patient with pseudomyxoma peritonei *(1)*. In collaboration with other researchers, he developed a delivery system using a "closed" technique, with both the fascia and skin closed.

Since that time, there has been increasing interest around the world in the delivery of HIPEC. The most widely used methods have involved perioperative perfusion of chemotherapy in heated perfusate performed at the time of open laparotomy (*see* the following sections), but delivery of HIPEC has also been reported with laparoscopic placement of inflow and outflow tubing *(2)* and regional *(3)* and whole-body hyperthermia *(4)*.

Hyperthermic intraperitoneal chemotherapy requires an organized team within the operating room who all understand their roles. The anesthesiologist manages the cooling of the patient's core temperature before the hyperthermic perfusion and monitors the patient's vital parameters, particularly the core temperature, during the perfusion. The perfusionist, often recruited from cardiac surgery because of experience with the techniques of cardiopulmonary bypass, operates the heat exchange pump and equipment for the perfusion. Although it is everyone's responsibility, the scrub technicians and circulating nurses are charged with the specific duty of ensuring proper adherence to operating room protocol for the use of hazardous agents.

The two main techniques for hyperthermic IP perfusion are "open," where the incision is open during the HIPEC, and "closed" where the abdominal skin and/or fascia are closed. Both basic methods have been extensively utilized, with many individual variations. In this chapter, the most widely used open technique, the "Coliseum," and the closed technique will be described and discussed.

Key Words: Hyperthermic intraperitoneal chemotherapy; open coliseum technique; closed technique.

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1. HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY USING THE COLISEUM TECHNIQUE

Most cancers that occur within the abdomen or pelvis will disseminate by the following three different routes: hematogenous metastases, lymphatic metastases, and implants on the peritoneal surfaces. Significant recent advances have been made in the field of cytotoxic chemotherapy and biological agents in the management of unresectable metastatic gastrointestinal cancers with hematogenous and/or lymphatic dissemination. The earliest success with the surgical management of metastatic disease was complete resection of locally recurrent colon and rectal cancer. Next, the resection of liver metastases from the same disease was shown to be of benefit in a selected group of patients. Isolated peritoneal metastases are a common site of recurrence after potentially curative resections of gastrointestinal cancers, and also account for significant morbidity and mortality in this group of patients, as well as those with recurrent gynecological malignancies. Increasingly, the concept of complete surgical eradication of metastatic disease is being extended to improve the long-term survival of patients with peritoneal surface malignancies secondary to gastrointestinal and gynecological cancer. Better surgical techniques, including peritonectomy procedures, standardized methods to deliver intraoperative IP hyperthermic chemotherapy, and better patient selection criteria, have resulted in a significant improvement in survival and in morbidity and mortality of the surgical management of this particular group of cancer patients.

2. PRINCIPLES OF MANAGEMENT

The successful treatment of peritoneal surface malignancy requires a combined approach that utilizes peritonectomy procedures and perioperative IP chemotherapy. Favorable treatment results are occurring because of changes in the surgeon's use of chemotherapy in patients with peritoneal carcinomatosis from gastrointestinal or gynecological malignancies, peritoneal sarcomatosis, and peritoneal mesothelioma *(5)*. The route of drug administration has changed. Chemotherapy is given intraperitoneally, or by combined IP and intravenous routes. Also, a change in timing has occurred in that chemotherapy begins in the operating room and may be continued for the first 5 postoperative days. Last, the selection criteria for treatment of abdominal and pelvic malignancy have changed. With the nonaggressive peritoneal surface malignancies as an exception, the lesion size of peritoneal implants is of crucial importance. Only patients with small IP tumor nodules that have a limited distribution within the abdomen and pelvis are likely to show prolonged benefit.

Complete cytoreductive surgery is necessary before the IP chemotherapy instillation, and this is unlikely for advanced sarcomatosis or carcinomatosis. However, as much as it is possible, normal peritoneum is not resected; only parietal or visceral surfaces visibly involved by cancer are removed. Aggressive treatment strategies for an advanced and invasive IP malignancy will not produce long-term benefits and is often the cause of excessive morbidity or mortality. Treatments to prevent the occurrence of or to eradicate established seeding must be initiated as early as possible in the natural history of these diseases to achieve the greatest benefits. In some patients the cytoreduction and IP chemotherapy should be considered with the management of the primary cancer.

Intraoperative IP hyperthermic chemotherapy is used in the operating room. The large volume of chemotherapy solution required to administer the IP hyperthermic chemotherapy removes tissue debris and blood products from the abdominal cavity to minimize fibrin entrapment of cancer cells. The chemotherapy not only directly destroys tumor cells but also eliminates viable platelets, neutrophils, and monocytes from the peritoneal cavity. This diminishes the promotion of tumor growth associated with the wound healing process.

Heat is part of the optimizing process and is used to bring as much dose intensity to the abdominal and pelvic surfaces as possible. Hyperthermia with IP chemotherapy has several advantages. First, heat by itself has more toxicity for cancerous tissue than for normal tissue. This predominant effect on cancer increases as the vascularity of the malignancy decreases. Second, hyperthermia increases the penetration of chemotherapy into tissues. As tissues soften in response to heat, the elevated interstitial pressure of a tumor mass may decrease and allow improved drug penetration. Third, and probably most important, heat increases the cytotoxicity of selected chemotherapy agents. This synergism occurs only at the interface of heat and body tissue at the peritoneal surface.

3. TECHNIQUE

The open abdominal technique of delivering the IP hyperthermic chemotherapy at the time of surgery has also been referred to as the "Coliseum technique" *(6)*. After the cancer resection is complete, a Tenckhoff catheter and closed suction drains are placed through the abdominal wall and made watertight with a purse-string suture at the skin. Temperature probes are secured to the skin edge. Using a long-running #2 monofilament suture, the skin edges are secured to the self-retaining Thompson retractor. A plastic sheet is incorporated into these sutures to create a covering for the abdominal cavity. A slit in the plastic cover is made to allow the surgeon's double-gloved hand access to the abdomen and pelvis (Fig. 1). During the 90-min perfusion, all the anatomic structures within the peritoneal cavity are uniformly exposed to heat and to chemotherapy. The surgeon gently, but continuously, manipulates all viscera to

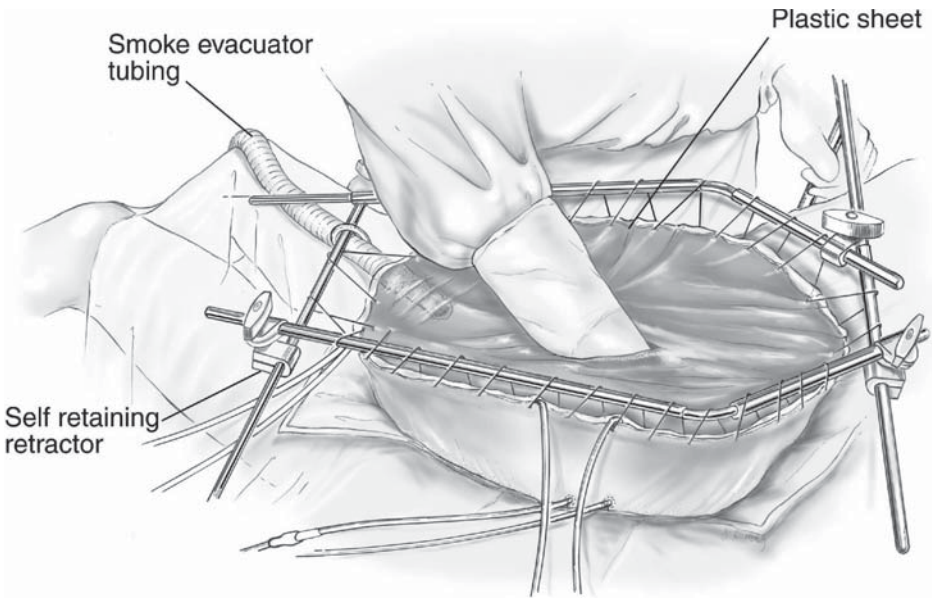

Fig. 1. Set-up for the Coliseum technique.

keep adherence of peritoneal surfaces to a minimum. Roller pumps force the chemotherapy solution into the abdomen through the Tenckhoff catheter and pull it out through the four drains. A heat exchanger keeps the infusing fluid at 44°C–46°C so that the IP fluid is maintained at 42°C–43°C. A smoke evacuator is used to pull air from beneath the plastic cover through activated charcoal, reducing the potential for contamination (by chemotherapy aerosols) of air in the operating room.

After the intraoperative perfusion is complete, the abdomen is suctioned dry of fluid. The abdomen is then reopened, the retractors are repositioned, and reconstructive surgery is performed. It should, again, be emphasized that no suture lines are constructed until after the chemotherapy perfusion is complete. One exception to this rule is closure of the vaginal cuff to prevent leakage of IP chemotherapy solution.

4. ADVANTAGES OF THE OPEN "COLISEUM TECHNIQUE"

Having access to the entire abdomen and pelvis during the IP perfusion ensures that the surgeon will have adequate treatment with heat and chemotherapy of every abdominopelvic region, and also prevents excessive heating of normal tissue that can exacerbate postoperative ileus and increase the incidence of postoperative perforation or fistula formation. In addition, the open method provides an access to sample the perfusate and measure concentrations of the chemotherapeutic solution. It is also possible to sample tumor nodules

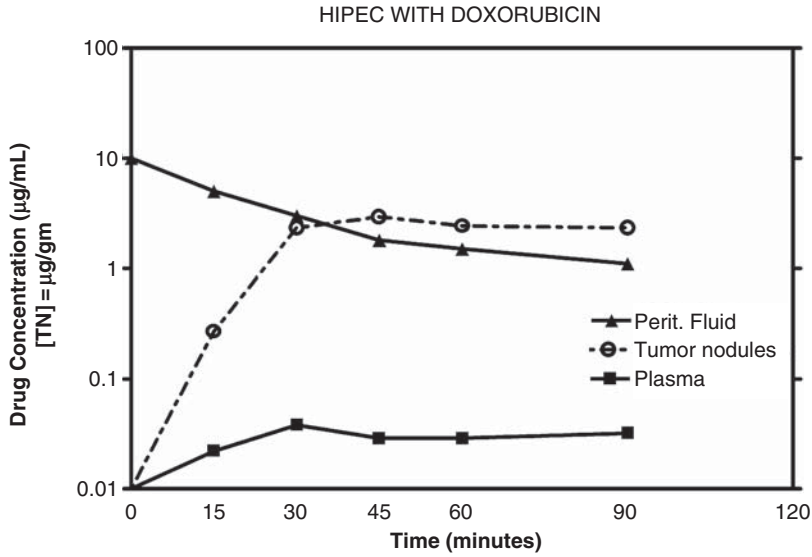

Fig. 2. Concentration/time curve for HIPEC doxorubicin in perfusate, serum and tumor.

throughout the 90 min or 120 min, and then determine the concentration of the chemotherapeutic agent in the tumor nodules (Fig. 2). Another advantage is that in the event of bleeding during the IP perfusion, the volume in the abdomen can be decreased quite rapidly by decreasing the rate of the inflow and keeping more fluid in the reservoir. This maneuver will assist in identifying and controlling the bleeding site.

5. POTENTIAL DISADVANTAGES

Having an open abdomen during the IP hyperthermic chemotherapeutic perfusion leads to heat dissipation and makes it harder to achieve a uniform hyperthermia throughout the entire 90 min–120 min, particularly if higher temperatures are desired.

Another disadvantage when compared to the closed method is the potential exposure of the operating room personnel to the chemotherapeutic agents. Because the surgeon is required to manipulate the viscera, increased potential also exists for contact exposure. The heated chemotherapy can aerosolize, creating a potential inhalational exposure. Sugarbaker and colleagues *(7)* evaluated the safety of the operating room personnel. Urine from members of the operating team was assayed for chemotherapy levels. Air was sampled proximal to the operative field and levels were measured. Finally, sterile gloves commonly used in the operating room were examined for permeability to chemotherapy. All assessments of potential exposures were found to be in compliance with established safety standards. Thus, the theoretic risk of exposure of the

operating team to chemotherapy during the open "coliseum technique" has not been substantiated.

6. PERITONEAL CAVITY EXPANDER

To expand the volume of the peritoneal cavity and facilitate distribution of the perfusate, Fujimura developed a technique of using a peritoneal cavity expander *(8)*. The expander is composed of a cylinder made of acrylic that contains inflow and outflow catheters that are secured over the wound. The cylinder fills with the perfusate as it is instilled into the peritoneal cavity, allowing the small bowel to float freely. This technique has been used by several researchers in Japan and South Korea *(8–12)*. Disadvantages were reported by Elias *(13)*, who found oozing around the wound and tumor recurrences inside the parietal wound that had not been treated because of the presence of the expander.

7. CLOSED TECHNIQUE

The use of a closed technique has been reported by many different centers *(14–22)*. Although the same basic principles are involved, many clinicians have used their own adaptations of the essential inflow and outflow tubing, a heat exchanger, and a roller pump. At the University of Louisville, we use a modified heat exchange pump, Thermochem™ HT-1000 machine (Thermasolutions, Inc., Pittsburgh, PA), which is supplied with all the necessary accessories and is presently used in 22 centers in the United States and 2 in Europe (Fig. 3).

7.1. Procedure

The procedure for the closed technique is demonstrated on the DVD. After induction of anesthesia, a urethral catheter with a heat-sensor probe is placed in the bladder (Precision 400; Tyco Healthcare Group, Mansfield, MA) and the anesthesiologist places an esophageal heat sensor (DeRoyal, Powell, TN). After the initial draping of the chest and legs, a large sterile Ioban™-2 adhesive drape (3M Corp., St. Paul, MN) (Fig. 4) is placed over the entire operative area, extending laterally beyond the anterior superior iliac spine, midaxillary line on each side. One hour before completion of surgery, the patient's core temperature is gradually lowered to about 34°C, as assessed by the bladder and esophageal probes, by turning the warming blanket off and lowering the air temperature in the operating room.

Upon completion of debulking surgery, the patient is readied for IP hyperthermic chemotherapy. Two inflow tubes are placed, one above the right lobe of the liver with a temperature probe attached to the tip and the other in the left upper quadrant (Figs. 5 and 6).

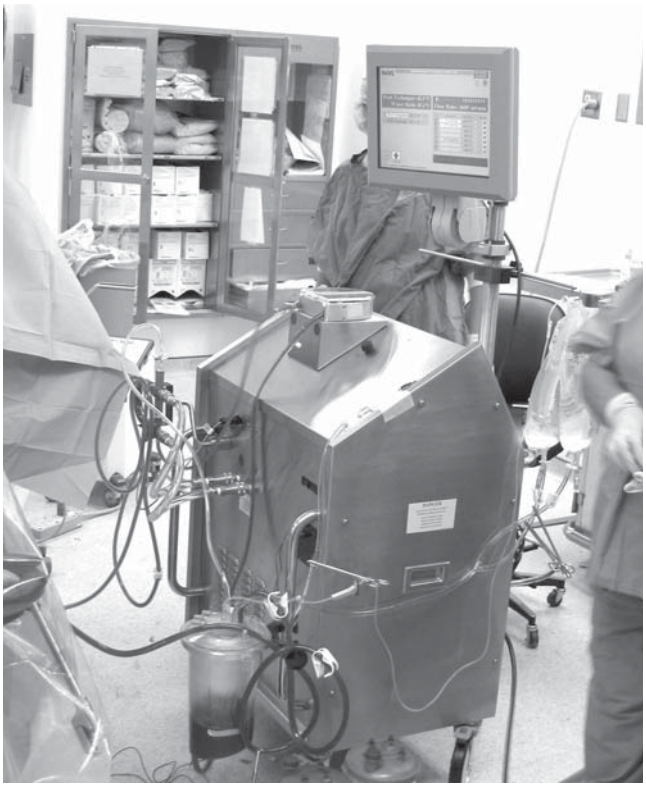

Fig. 3. ThermoChem HT1000.

Two outflow tubes are placed one on either side of the pelvic floor, with a temperature probe connected to the end of one (Figs. 7 and 8).

Before skin closure, the surgeon must ensure that the inflow and outflow tubes are correctly placed. The outflow tubing is laid at the back of the abdomen, behind the small bowel, and the single connecting tube is brought out in the upper abdomen (Fig. 9). The skin of the abdominal incision is closed using a free Richard-Allan 2090-1 3/8″ needle connected to a 96″ PDS #1 loop (Ethicon, Inc., Somerville, NJ) in a running, "baseball" fashion. Care is taken to ensure that the skin edges are not inverted and that the skin is tightly apposed around the tubing (Figs. 10 and 11).

Approximately 30 min before placement of the tubing, the perfusionist prepares the Thermochem™ HT-1000 modified heat-exchange pump (Thermasolutions, Inc., Pittsburgh, PA). With the wound closed, the inflow and outflow tubing is connected, and the preheated Deflex™ peritoneal dialysis solution (Fresenius Medical Care, Lexington, MA) is allowed to fill the cavity (Fig. 12).

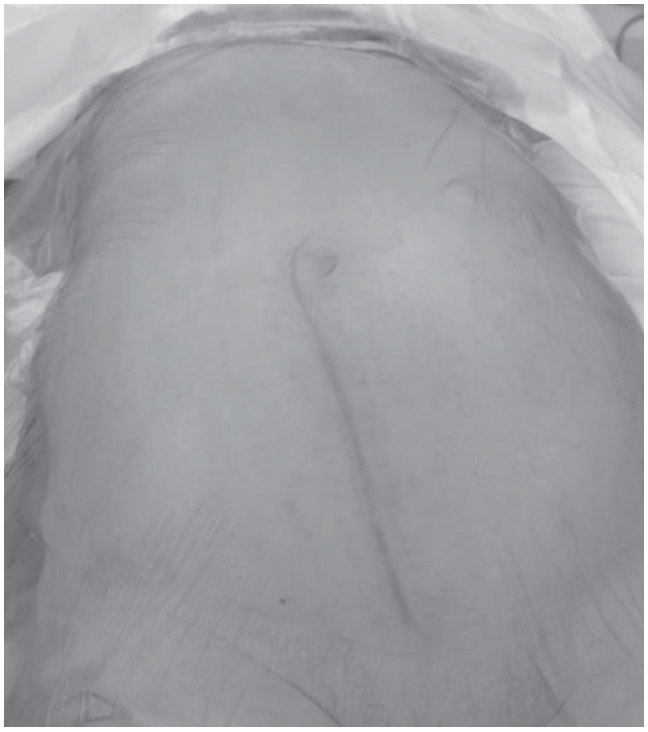

Fig. 4. Adhesive drape placed over the operative field.

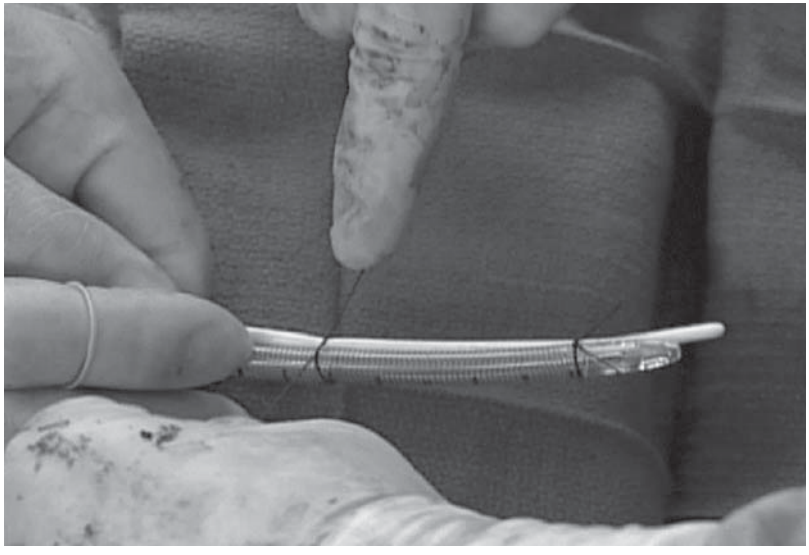

Fig. 5. Inflow catheter with temperature probe being attached.

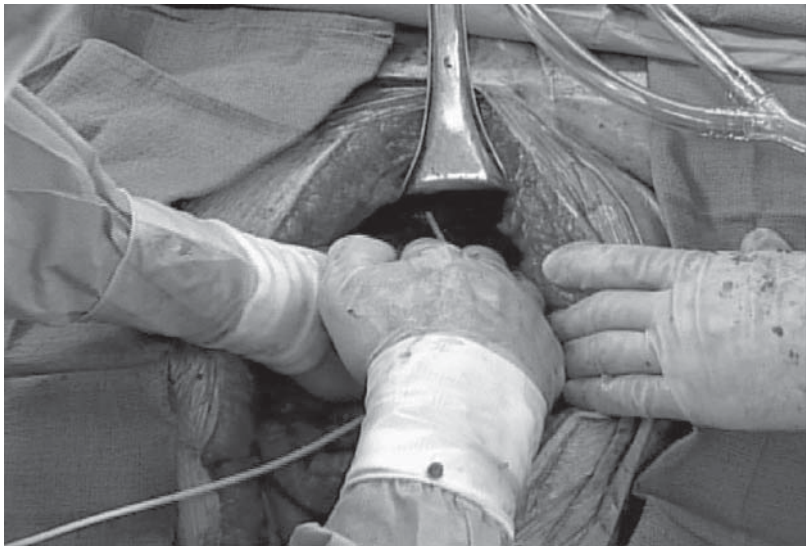

Fig. 6. Inflow catheter being placed above right lobe of liver.

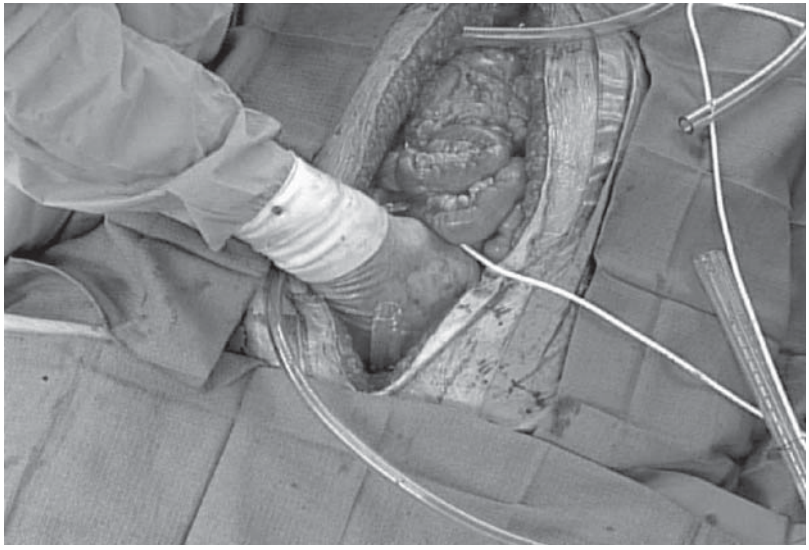

Fig. 7. Outflow catheter being assessed for placement in pelvis.

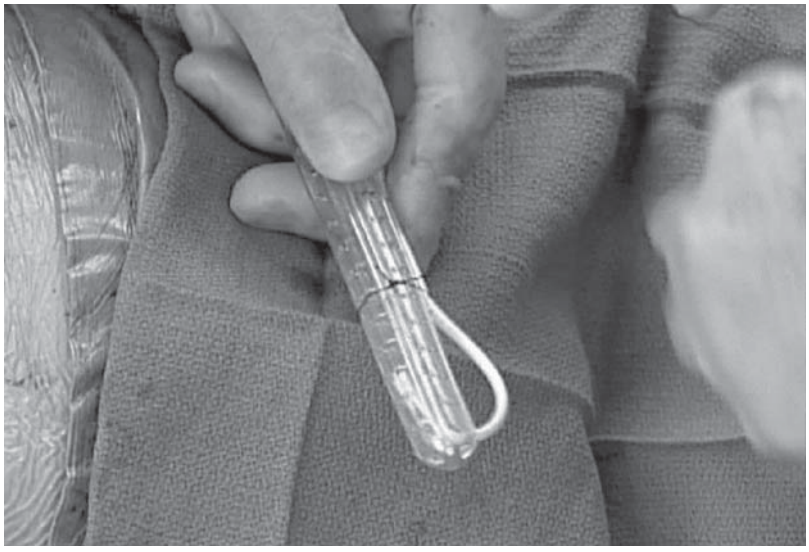

Fig. 8. Temperature probe attached to outflow tubing.

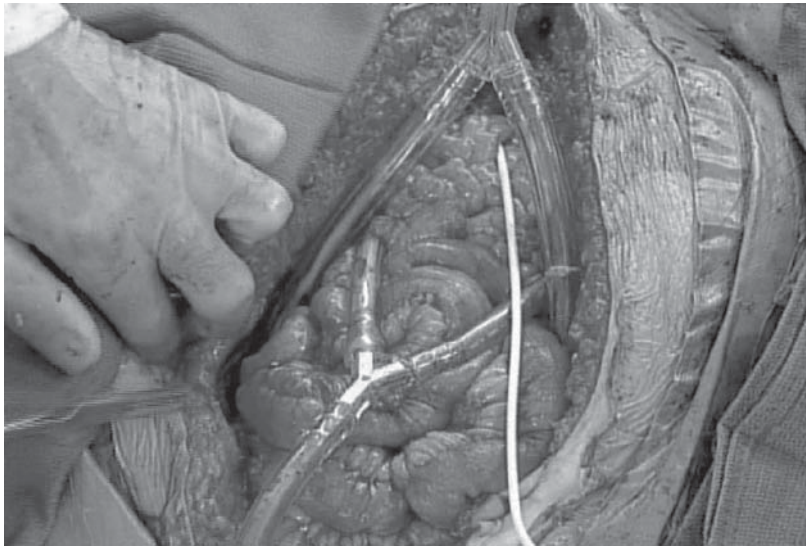

Fig. 9. Layout of tubing before skin closure.

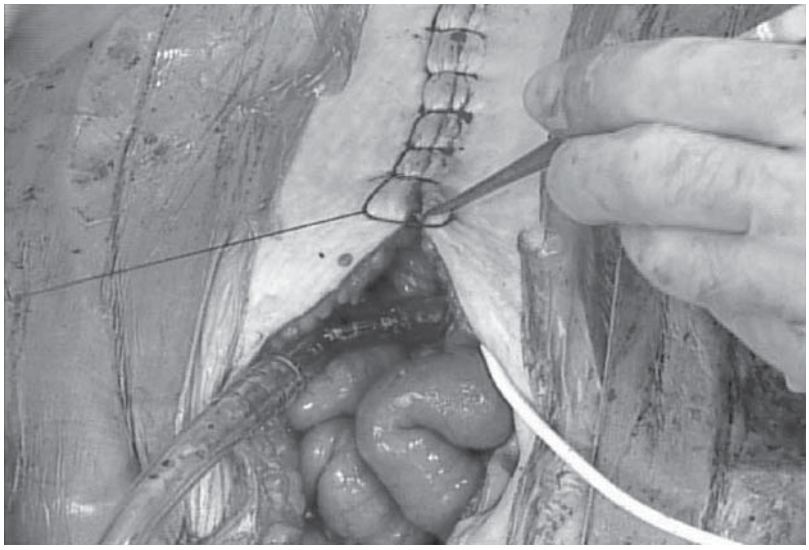

Fig. 10. Closure of the skin, ensuring dermis approximated.

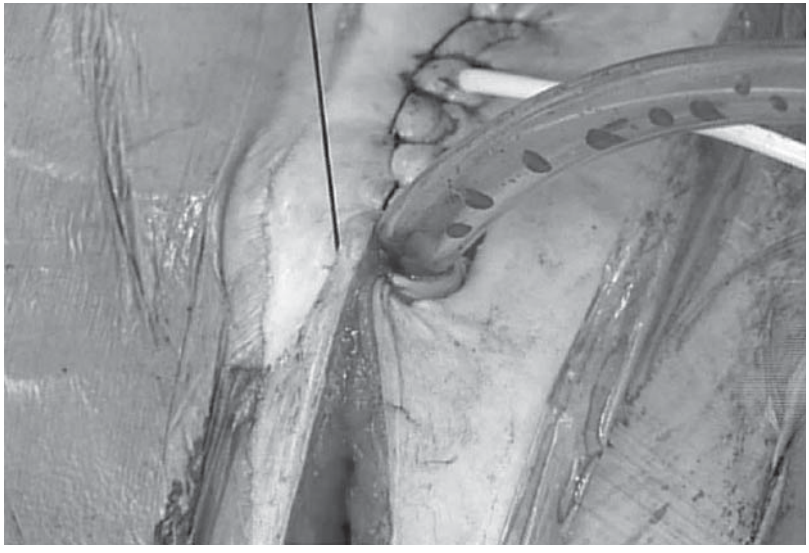

Fig. 11. Closure of skin, ensuring snug fit around tubing.

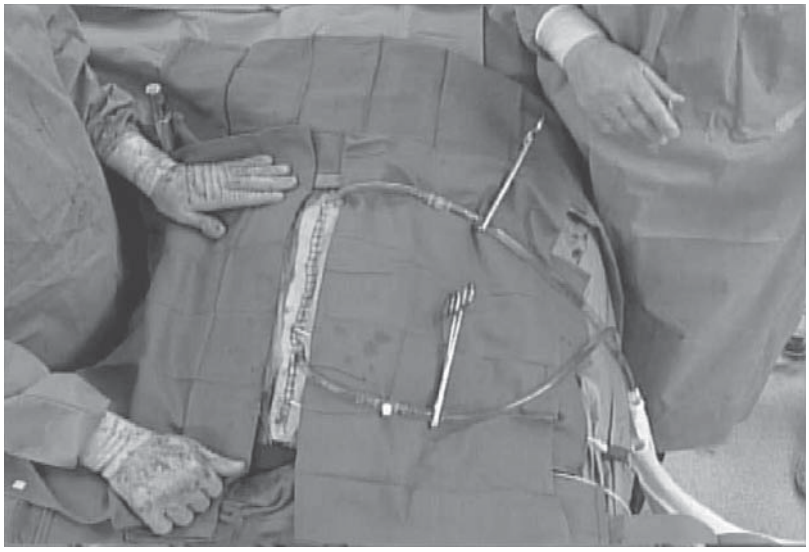

Fig. 12. Skin closed and connections made.

While this is happening, the patient is placed in steep Trendelenberg to allow air to be expelled through the outflow tubing. Usually, 2–3 L is required to distend the cavity and achieve a flow rate of approximately 1,500 cc/min. The patient can be leveled once equilibrium is reached. When the temperature probes show a consistent inflow temperature of approximately 43°C and outflow of approximately 42°C (Fig. 13) the chemotherapy agent is added to the perfusate. The perfusion is allowed to circulate within the abdominal cavity for 90 min, with an assistant on each side of the patient gently kneading the abdomen to ensure good distribution. Care is taken to watch for leakages, and these are secured with sutures of 0 polyglactin 910 (Vicryl; Ethicon Inc., Somerville, NJ).

At the completion of perfusion, the perfusate is drained into the waste container attached to the Thermochem™ HT-1000 machine. The abdomen is carefully opened, with a disposable sump sucker at the ready to aspirate residual fluid. The abdomen and pelvis are gently irrigated with 2–3 L of saline to wash away any residual chemotherapy agent and avoid contamination during the remainder of the procedure. All contaminated instruments and tubing are passed off and placed in dangerous substance containers. Gowns and gloves are changed and the surgery is completed.

Postoperatively, patients are routinely followed in the Intensive Care Unit, and attempts made to maintain a urine output of at least 100 mL/hr for the first 72 hrs.

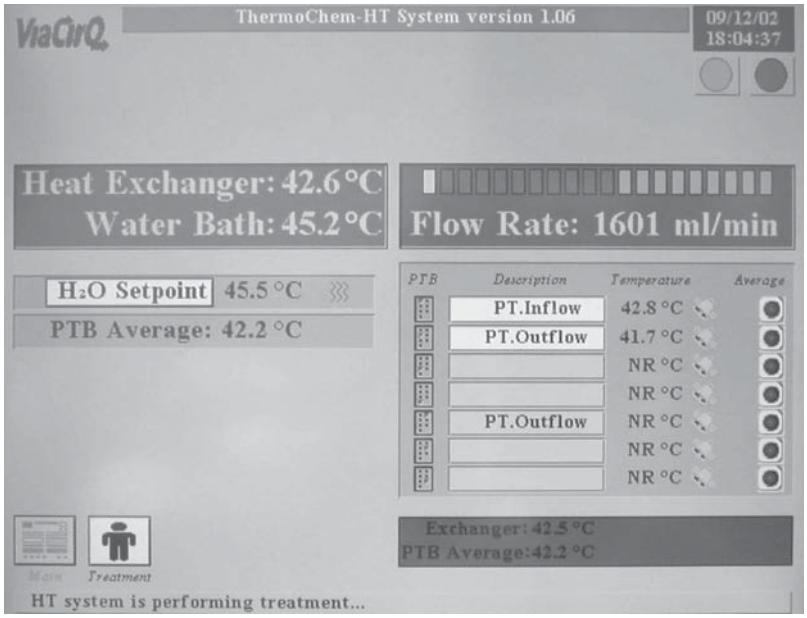

Fig. 13. Monitor gives real-time temperature and flow-rate information.

7.2. Advantages of the Closed Technique

The principal advantage of the closed technique is that the potential for environmental contamination with chemotherapy agents is greatly diminished over the open technique, and there is less opportunity for heat loss anteriorly, allowing the appropriate IP temperature to be reached faster and maintained more easily. By closing the skin while leaving the fascia open, better flow and distribution of perfusate is achieved.

In some centers, the HIPEC procedure is performed after completion of the entire surgical phase, with inflow and outflow tubes inserted through the abdominal wall before the final closure of the laparotomy incision. At the completion of the perfusion, the tubing is removed and anesthesia can be reversed. This saves the need for reopening of the abdomen, completion of anastomoses, and final closure. However, many surgeons are not comfortable with performing bowel anastomoses before HIPEC.

7.3 Potential Disadvantages

The disadvantage of the closed technique is that there may be less uniform distribution of perfusate throughout the peritoneal cavity. Theoretically, this

could lead to reduced exposure to both chemotherapy agents and heat in some areas of the abdomen, but no study has shown a difference in outcome between the two methods *(13,23)*.

There is some concern for exposure of localized areas, particularly the bowel, to higher temperatures, with these "hot spots" having the potential for tissue damage resulting in impaired wound and anastomotic healing *(24)*. However, provided the maximum inflow temperature is kept well below 44°C and sufficient volume of perfusate is used to achieve expansion of the cavity and maintenance of a sufficiently high flow volume (500–1,500 mL/min), this should not be a problem.

Because efficacy, morbidity, and mortality using a closed technique are equivalent to the open technique, its ease of performance and the reduced risk of environmental contamination make it a valuable method.

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12 Future Directions in the Delivery of Hyperthermic Intraperitoneal Chemotherapy

Scott Richard, MD, and
Robert P. Edwards, MD

Summary

Although striking evidence exists that argues for the usefulness of hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis (PC), many aspects of this therapy have yet to be standardized. As interest in this modality increases, there are several avenues of research to be explored. How important is the cytoreductive effort, the temperature elevation increment, and the length of time for the hyperthermic perfusion? We review what is known and what may be explored in the near future.

Key Words: Hyperthermic intraperitoneal chemotherapy; future directions; IP delivery methods.

1. THERAPEUTIC AGENTS

Most of the current studies published on HIPEC use cisplatin or mitomycin C as the agents infused during surgery. Although there are compelling data about the effectiveness of both these compounds, recent studies have looked at other agents that may be useful in HIPEC. By exploring different agents, or combinations of agents, we hope to find alternatives for patients that present with platinum-refractory disease and to decrease the side effects noted with cisplatin and mitomycin C.

2. CARBOPLATIN

Carboplatin is an analog of cisplatin, which has been shown in multiple studies to have less nonhematologic toxicity. Although myelosuppression continues as a main toxicity, carboplatin has been shown to decrease nephrotoxicity, neurotoxicity, and emetogenesis compared with cisplatin *(1)*. Initial

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traditional intravenous studies compared cisplatin and carboplatin in suboptimally debulked ovarian cancers and suggested that there was equivalent activity between these two compounds *(1,2)*. In 2003, Ozols published the results of Gynecologic Oncology Group (GOG) 158, which was a large multicenter trial for optimally resected stage III ovarian cancer patients. This noninferiority study concluded that carboplatin plus paclitaxel was as effective in the treatment of optimally resected ovarian cancer as the previous standard of care, cisplatin/paclitaxel *(3)*. Based on this study, as well as two European studies, carboplatin/paclitaxel became the standard of therapy for ovarian cancer in the United States. Because of the superior toxicity profile, ease of use, and reduced toxicity, most infusion centers had switched to outpatient carboplatin infusion for ovarian cancer in the mid-1990s.

The use of HIPEC with carboplatin has been used little in published studies, especially in comparison to cisplatin. Cisplatin and carboplatin have been compared in the presence of hyperthermia in a rat tumor model. Intratumor platinum concentrations were notably higher in the cisplatin rat models at 37°C and 41°C compared with carboplatin, but both were shown to have increased cytotoxicity with the increase in temperature *(4)*. Additionally, hematologic toxicity of carboplatin and cisplatin were similar when combined with hyperthermia in another rat tumor model *(5)*. To date, there is a dearth of published studies in patients with carcinomatosis comparing carboplatin and cisplatin. A phase I study by Steller (see Chapter 10) evaluated the feasibility, toxicity, and pharmacokinetics of carboplatin administered by HIPEC in small-volume ovarian cancer patients *(6)*. Six patients underwent optimal cytoreductive procedures as initial treatment for stage II/III epithelial ovarian cancer (EOC). During a 90-min perfusion, carboplatin infusions were performed at 41°C–43°C. There was wide variability of the dose absorbed into the systemic circulation, ranging from 27%–77%, but 5 of the 6 patients absorbed >50% of the drug dose systemically. Systemic toxicities, particularly myelosuppression, were significant, which is an indirect reflection of substantial systemic absorption. Based on this data, it would appear carboplatin is not an ideal choice for IP therapy because of the high rate of systemic exposure and resulting toxicities, but head-to-head comparisons with cisplatin have not been reported.

3. TAXANES

Since the publication of GOG 111 in 1996, normothermic intravenous paclitaxel with a platinum agent has been the standard of care for the front-line treatment of ovarian carcinoma, with response rates of between 60% and 80% *(7)*. Two studies have looked at paclitaxel and thermal enhancement. Rietbroek showed that paclitaxel exposed to two different murine tumor cell lines at 41°C and 43°C showed no enhancement of cytotoxicity when compared to a

nonhyperthermia control *(8)*. These findings were confirmed with a mouse fibrosarcoma cell line *(9)*.

Docetaxel, which is a semisynthetically produced agent of the taxane family, has been shown to have similar activity to paclitaxel in both solid tumor and leukemic cell lines *(10,11)*. Unlike paclitaxel, docetaxel has been shown to have some thermal enhancement. Moderate hyperthermia demonstrated a decreased tumor growth time in a fibrosarcoma cell line, and at higher doses, was shown to have the greatest decrease when compared to four additional agents *(8)*. Additional studies have shown that the reduction in tumor growth time with hyperthermic docetaxel was time dependent, where greater decrease in growth time was seen at 90 min exposure compared to 30 min exposure *(12)*.

A recent study of 19 patients has reviewed the role of HIPEC and docetaxel for second-line treatment for persistent ovarian cancer after systemic chemotherapy. Patients treated with this regimen had a high rate of wound complications, but very little hematologic toxicity. Three-year survival rate was 63% *(13)*. This study suggests a role for docetaxel for HIPEC in recurrent ovarian cancer patients, and possibly for other solid tumors of the abdomen.

4. OXALIPLATIN

This is a third-generation platinum derivative that has increasingly become part of the standard systemic therapy for colorectal cancer, although it is currently only being used in phase I and II trials for ovarian cancer. It has a similar mechanism of action to cisplatin, but with a different side-effect profile, primarily, no renal or hepatic toxicity *(14)*. In vitro studies performed on a murine tumor cell line have shown that oxaliplatin with HIPEC increased cytotoxicity by 180% compared with normothermic controls *(15)*.

A recent phase III trial of oxaliplatin with HIPEC in colorectal carcinomatosis has indicated promising results. Twenty-four patients diagnosed with colorectal peritoneal carcinomatosis underwent CRS to a volume of disease consistent with CCR-0 (microscopic disease) or CCR-1 (tumor <2.5 mm), followed by HIPEC and oxaliplatin. Two-year survival data was noted to be 74% in this patient population, with a 32% peritoneal recurrence rate *(16)*. Comparing this study to one by Witkamp, where HIPEC and mitomycin C in 29 colorectal patients showed a 2-yr survival of 45% *(17)*, oxaliplatin would seem to be a better choice to effect long-term survival. The use of oxaliplatin in HIPEC should be studied further in randomized trials, particularly for ovarian cancer.

5. TOPOTECAN

Topotecan as a second- or third-line agent for recurrent ovarian cancer has had modest success when given systemically. Recent studies have looked at the efficacy of administering IP topotecan. Fifteen ovarian cancer patients treated

with IP topotecan in a dose-escalating fashion were found to have few hematologic toxicities, while achieving systemic cytotoxic levels with few complications *(18)*. No current studies have explored the role of thermal enhancement on topotecan when exposed to solid tumor cell lines.

6. DOXIL

Liposomal encapsulation of doxorubicin (Doxil™) has been utilized for the treatment of EOC systemically as a second-line agent, with an approximately 30% response rate in platinum-refractory disease. Use of liposomally encapsulated agents via an IP or an HIPEC route has been limited because of concerns about the inability for appropriate tissue penetration of the drug into tumor tissue. In vitro studies suggest that hyperthermia increases the release of doxorubicin from encapsulated liposomes, as well as increasing its cytotoxic effect *(19)*. Additional studies have confirmed these findings in a murine model *(20)*. Phase I and II studies using peritoneal dosing with liposomal doxorubicin, with and without hyperthermia, would seem to be warranted for PC.

Newer encapsulations with temperature-sensitive liposomes have increased interest in this modality for drug delivery. These thermally sensitive liposomes show increased level of drug release with mild hyperthermia (39°C–40°C) and moderate hyperthermia (43°C) when compared with free and traditional encapsulated doxorubicin *(21)*. This would suggest a potential use for liposomally encapsulated doxorubicin in HIPEC. Additionally, if liposomal encapsulation of other chemotherapy agents can be engineered, they may have enhanced uptake into tumor cells, with increased cytotoxicity. Thus, future studies with liposomal encapsulated agents, such as cathepsins, are warranted.

7. IRINOTECAN

Irinotecan is an inhibitor of topoisomerase I, which has been used as a component for the systemic treatment of advanced colorectal cancer. Mohamed recently studied the effect of hyperthermia on tumor cell growth for irinotecan *(12)*. A slight increase in tumor cell growth time was noted with this agent, which was further increased when oxaliplatin was used in addition to the irinotecan *(8)*. Use of irinotecan as a single agent in HIPEC may be limited as a front-line agent because of impressive results with platinum compounds and mitomycin C for colorectal cancer, but its use as a second-line agent may be explored in future studies.

8. MULTIPLE AGENTS AT TIME OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Tumor cell biology warrants the use of concurrent agents to minimize the phenomena of drug resistance. Solid tumors are derived from a multitude of

clonal variants with different mutations and patterns of resistance. After several cycles of chemotherapy, clinical response may occur, but at the expense of selecting for clonal lines with intrinsic drug resistance. Several first-line treatments for solid tumors of the abdomen include multiple drug regimens, in the hopes of decreasing the production of intrinsic drug resistance and obtaining a complete clinical response.

Multiple drug regimens at the time of HIPEC are of interest. Factors that should be considered include potential drug–drug incompatibility when mixed in the HIPEC perfusate, increased toxicity of multiple agents during HIPEC, and the increase in operative time and HIPEC time if two or more agents are used to treat carcinomatosis. Currently, there are no studies published that explore simultaneous use of two agents during HIPEC for ovarian carcinoma. If future studies show docetaxel and platinum agents to be compatible with simultaneous infusion in the peritoneum, then phase II trials with HIPEC for ovarian cancer patients should be explored.

Simultaneous use of two agents for the treatment of colorectal carcinoma using HIPEC is relatively uncommon. Elias reported on a pharmacokinetics trial using standard-dose oxaliplatin and escalating doses of irinotecan with HIPEC at 43°C *(22)*. Irinotecan levels in tissue were noted to be 16–23 times higher than in nonbathed tissues, while having no effect on the oxaliplatin concentration in these tissues. Interestingly, they reported a 58% rate of grade 3–4 hematologic toxicity, which is higher than seen with oxaliplatin alone in HIPEC *(22)*. Long-term survival information for the 39 patients studied in this project are unavailable, but may warrant a phase III trial of oxaliplatin vs oxaliplatin plus irinotecan with HIPEC.

Several HIPEC studies involving colorectal patients utilize perioperative infusions with 5-fluorouracil (5-FU) and leucovorin. These drugs are components of the systemic therapy for colorectal cancer, but 5-FU has shown no increased cytotoxicity with hyperthermia *(23)*. These same principles can potentially be used during HIPEC treatments for ovarian cancers, with IV paclitaxel given during the perioperative period to see if greater long-term response rates occur.

9. TEMPERATURE

The chaotic vasculature of solid tumors results in areas of hypoperfusion and, subsequently, regions of relatively low pH and hypoxia that are not seen in normal tissue *(24)*. Studies of hyperthermia alone have shown increased tumoricidal effect with increasing temperature, with a decrease in the time of exposure needed for equivalent cell kill *(25)*. Additionally, increasing temperatures to 42°C–43°C sensitizes tumor cells to chemotherapy drugs by increasing vascular permeability of the tumor cells, and increasing the intratumor drug

concentrations. Currently, most clinical studies utilizing HIPEC employ infusion temperatures between 40°C and 42°C, with perfusion time of 60 min–100 min. Various morbidities have been reported, such as tissue swelling, bleeding, discomfort, pain, and systemic toxicities *(26,27)*. Most of these side effects are noted to be temporary, and decreased with the use of newer standardized heating devices for HIPEC.

Increased temperature of the perfusate during HIPEC would theoretically increase the cytotoxic effect of the chemotherapy. Rietbroek looked at the effect of increasing temperature for the platinum agents cisplatin and oxaliplatin in vitro. By increasing the temperature from 37°C to 41°C, an increased cytotoxic effect was noted. By further increasing the temperature from 41°C to 43°C, a small, but not statistically significant, increase in cytotoxicity was shown *(14)*. Additional studies are warranted to compare the effect of increased temperature on cytotoxic effect for individual agents, while also comparing the potential side effects of increased temperature on human subjects. The technique for the measurement of temperature levels in the abdomen is variable between centers. Some investigators report the temperature of the perfusate as it exits the outflow cannula and enters the intake cannula. Others place temperature probes in the peritoneum and measure actual tissue temperatures at various points in the abdominal cavity. Peripheral body or core temperature is usually actively cooled before the initiation of hyperthermic infusion to relieve the effects on hot peritoneal tissues.

10. DWELL TIME

Currently, there is no standardization of the time necessary for adequate cell kill during HIPEC. Most studies have looked at times of exposure between 60 min and 100 min. Underexposure of the cancer cells to the perfusate would allow for increased survival of cells, whereas over exposure would increase the harmful effects associated with the hyperthermic chemotherapy, including burn-like symptoms, tissue edema, delayed return of bowel function, and nephrotoxicity. Some clinicians dose chemotherapy at multiple time points during the infusion to maintain high IP drug levels and replace chemotherapy that has diffused out of the hyperthermic circuit and into the body. It is felt that molecularly larger compounds are more likely to be retained in the peritoneal cavity and produce fewer systemic side effects, but may also have reduced tumor penetration. Future studies should therefore look at time of exposure during HIPEC to disease-free survival.

11. TIMING OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

There has been a general belief that much of the toxicity seen with HIPEC is caused by the extensive debulking that precedes the procedure. If the HIPEC

could be planned as an interval treatment preceded by neoadjuvant chemotherapy, there may be a theoretical benefit in reduction of morbidity because of a reduced need for extensive cytoreduction. Ovarian cancer would seem to be an ideal disease in which to attempt to address this issue, as over 75% of patients demonstrate initial complete clinical responses after primary therapy. A randomized assessment of hyperthermic chemotherapy perfusion at the time of primary debulking vs at the completion of systemic therapy could be performed to evaluate the relative toxicity and efficacy of each approach. Studies such as this are less applicable in other tumor sites because of the reduced efficacy seen with systemic therapy for patients with abdominal carcinomatosis.

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