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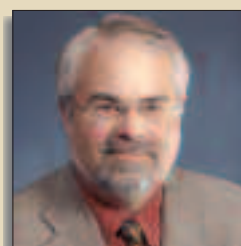
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# Advanced Colorectal Cancer: Consensus Group Recommends Heated Chemotherapy after Surgery, but Other Experts Disagree, Citing Need for Phase III Data

By Paul Watson

**A** consensus statement signed by the Peritoneal Surface Malignancies Group (PSMG), a collection of 72 national and international surgical oncologists from 14 countries, concluded that delivering heated chemotherapy into the peritoneal cavity following cytoreductive surgery may significantly increase the life expectancy of some Stage IV colorectal cancer patients.

"Intravenous chemotherapy alone is not beneficial for all patients with Stage IV colorectal cancer," the lead author of the statement, Jesus Esquivel, MD, Director of the Peritoneal Surface Malignancy Program at St. Agnes Healthcare in Baltimore, said in an interview. "There is a subset of patients

*Hyperthermic intraperitoneal chemotherapy (HIPEC) is a procedure in which the abdomen is bathed in conventional chemotherapy heated to such a high degree that it kills tumor cells.*

whose colon cancer has spread inside the abdomen who can benefit from surgical intervention with hyperthermic

intraperitoneal chemotherapy."

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a procedure in which the abdomen is bathed in conventional chemotherapy heated to such a high degree that it kills tumor cells. The consensus statement was published online ahead of print in *Annals of Surgical Oncology*.

The Peritoneal Surface Malignancies Group, which included doctors from 31 US Medical Centers, wrote the consensus statement after reviewing several clinical studies on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, the paper explained. The group concluded that the ideal candidates for this surgical procedure were patients with Stage IV colorectal cancer confined to the abdomen with no evidence of hematogenous

spread.

"A large international group of physicians with extensive experience in treating patients with peritoneal carcinomatosis have now formed a consensus opinion that colorectal cancer patients with low-volume peritoneal involvement should be considered for surgical debulking and HIPEC," the second author, Robert P Sticca, MD, Chairman, Program Director, and Professor in the Department of Surgery at the University of North Dakota School of Medicine and Health Sciences, said in an interview.

"There is now enough evidence to indicate that this treatment is beneficial to this select group of patients and can be curative in a small percentage. Other treatments for this problem have been  
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## Vanderbilt-AZ

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processes.

Carlos L. Arteaga, MD, Vice Chancellor's Chair in Breast Cancer Research and Director of Vanderbilt-Ingram's Specialized Program of Research Excellence (SPORE) in Breast Cancer, is the center's scientific point person.

"My job is to harness the best intellect of the center, he said during a telephone interview. "I think this is going to be a very productive collaboration. It's just like marriage; we just have to ride it as we go. Right now our only limits are our own creativity or joint ideas."

### Still an Experiment

He described the relationship as an experiment, noting that it would be interesting to see how process-oriented companies would work with more flexible academic researchers. He stressed the importance of constant communications, saying that he would have to make sure that his investigators know about the arrangement and can think about how to work within the research constraints of the company. There would be two scientific meetings a year between the center and the company, he added.

"Right now I'm proposing a major research project dealing with hormone-dependent breast cancer. It's the kind of thing I wouldn't do unless I knew they'd fund it. I would only do it if I knew I had a very strong partner. This is the kind of thing I wouldn't even bother talking to NCI about. They don't

have the money to support this."

Dr. Arteaga said that this type of agreement had been incubating for about five years, and was born out of an encounter at a cancer seminar hosted by AstraZeneca, where he and others began talking about scientific alliances between high-profile companies and academic centers of excellence to investigate working together in areas of common interest scientifically that would eventually fit the marketing plans of the companies.

"It took a while," he said. "We had several meetings and went back and forth with legal agreements, but the timing had to do with the fact that AZ has a lot of drugs for which there are no clear biomarkers and many possible combinations of drugs."

### Fits with Comment by NCI Director

This relationship was also described generally by NCI Director John E. Niederhuber, MD, as "our partners in industry," when he said that pharmaceutical and biotech companies would want help finding biomarkers (*OT*, 11/25/06) from NCI and academic centers.

AstraZeneca has already entered into collaborative agreements with NCI, and for the past two years, industry has been invited to attend the SPORE Investigators' Workshops.

"I don't think we entered into this agreement for money reasons," Dr. Arteaga said.

"We did it because strategically it was the right programmatic thing to do. We weren't thinking of money or lack of money—that didn't register at all."

The alliance is built on mutual respect, he said, noting that AstraZeneca came to Vanderbilt-Ingram since they thought they would be the right research partner.



**Carlos L. Arteaga, MD, Vanderbilt-Ingram's scientific point person, described his job as harnessing the best intellect of the center. "I think this is going to be a very productive collaboration. It's just like marriage; we just have to ride it as we go. Right now our only limits are our own creativity or joint ideas."**

"Our ultimate goal is to shorten the time to approval of more effective new drugs and new combinations, so in the end patients win," he said.

AstraZeneca's Mr. Strand concurred. "Our overall goal is to smooth

interaction between scientists," he said. "We have a very strong pipeline of potential new drugs that will help cancer patients, but we need to learn things about those drugs to know what patient populations they'll work in, and which patients are most likely to benefit in some way.

"We can't do that completely on our own," he continued. "We need to collaborate to be successful, and there are really key centers we need to work with. We foster a lot of scientific interchange and have science days where we share data and this can lead to project proposals coming out. So we end up doing more science with them than we would have done otherwise."

The cultural differences between project- and brand-focused industry and intellectually independent academic researchers have traditionally caused trust issues.

"One of the things this alliance has accomplished tremendously has been to help build respect for each other, and knowing that trust, integrity, and quality of the science is really important helps build stronger interactions so we become someone they think of first when they have an idea," Mr. Strand said.

The goal is the scientific partnership, he said.

"Science is the driver. We've gotten very positive feedback from our partners regarding our ability to integrate business and science aspects together, and with these master agreements we can address the administrative, legal, and intellectual property issues, and get on doing good science."

## HIPEC

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found to be ineffective, with almost all patients eventually succumbing to the disease."

The statement also noted that a surgical oncologist experienced in cytoreductive surgery and HIPEC should evaluate Stage IV colorectal cancer patients to determine if they are eligible for the procedure.

"Ideal candidates have a small amount of disease in the peritoneal cavity without any evidence of metastases in other locations," Dr. Sticca said. "All gross disease must be able to be removed surgically.

*"There is now enough evidence to indicate that this treatment is beneficial to this select group of patients and can be curative in a small percentage. Other treatments for this problem have been found to be ineffective, with almost all patients eventually succumbing to the disease."*

"These criteria can be extended to other categories of tumors, although depending on the type of tumor, the evidence may or may not be as well documented. HIPEC has been proven to be effective in appendiceal malignancies and is curative in most cases of low-grade mucinous tumors of the appendix, or pseudomyxoma peritonei."

### HIPEC & Systemic Therapy

"We are trying to convince American oncologists that HIPEC will be an adjunct to intravenous chemotherapy," Dr. Esquivel said. "HIPEC is not trying to replace systemic therapy."

"Systemic therapy has improved tremendously in the last five or six years. For 40 years there was nothing but 5-FU. At that time, patients with Stage IV colon cancer were looking at a 12-month median survival. With the new systemic therapies, median survival is up to 26 months—a tremendous improvement. That doesn't mean, however, that every patient who is Stage IV should receive systemic therapy."

Such is the case for patients with peritoneal surface malignancies.

"For example, if a tumor is in the liver, that means that it got there through the bloodstream," Dr. Esquivel said. "For that type of a tumor, sys-

temic therapy is very advantageous. But if the tumor is on the liver, meaning it's just sitting on top of the liver, it is very difficult for any drug given intravenously to reach that particular tumor."

### Ostensible Benefits

HIPEC enables physicians to deliver higher doses of chemotherapy directly to the abdominal cavity. "With HIPEC, we can give a concentration of chemotherapy that is approximately 30 to 50 times higher than intravenous chemotherapy," Dr. Esquivel said.

"Obviously, if that concentration of the drug were delivered through the bloodstream it would get everywhere and be highly toxic."

According to Dr. Esquivel, heated chemotherapy is ideal for localized therapy.

"We know that heat is cytotoxic and that it makes chemotherapy more powerful. By itself, heat can kill cancer cells when it is between 40°C and 44°C. Also, heat softens up the tumor nodule so that penetration of intraperitoneal chemotherapy into the tumor nodule is augmented. So, from a conceptual standpoint, it just makes sense that HIPEC is the way to go."

"Other forms of therapy, such as chemotherapy, do not penetrate into the peritoneal cavity very well and are therefore ineffective," Dr. Sticca noted.

"HIPEC allows the surgeon to give much higher doses of chemotherapy directly into the peritoneal cavity without significant toxicity. In addition the heat potentiates the chemotherapy, and heat itself can help in killing cancer cells. The additive effects of these components of the treatment increase the efficacy of the treatment and make cure possible in a disease that was previously considered to be uniformly fatal."

### Genesis of the Statement

"For some odd reason this technique has failed to blossom," Dr. Esquivel remarked. "Part of the problem was that all of these institutions were reporting on a small number of patients



**Jesus Esquivel, MD: "For some odd reason this technique has failed to blossom. Part of the problem was that all of these institutions were reporting on a small number of patients here, a small number of patents there. One institution would do it this way and another would do it that way. There was no uniform way to perform this technique or report on what we were doing....We are trying to convince American oncologists that HIPEC will be an adjunct to intravenous chemotherapy. HIPEC is not trying to replace systemic therapy. Systemic therapy has improved tremendously in the last five or six years. For 40 years there was nothing but 5-FU. At that time, patients with Stage IV colon cancer were looking at a 12-month median survival. With the new systemic therapies, median survival is up to 26 months—a tremendous improvement. That doesn't mean, however, that every patient who is Stage IV should receive systemic therapy."**

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As a result, Dr. Esquivel decided to e-mail his fellow peritoneal surface malignancy surgeons and form the PSMG. The group's first meeting was held in January at the first International Symposium on Regional Cancer Therapies in Snowmass, CO. At that time, the group reviewed and discussed surgical options in the management of peritoneal surface malignancies of colonic origin with representatives from the major peritoneal surface malignancy centers from around the world.

*Robert Sticca, MD: "A large prospective randomized clinical trial would be optimal in demonstrating the absolute efficacy of the treatment, but unfortunately this type of trial—patients randomized to HIPEC or systemic chemotherapy—is probably not possible. It would be very difficult and probably not ethical to randomize patients to no surgery and HIPEC when there is evidence that indicates that there is substantial benefit to this treatment."*

A follow-up meeting, held in March at the Society of Surgical Oncology Annual Meeting in San Diego, found the group agreeing on a registry database sheet using the Peritoneal Cancer Index as a scoring system.

"I then opened up the discussion to even more institutions via e-mail," Dr. Esquivel noted. "Finally, after gathering together all the information, and with everyone's approval, we presented the consensus statement."

### Reviewing the Literature

The group reached its conclusion after conducting a literature review of the most recent studies on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (using mitomycin C or mitomycin C plus oxaliplatin) in the treatment of patients with Stage IV colorectal cancer with peritoneal carcinomatosis.

These patients underwent cytoreductive surgery, which included peritonectomy procedures to remove all visible tumors, followed by HIPEC, which involved a sterile solution heated to 42°C (107.6°F), and mitomycin C continuously circulated throughout the abdominal cavity for up to two hours.

The literature review involved nine international studies, an international registry of 506 patients from 28 institutions, and one single-institution Phase III randomized study with 105 patients. The nine studies showed a three-year survival rate of 25% to 58%, and a five-year survival rate of 11% to 32%.

The registry showed an overall median survival rate of 19.2 months, with a three-year survival rate of 39% and a five-year survival rate of 19%. In the Phase III study, the median survival rate for the chemotherapy-arm was 12.6 months vs 22.3 months for the patients in the HIPEC arm.

After reviewing the literature, the consensus group further concluded that cytoreductive surgery combined with HIPEC (using mitomycin C) followed by postoperative systemic chemotherapy resulted in a median survival of up to 42 months when a complete cytoreduction was achieved.

Although the literature review concentrated on HIPEC with mitomycin C, the group members noted that HIPEC with oxaliplatin also showed promising results.

### A Controversial Consensus

Not all experts, however, believe that surgical oncologists should immediately begin performing hyperthermic intraperitoneal chemotherapy and cytoreductive surgery based on the findings of this consensus statement.

"A group of believers arriving at a consensus is not exactly persuasive.

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## HIPEC

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Data are persuasive," said Robert J. Mayer, MD, Professor of Medicine at Harvard Medical School and Director of the Center for Gastrointestinal Oncology at Dana-Farber Cancer Institute.

"Everything that we've learned in the treatment of breast cancer, colon cancer, and lung cancer has come from prospectively defined clinical trials using informed consent and some sort of a randomized variable. That's not the situation here. What you really want to do is a proper, Phase III multi-institutional study showing that this procedure works. And if it works, everybody will buy into it."



**Robert J. Mayer, MD: "A group of believers arriving at a consensus is not exactly persuasive. Data are persuasive. Everything that we've learned in the treatment of breast cancer, colon cancer, and lung cancer has come from prospectively defined clinical trials using informed consent and some sort of a randomized variable. That's not the situation here. What you really want to do is a proper, Phase III multi-institutional study showing that this procedure works. And if it works, everybody will buy into it."**

"I agree 100 percent," Dr. Esquivel responded when told what Dr. Mayer said. "HIPEC has been around for a long time, at least 20 years, and indeed it has not been accepted by many for a number of reasons.

"Our strategy is to first get all the surgeons involved in this particular treatment modality to perform the operation as similarly as possible, to document the amount of carcinomatosis before and after the procedure in a standard fashion, and then to report outcomes in a similar way. This consensus statement is just the beginning and I agree that we need a Phase III trial to put this issue to rest."

Dr. Sticca added that a large prospective randomized clinical trial would be optimal in demonstrating the

*"One of the major benefits of this consensus statement has been to get the majority of the physicians, in the US and Europe, who use this treatment to come together and begin sharing data and techniques for patients afflicted with this type of cancer. With this consensus as a start, I believe that there will be clinical trials in the near future incorporating this treatment into the appropriate subset of patients with peritoneal carcinomatosis."*

absolute efficacy of the treatment. "Unfortunately, though," he said, "this type of trial—patients randomized to HIPEC or systemic chemotherapy—is probably not possible. It would be very difficult and probably not ethical to randomize patients to no surgery and HIPEC when there is evidence that indicates that there is substantial benefit to this treatment.

"I do not think patients would agree to this randomization. Trials have been proposed for HIPEC but unfortunately have not been funded by the NCI.

"One of the major benefits of this consensus statement has been to get the majority of the physicians, in the US and Europe, who use this treatment to come together and begin sharing data and techniques for patients afflicted with this type of cancer," Dr. Sticca continued.

"With this consensus as a start, I believe that there will be clinical trials in the near future incorporating this treatment into the appropriate subset of patients with peritoneal carcinomatosis."

Although Dr. Mayer did not dispute the expertise of the physicians who signed Dr. Esquivel's consensus statement, calling them "technically extraordinary surgeons," he said he still believed that a Phase III trial should be done before surgical oncologists begin rigorously applying this procedure to Stage IV colon cancer patients around the nation.

"Fifteen years ago, there was a tremendous belief among many surgical oncologists that high-dose chemotherapy with the re-infusion of autologous hematopoietic stem cells would prove beneficial, and potentially life-saving, in women with advanced breast cancer after their initial diagnosis and surgery," said Dr. Mayer, a member of OT's Editorial Board. "There were even people who felt it immoral not to perform this procedure.

"As it turns out, after a lot of frayed nerves and disagreements, several randomized trials were conducted that showed there was no added advantage. Eventually the breast cancer world moved on to something else and nobody does this procedure anymore."

According to Dr. Esquivel, however, cytoreduction surgery and HIPEC has already become the standard of care for treating patients with appendiceal cancer.

"Medical oncologists recognize that systemic therapy doesn't do much for appendix cancer," he said. "If you search the Internet on appendix cancer you will find an incredible amount of information about HIPEC, as well as patients warning other patients not to get systemic therapy. And if you have appendix cancer you are going to find a way to get to a center like ours."

It was this very fact that caused Dr. Mayer to question whether members of the PSMG were reluctant to pursue a Phase III trial owing to the business incentives of specializing in HIPEC therapy.

"I don't want to sound cynical, but this procedure is a very large source of patient referrals as well as a mechanism by which hospitals stay busy," Dr. Mayer said.

"I believe all of us using this therapy are confident in its benefits," Dr. Sticca said. "All of the surgeons in the group are very busy surgical oncologists and would continue to be busy without these procedures. Most do not do this procedure exclusively.

"In fact, the reimbursement for these cases is poor compared with other surgical oncology procedures. The pre- and postoperative care is extensive and time consuming. The surgeons who perform these procedures believe in, and have seen the benefits of, this treatment and continue to provide it to their unfortunate patients who usually do not have many other options."

He added that treating such patients with systemic chemotherapy is usually ineffective, as well as highly toxic. "Most of these patients eventually succumb to their disease after many months of chemotherapy and experience a poor quality of life," he said.

"We are all interested in the science behind the proper treatment of patients with carcinomatosis from colon cancer," Dr. Esquivel said. "We are intellectually honest and at the present time we are working on developing a Phase III trial in which patients would be randomized to best systemic therapy versus cytoreduction and HIPEC followed by best systemic therapy."

In the meantime, Dr. Esquivel said

he believed that the consensus statement would have a galvanizing effect on the surgical community, thereby leading to a Phase III trial.

### Major Centers Missing

Notably absent from the consensus statement were the names of major North American cancer centers. "This implies that there are those who have not accepted this premise at this point," Dr. Mayer said.

Dr. Sticca said that yes, there are some major cancer centers in the US that have not accepted this treatment option in the management of peritoneal carcinomatosis.

Still, "the number of centers performing this treatment grows every year," he said. "As more publications enter the literature and the evidence grows in favor of HIPEC, I believe most large multidisciplinary cancer programs will be using this therapy for peritoneal carcinomatosis patients.

"It was not long ago that this therapy was considered almost heretical by the established oncology community. As the oncology community has seen some of these patients experience long-term survival, and in some cases cure, more and more are becoming believers."

*The consensus statement by the Peritoneal Surface Malignancies Group, a collection of 72 national and international surgical oncologists from 14 countries, concluded that delivering heated chemotherapy into the peritoneal cavity following cytoreductive surgery may significantly increase the life expectancy of some Stage IV colorectal cancer patients.*

He explained that as with most forms of therapy for any illness, the key is proper selection of patients who will benefit from the therapy. "With increasing cooperation among surgeons who perform this therapy, the appropriate patients and techniques of treatment will be better defined and HIPEC will become a standard of care," he said.

Although Dr. Esquivel conceded the point that few North American cancer centers signed on to the consensus statement, he said he did not agree that these centers inherently disagreed with

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**ASTRO** *Annual Meeting*  
AMERICAN SOCIETY FOR THERAPEUTIC  
RADIOLOGY AND ONCOLOGY

## Adding Radiation Extends Survival Time for N2 NSCLC Patients

By Charlene Laino

**P**HILADELPHIA—Adding radiation following surgery and adjuvant chemotherapy can extend survival in patients with non-small-cell lung cancer (NSCLC) with N2 disease, researchers reported in a plenary study at the ASTRO Annual Meeting here.

However, both radiation and chemotherapy are deleterious to NSCLC

patients with no lymph node involvement, said the chief investigator, Jean-Yves Douillard, MD, PhD, Professor and Head of the Department of Medical Oncology at Centre René Gauducheau in Nantes, France, reporting a new

analysis of data from the Adjuvant Navelbine-Cisplatin Chemotherapy versus Observation (ANITA 1) study.

“We should tell patients with N0 disease that, after surgery, they can go home and they do not need radiation or

chemotherapy. Patients with N1 disease should be given chemotherapy, or radiation only if chemotherapy is contraindicated. Patients with N2 disease should be given adjuvant chemotherapy.”  
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### HIPEC

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the group’s assessment.

“In fact, Memorial Sloan-Kettering Cancer Center and Johns Hopkins have recently visited St. Agnes and are in the process of doing their first case on cytoreductive surgery and HIPEC,” he said.

“Believe me, I am the biggest proponent for a Phase III trial, especially in this era of improving systemic therapy. I just want to make sure that we do it the right way. But as we know, 90 percent is in the planning and 10 percent in the execution. We are still in the planning phase.”

Dr. Mayer said that the very fact that so many institutions could agree to sign the statement means that there are a sufficient number of technically able people to carry out a Phase III trial. “They have a marvelous opportunity to prove once and for all to every doubter and to every skeptic that this approach is valid. And if their premise turns out to be valid, everybody benefits.”

### Conclusion

Despite the controversy, Dr. Esquivel said he remains upbeat about the future of treating Stage IV colorectal cancer patients.

“In the past, patients with incurable disease would not be candidates for surgery,” he said. “But those days are gone. I think that surgery is making a comeback and will play a role in these particular patients. We’re now trying to make colorectal cancer a chronic condition. So even if you cannot cure the patient you can prolong meaningful lifetime with new methods.”

And his feeling is that the major cancer centers are gradually coming around. As evidence, he noted that for the first time ever there will be a symposium dedicated to Peritoneal Surface Malignancies at the next Society of Surgical Oncology Annual Meeting in March.

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