

Treatments for Rare and Complex Cancers

March 25, 2009 from St. Joseph's Hospital and Marshfield Clinic in Marshfield, WI

Welcome to this "OR-Live" webcast presentation from Saint Joseph's Hospital and Marshfield Clinic in Marshfield, Wisconsin. During the program it's easy for you to make referrals or request more information. Just click on the buttons on your screen and open the door to informed medical care. "OR-live," the vision of improving health.

Welcome. We are coming to you to live his evening from Saint Joseph's Hospital and Marshfield Clinic in Marshfield, Wisconsin. I'm Dr. William Hocking, a medical oncologist and hematologist at Marshfield Clinic and moderator for tonight's program.

The focus of our program this evening will be on two rare and challenging cases. As you can see on this slide, we will be talking about hepatocellular carcinoma, an unresectable case, and a procedure used to treat that called "trans-catheter arterial chemoembolization." The second patient we will be talking about has a peritoneal mesothelioma. And we will talk about a procedure called "surgical debulking" or "cytoreduction" and "hyperthermic intraperitoneal chemotherapy." Both of these patients will be presented in some detail a little bit later in the program.

The treatments that we're talking about are what we call "combined modality therapies" because they use different treatment approaches for the same patient, and we find that that often enhances the effectiveness of a treatment. The patient's that we are talking about this evening, as you can see on this slide, are patients in whom cure is not likely with our currently-available therapies.

The goals of treatment in this situation include control of symptoms, prolongation of life, and prevention of complications related to the cancer. When treating a patient in a palliative care setting, one of the things that is most important is avoiding risk of excessive toxicities. Patients must be -- the risk of the toxicity must be carefully balanced against the potential to do harm to the patient and the benefit that they receive from the therapy.

Before we go on with further discussion of these patients, I'd like to tell you a little more about the cancer center and our cancer program. Marshfield Clinic has been a clinical community oncology program, sponsored by the National Cancer Institute for more than 25 years. And along with Saint Joseph's Hospital, we provide comprehensive cancer care services, including programs such as stem cell transplantation and have more than a hundred clinical trials available at any time for our patients, really bringing them state-of-the-art care. We see more than 3500 new oncology and hematology patients annually throughout our system, and many of those patients are referred here to Marshfield for tertiary care where we serve as a referral center for central and northern Wisconsin, a largely rural part of the state of Wisconsin.

Now let me talk a little bit about on the next slide some of the features of the two patients that we will be discussing this evening. The two cases share some common features. Both of these are, as we've alluded to are rare cancers, and we'll elaborate on what we mean by "rare cancers" a little bit later. And both of these cases are patients that have no curative treatment in the setting of advanced, more advanced stages of disease. Both of the patients that we'll be talking about this evening have local regional extent of disease as opposed to more widespread disease, but still are considered to be incurable based on currently available therapies. The fact that the disease is localized, however, allows the

application of certain treatments directed at these local areas of disease, and you'll hear more about that as the program goes on.

There are some other aspects of managing rare cancers that are outlined on this slide. One of the issues that we deal with is that randomized trials, which really set the standards for care in cancer, are generally not available for patients with these rare cancers due to the difficulty of conducting those kinds of trials in rare diseases. And as a result, fewer treatments have been established to provide to patients with rare cancers, and therapies are often likely to be based on personal or anecdotal experiences or single-arm studies.

Now let me introduce the members of our expert panel that are with us this evening, starting with Dr. Seth Fagbemi medical oncologist and hematologist at Marshfield Clinic and Saint Joseph's Hospital. He will, in a little bit, be giving us an overview of hepatocellular carcinoma and mesothelioma, and will be doing a presentation of the two patients that we'll be talking about this evening.

Next to Dr. Fagbemi is Dr. Kristin Gerndt, also at Marshfield Clinic and Saint Joseph's Hospital, an interventional radiologist and an expert in procedures designed the treat cancers locally. She will be talking specifically this evening about trans-hepatic arterial chemoembolization with our first patient.

And finally, Dr. Sanjoy Saha, surgical oncologist at Marshfield Clinic and Saint Joseph's Hospital. Dr. Saha will be showing us, later in the program a very complex procedure, the surgical debulking and hyperthermic intraperitoneal chemotherapy for our second patient this evening. So let me now turn the program over to Dr. Fagbemi, who will introduce and tell us a little more about hepatocellular carcinoma in the first patient that we will be discussing.

Thank you, Dr. Hocking. Our first case is a patient with hepatocellular carcinoma. I will give a brief overview of this condition. It's an uncommon condition, both in the United States of America and well as worldwide, but incidents worldwide is actually much higher because of a number of factors. In the United States, if the year 2008, the estimated number of cases, new cases was 8,500, while worldwide, about 50,000 new cases had been identified. It's a disease that is more common in males.

There are some risk factors that have been identified as predisposing to develop into hepatocellular carcinoma. The identification of this risk factors actually helps if defining what kind of preventive strategies can be instituted as well as screening to make sure that patients are seen at the stage where they can be better treated.

These factors include an underlying liver dysfunction as a result of viral hepatitis, particularly Hepatitis B and Hepatitis C. Also, any form of chronic disease from the alcoholism related in cirrhosis can also lead to developing into hepatocellular carcinoma. A genetic condition called "hematochromatosis" is also one in which once it's identified, prevention of liver disease as a result of this is useful in helping prevent hepatocellular carcinoma developing in those patients. In some parts of Africa, some toxins such as aflatoxins, which have been identified as related to the development of hepatocellular carcinoma.

The diagnoses of any malignancy, and hepatocellular carcinoma is not an exception, is based on biopsy. But to decide on which patients need to be biopsied, a number of things will be need to be done, such as an appropriate history, a well-done physical examination, as well as a directed set of laboratory studies. These studies have particular relevance to

hepatocellular carcinoma is one that measures the level of hepatic protein, as well as levels of the baseline liver function of any patient. Of course, in directing such a biopsy, radiology tech tests are very helpful, including an ultrasound, a CT scan, sometimes an MRI or MRE or angiography that defines the vascular structure of the liver that would be helpful in those patients that end up having such procedures as will be defined later today, as well as the PE CT scan to identify whether or not this patient has a widespread pattern of disease.

The treatment options would be dependent on the stage of the patient at presentation, the nature of the patient's background liver function, as well as other health conditions in these patients that affect the ability of the patient to tolerate treatments. For those patients who are found early and who have disease limited to the liver, the surgical option is preferred. For those that have regionally advanced disease, an option that is appropriate is the one that will be described by Dr. Gerndt later today. And for those in whom the disease is outside the liver, more widespread, we offer systemic therapy.

In this instance we recognize that these treatments are palliative in nature, where we afford longer life or the relief of symptoms. The agents are not very edifications, which affects the ability to use them. Where they are sometimes helpful, as lieu of agents include hormonal treatments such as Tamoxifen or megestrol acetate. We have a variety of conventional cytotoxic agents including doxorubicin or cisplatin or fluorouracil, as well as more recently, targeted agents such as sorafenib or the bevacizumab. These agents are sometimes offered, either solely, or in various combinations for patients.

Our patient this evening is a 55-year-old male whose past medical history is of hypertension, diabetes mellitus, coronary artery disease, and prostatic hypertrophy. It was an elevation of his hypertension that resulted in the identification of his liver lesions. He had an MRI done, and the MRI showed multiple liver lesions. At the time, the rest of his examination was defined as unremarkable. A biopsy of one of the lesions was performed and it was consistent with hepatocellular carcinoma. Because of the pattern of distribution of the masses in his liver, the patient was considered not a candidate for primary surgical intervention; however because of the fact that the lesions were limited the to the liver, the original therapy was recommended to the patient.

Thank you very much, Dr. Fagbemi. Before we go onto talk more about this patient, let me just ask you to comment a little bit and maybe put in context what we mean by "a rare cancer," since we're talking about rare cancers this evening and how that might compare to some more common cancers like lung cancer or breast cancer.

Thank you. The hepatocellular carcinoma has the U.S. incidents of 8,500 estimated for 2008. Let us compare that to the most common cancer in the country by incidents, which is lung cancer, where for that same year, the estimated incidents is 220,000 new cases, or breast and prostate cancer, that would be responsible for 180-plus new cases a year or colon cancer, 150,000 new cases. So by comparison, 8,500 is quite low, yeah.

Yeah. And that points out some of the difficulty in doing studies to determine the optimum treatments when you really don't have a very large number of cases. Let me also just ask our viewing audience that if you have questions as the program proceeds, we're glad to try to address those, and you can send them to us by clicking on the "ask a question" button on your computer screen, and they will be sent to us. And we'll try to get to any of the questions that come in if possible during the hour. Now let me reintroduce Dr. Gerndt, who is going to continue to tell us the story of this first gentleman and how he was treated. Dr. Gerndt.

Thank you, Dr. Hocking. This gentleman presented and had extensive disease that could not be addressed with surgical resection. In that scenario, we evaluated whether we could do regional therapy for him to try and control the disease and extend lifespan. As Dr. Hocking already mentioned, with regional cancer therapy you need to keep in mind that occult disease outside the area that you're treating could be present and will not be affected by the treatment you're offering.

The regional-image-guided modalities that are currently available are listed on this slide. Chemoembolization is what we'll see today, and that involves injecting chemoembolic material into the hepatic arterial circulation while sparing the portal circulation. Radiofrequency ablation and cryoablation are both local methods that use heat in the case of radiofrequency ablation and cold in the place of cryoablation to kill tissues. They can be used in other organs besides the liver.

Chemoembolization and radioembolization are both limited to use in the liver. Radioembolization is similar to chemoembolization in some ways but does not involve chemotherapy. It involves small particles, which are impregnated with yttrium-90 radioactive material. So they combine arterial occlusion with localized radiation therapy that has very limited permeation. The chemoembolization is performed by mixing standard chemotherapeutic drugs with a medication called "ethiodol," which is an oil-based contrast derived from poppy seed oil. That is administered into the artery feeding the area that you wish to treat. The treatment is usually performed in a lobar fashion or treating about half the liver at a time to minimize overall chemical irritation in the liver. This is possible because of the specifics of liver circulation. And basically because tumors tend to be supplied by the artery, whereas as the normal liver is dependent on portal vein flow, this allows us to selectively insult the tumor's blood supply without insulting the normal liver supply to the same degree. It's estimated that this allows between 100 and 125-fold higher dose to the liver tumor than what can be accomplished by IV chemotherapy.

The overall lesser toxicity to the rest of the body is accomplished by getting this medication to the liver and keeping it in the liver so that exposure to heart, bone marrow, skin, and gut is minimized. Side effects like diarrhea, neuropathy, skin changes, and heart toxicity are therefore less than if it was given in the venous form.

This is one image that I'll show you just before we roll the video, which is an arteriogram image from a chemoembolization of this type of tumor but not in this particular patient. I think it illustrates nicely how this material deposits very focally in the lesion and not to the same degree in the background liver, which in this case lists a background of cirrhosis. If we could roll the video clip now we'll watch some footage from this procedure.

This procedure is actually the tenth procedure for this patient. The patients come into our room awake. This procedure is performed with conscious sedation, usually at a level one initially and then deepened to a little bit deeper sedation later in the procedure. The level of sedation is similar to what one might have for a colonoscopy or an ERCP. They are prepping the groin area there. We usually use a femoral-artery approach similar to what would be used for a heart catheterization. Now as you're watching now we're doing the local anesthetic, which is Lidocaine, and stings for just a couple second. The patient at the this point has already had some Versed and some Fentanyl to take the edge off of that sting. We're going to use a 21-gauge needle to puncture the artery, and this is all done through a small incision, which we just made, that will not require sutures or anything more than a band-aid afterwards.

The artery is accessed, and then a small guide wire is placed, and over that guide wire the catheter is then placed, and we change to another guide wire that allows the sheathe placement. These procedures are performed in the angiography suite in OR-compatible room. They take about an hour-and-a-half to two hours per case, depending on whether the anatomy has been defined previously or not. This is the exchange catheter that we're putting in now, and next we'll be changing that for a sheathe, which is what we'll work through for the remainder of the procedure.

At this point, the patient feels some pressure at the leg, but it's generally not particularly uncomfortable. They are relatively awake at this point because one of the first angiographic runs we need to do is imaging the portal vein. For that run they need to hold their breath for about 12 seconds, so they need to be relatively awake at least to be able to follow instructions. Later, when we put in the chemotherapy, we tend to sedate people a little bit more, and they're usually dozing in and out through that part of the procedure.

What we will be doing next here is placing a catheter, and that catheter will be selectively placed in the celiac access origin, which is the blood vessel that supplies branches to the spleen, the stomach, and the liver, as well as small bowel. That imaging is important to lay out the anatomy and a road map, so to speak, so that we know where we need to be going. This particular patient does have some normal variant anatomy, which is fairly common. 25 percent of patients will have some type of normal variant anatomy in terms of their arterial supply to the liver.

On this picture in the right upper quadrant, you see some dark spots, and that's residual material within the liver. This is his celiac access, and you can see the big vessel going off to the right on the screen is a splenic artery. The vessel going to the left is the common hepatic artery, which splits into two vessels, and the smaller of those is the one we're going to treat today.

This run is going to image the splenic artery and the portal vein. The catheter is being moved out now selectively into the splenic artery so that that can be injected. If we image out to the venous phase, then we can pacify the portal vein. The artery will be much more dense at the beginning of this run, and then if you watch into the venous phase you will be able to see contrast sort of wafting across the middle of the image over towards the liver, which is on your left side of the screen. That's the main portal vein with some right and left portal venous branches showing up as well. This patient had a Wiley Paton portal vein. And, again, the two density showing up on the non-subtracted images are the residual chemoembolic material.

This is his right hepatic artery arriving from the superior mesenteric artery, the variant anatomy that he has. This branch was the major feeder to this tumor, supplying about two-thirds of the tumor, and then about one-third of the tumor was supplied by the small branch that we were actually treating at this session.

The previous study that he had in that artery is actually a little bit more elucidating than this one but I'm going to show you a run into that right hepatic artery from the current study, and then we'll flash back to what it looked like before he had his many treatments. The tumor vascularity has changed quite a bit. So this is what it looks like currently, and you can see some abnormal vessels and the tumor, but this is what it looked like before we had gotten very many treatments in.

There's a lot of tumor blush, all the gray blotchy areas that are showing up are tumor. That big round area is all the main tumor mass. And that vascularity has diminished significantly with his previous treatments. He's had five previous treatments to this vessel, and today's

treatment will be the fifth treatment to his left hepatic artery, which is the vessel you're seeing now. That supplied the left or medial aspect of the tumor and has that same grayish tumor blush that we saw with the right.

Those are the monitors that we're looking at while we're doing the procedure, and next we will be moving the catheter super-selectively into the area that we wish to treat. This will be a micro catheter placed inside a five-French catheter. So that allow us to get out farther into these small branches where we with do the treatment. That is the bifurcation of the left hepatic artery shown on the screen there, which is where we're going to do the treatment for this procedure. This is the five-French catheter doing a run and then moving out towards the origin of that left hepatic artery, and now the small micro catheter is being placed into that left hepatic artery near its bifurcation or splitting branch point. Both of these vessels are supplying some branches to the tumor. If only one of them was, we would go out into just one to isolate it.

Now we're going to mix the chemotherapy and the Gelfoam. The first thing that I'll show you is the Gelfoam slurry, which is Gelfoam pledget, which is cut into little pieces and then essentially macerated through a staff caulk to create solution of smaller particles mixed with contrast. We use that to slow down the flow in the vessel that we treat after the treatment is completed. This helps increase the dwell time or the length of exposure to the tumor to the chemotherapy. We don't want to block that vessel completely, we just want to slow the flow.

The ethiodol is being drawn up now, and again that's based on poppy seed oil or derived from poppy seed oil. It has a consistency similar to olive oil. To allow good mixing with that oil-based contrast, the chemotherapy agents are mixed in a solution with similar viscosity, which involves contrast material and sterile water or normal saline.

This is the cisplatin, which is 50 milligrams of cisplatin in this small volume. It's important to have it in a small volume because when we administer the drug we don't want to overwhelm the arterial circulation in which it's being placed because that would increase the systemic exposure. So it's crucial to have these drugs mixed specifically for this procedure in a very small volume.

The doxorubicin will be next, which is red. That, again, is 50 milligrams. For hepatocellular carcinoma I typically use 50 milligrams of each of these drugs. One could use 100 milligrams of either drug or a 50-milligram dose of either drug, but I think it's beneficial to combine them both. These agents will then be mixed via a staff caulk to get them thoroughly and evenly districted in the solution. You have to do this fairly expeditiously because the ethiodol will degrade plastic staff caulks and start to leak, and then you would lose some of the drug. So we load it into smaller syringes for administration through the micro catheter, which is what we're looking at here.

The micro catheter is a three-French catheter, which we don't always need to use, but when we're out in a small branch it is better tolerated than the five-French catheter and allows us to go around more turns and bends.

The material is going to be injected under continuous fluoroscopic observation so that we can see exactly where it's going. It's critical to make sure that there is no backflow into an undesired vessel which would, in this case, potentially expose the gastroduodenal artery feeding the pancreas and the duodenum to the chemotherapy. We want the chemotherapy to go to the liver in the area we're trying to treat, not to any other organ it. In a little while we'll flip forward to the angiographic images showing that material going in.

After the material is in and the small amount of Gelfoam is administered, then that catheter is removed and the sheath is removed. We use a variety of closure devices, which sometimes allow the patient to be up and walking within about 30 minutes.

This is footage from the procedure just showing in a minute here the contrast going in. But I want you to pay attention to a still shot that's coming up very shortly here that will show a lot of black or gray density at the top of the liver. That is after we're done treating, and if you kind of keep that fixture in your head as we go forward, the next shot of the liver will show the smaller amount of material here that was present before we treated today. The stuff that's being put in now is the chemoemulsion mixture and that is being put into that vessel now and will gradually build up in the area of tumor to end with that darker gray appearance that you saw on that still shot just a few moments ago.

So that is basically the gist of the procedure. And at this point, we would take the catheter out after we finish, and the patient would go to a recovery area. The procedures are usually staggered with treatments every three to four weeks to alternating sides of the liver, and the patients are monitored overnight.

Thank you very much, Dr. Gerndt. That's a fascinating presentation. Can you tell us a little bit about how the patient feels after the procedure and over the next few days and few weeks after the treatment.

Sure. During the procedure there can be some abdominal pain, especially when the chemotherapy is being administered. It's usually a deep achy kind of pain and can vary from minimal to a pain requiring narcotics, and we have those available during the procedure to keep that pain well controlled. If it occurs, it usually lasts between two and six hours. Usually that evening or by the following morning, the pain will be pretty much resolved or well controlled with oral medication.

Not everybody gets that pain. And with hepatocellular carcinoma, I have anecdotally noted that those are the patients who tend to have very little pain actually. I don't know if it's related to cirrhotic changes within the liver and decreased innervation, but for whatever reason, they seem to breeze through it relatively speaking. Pretty much everybody does get two weeks of feeling a little bit tired and punky after the procedure though, regardless of whether they have pain or not.

Okay. Any other major complications that you worry about?

Complications that you can have would include complete occlusion of the vessel, with it not reopening, which is very well tolerated usually but does limit your ability to go back. You can get biliary strictures. And in patients who have had previous bile duct surgery such as a Whipple procedure or a sphincterotomy, they're at higher risk for abscess.

Okay. All right. Thank you very much. Let's go back to Dr. Fagbemi, and he is going to tell us a little bit about mesothelioma, and then we'll present the second patient that we're going to discuss this evening.

The next case we're going to be discussing is another uncommon malignancy, malignant mesothelioma. Again, estimated number of new cases for the year 2008 in the United States is 2,200 cases. In this instance, this case is in the plural cavity. Patient presented with an abdominal variety. It's interesting that malignant mesothelioma is experiencing an

increased incidents about the last decade in the United States. A number of factors has been adduced. Exposure in the workplace is probably one of them.

It also is a malignancy where risk factor through development has been identified, particularly asbestos exposure. What also noted is the risk of developing mesothelioma after radiation exposure. The diagnosis of mesothelioma is quite difficult. It's based on inadequate biopsy of a material. The biopsy will be directed by a patient's presentation in terms of symptoms, which will be elucidated in the history, as well as physical examination. Radiology tech tests would direct where to biopsy and what to biopsy. It also helps us to define whether the disease is locally advanced or systemic in nature, and this will include cross-sectional imaging with CT. The PET CT helps to identify disease outside and immediate area of interest.

In deciding what to do to a patient in terms of treatment, what is important is the patient's stage, as well as the pattern of involvement. It is also important to define the patient's ability to tolerate the treatments that are going to be offered.

For patients who present with disease that is local, resection is the option that is recommended, whether it's in the chest or in the abdomen. Sometimes the resection is accompanied by other modalities. Radiation therapy can also be offered to a patient who presents with local disease or locally advanced disease.

For patients who have systemic disease, the only option would be one of palliation using systemic therapy. It is important to know that systemic therapy for mesothelioma is not very efficacious. There are a number of reasons why. One of those reasons is the fact that there is such a paucity of cases that enough experience is difficult to gather in being able to develop an effective type of treatment. Nevertheless, there are a number of agents that are being used and that have some utility, including hormonal agents, again, Tamoxifen or regular cytotoxic chemotherapy such as cisplatin or pemetrexed or doxorubicin. Immune therapy is also sometimes used, or a combination of these agents.

Our patient this evening is a 50-year-old gentleman whose past history was significant for sleep apnea. He was also a smoker but did not have any known asbestos exposure. He presented with a recent history of abdominal distension and abdominal pain. An ultrasound that was done as part of his initial evaluation noted that he had ascites. He underwent a paracentesis of his ascetic fluid, which unfortunately was not diagnostic. Eventually, the gentleman underwent an exploratory laparotomy whereby a number of multiple masses were noted in his abdomen. The pathology report was consistent with mesothelioma. At this point, it was recommended that he undergo the original therapy.

Thank you very much, Dr. Fagbemi. And now we'll introduce Dr. Sanjoy Saha again, surgical oncologist, to talk about his involvement with this patient and describe a very complex and exciting relatively new procedure. Dr. Saha.

Thank you, Dr. Hocking. Thanks for giving me this opportunity. This gentleman was presented to our center with established diagnosis of peritoneal mesothelioma. This disease belongs to a group of diseases called "peritoneal surface malignancy." Peritoneal involvement with the tumor is called "peritoneal surface malignancy." It can arise primarily in the peritoneum in form of primary peritoneal carcinoma or primary mesothelioma of the peritoneum. This peritoneal surface can also be involved due to the other malignancy in the adjacent organ or the different abdominal organs like cancer of the colon, rectum, stomach, ovary, appendix, pancreas sarcoma, and those enumerated in the slide.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy has a treatment modality effective in controlling the disease, which usually has a very dismal outcome. Before I go into the details of the procedure, I would like to talk something about the peritoneum. Peritoneum is a membrane, which covers the inner - it's the inner lining of the abdominal wall and the retro peritoneum, the back of the abdominal cavity, and it also covers the different abdominal organs.

This has got a unique property; that it acts as a barrier to the circulation, and the drugs circulated in the normal circulation have got a limited secretion into the peritoneal cavity, and hence, when you give the chemotherapeutic in the effective concentration in the peritoneal cavity it's not achieved, and these cells thrive.

The other thing is about the hyperthermia, the increases the body temperature, and hyperthermia can be defined as an increase in the temperature of the body beyond the normally found in the body. Elevated temperature may be limited to a local or regional area of the body or it may be systemic involving the entire body.

Now the question is how the hyperthermia utilized in the management of the cancer patients. Hyperthermia has got unique general effect on the body that it has got a selective cytotoxic effect or the killing effect on the cancer cells. Normally the body tissue can tolerate the temperature up to 45 degrees Celsius without have any major problems and issues with that. But cancer cells cannot tolerate that temperature, and we take advantage of this uniqueness.

It also potentiates the effect of other treatment modalities utilizing the cancer treatment like radiation and chemotherapy. Specifically, with the chemotherapy, as we are going to test this, it increases the penetration of chemotherapeutic drug into the cancerous tissue. That's one thing. Second, not only it increases the concentration in the tissue but it also allows the increased concentration in the cells itself because of the increase in the permeability of the membranes of the cells. It also inhibits the repair mechanism of these cancer cells, which they utilize to escape the toxic effect or the kill effect of the chemotherapeutic drug. So in general, in totality, it increases the -- it potentiates the cytotoxic or the kill effect of the chemotherapeutic agents.

Besides the effect on the cancer cell itself, the heat also has got effect in the body's circulation itself. Due to the increased heat, the augmentation of the blood flow in the regular tissue because of the way the vasculature is and it helps in the dispersion of the tissues so the effect, the net effect of accumulation of heat in the tissue is not as much. But in cancer tissue, this micro circulation is disorganized, and they do not respond as well to the heat by shunting, and hence, they fail to dissipate this heat, and this heat gets accumulated, and hence, affects the cell killing of the cancer cells.

This gentleman was investigated, and he was found to have a localized disease in the peritoneal cancer and was considered to be a candidate for this cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and was suggested to undergo this treatment. This slide enumerates the steps on this procedure. The complete cytoreduction means removal of the tumor is achieved, inflow and outflow catheters are placed. Temperature probes are placed to monitor the temperature. Catheters are connected to the perfusion pump, and circuit is completed. And the perfusion with the heated perfusate is done starting at a temperature 42 degrees Celsius, and gradually increasing to 45, with an aim to achieve a target temperature of 40 to 43 degrees Celsius. Then the drug is injected in the circuit and perfusion is continued for one hour to two hours, 60 to 120 minutes, depending on the type of the cancer and the type of drugs used.

Thereafter, the drainage perfusate is done. The chemotherapeutic agent is removed from the peritoneal cavity. Continuity of the bowel is maintained, and anastomosis is performed, and thereafter we close the abdomen. In a nutshell, what we do is removal of the tumor, then through a specialized machine, which is the heart/lung machine, we perfuse this fluid in the peritoneal cavity.

Next question comes up, what are the current indications of doing this procedure and this is the list of the different cancers where this has been utilized. It has been highly investigated and effective in the pseudomyxoma peritonei after complete cytoreduction, peritoneal mesothelioma after complete cytoreduction, primary and recurrent colon cancer, and there are subgroups of those cancers where it can be done, enumerated on the slide. Similarly in recurrent ovarian cancer with the spread limited to peritoneal surface, other conditions like primary gastric cancer after complete reduction, and tumor spill during the resection of any recurrent cancer of perforated cancer as such, symptomatic malignant ascites where there is an accumulation of large amount of fluids that can reach the cancer, and then certain cases of sarcomas where there is involvement of peritoneal surface and it can be done after the complete cytoreduction. This is one of the modalities which is being investigated.

Next question comes up, who are the candidates for this therapy? The candidate selection has to be very carefully done because this is a prolonged surgery, and the patient should be in perfect medical condition to undergo this procedure if his medical general condition should be at least Eastern Cooperative Oncology Group, ECOG; ECOG performance status two or less so that they can undergo the rigors of this long surgery and HIPEC. There must not be any extra-abdominal disease. Peritoneal disease must be potentially completely resectable or could be significantly reduced, and there must be no parenchymal, hepatic parenchymal hepatic disease. This is a relative contraindication, there's a small module on the surface you can resect it and this treatment can be performed, and there must not be any bulky peritoneal disease. Now at this point, I would like to go to our video clip, and we can see the portions of this procedure being performed.

Here the patient is brought into the operating room and transferred to the operating room table. Various monitoring is placed, and this procedure is done under general anesthesia. Monitoring is an important component of this procedure. We mark the skin incision. This gentleman had a previous surgery, and these mesothelial cells have got propensity to be implanted into any raw tissue, previous surgical sites, and even the biopsy sites on the needle track, so those things have to be removed. And the skin is also marked for where the previous paracentesis was done, those two round spots, and those areas need to be excised also. So initially we start the case of any typical abdominal surgery to be done with the intent that we remove the scar and excise the scar, and this is being done this in this step.

Usually the entry in the peritoneal cavity could be challenging because of previous adhesions and tumor adhering to the scar down below, so we have to be careful not to injure any trapped abdominal viscera. Once the scar is removed and the entry into the peritoneal cavity is made, then we start exploring and the extent of the disease is assessed and it is facilitated by placement of self-retaining device, which we are trying to do in this area.

After this retractor is placed, we put different instruments to retract the abdominal wall, and the peritoneal cavity is thoroughly explored, all the tumor tissue, all the bowel loops are unraveled and extent of the disease is assessed, intraoperative assessment or the staging of the disease is done. The peritoneal cavity is divided into 13 different zones, and depending

upon the size of the lesion, zero for the no disease to the large disease, more than 2.5 centimeter in size is grade three, and we assess the extent of the disease and we calculate the peritoneal carcinoma index, and it has got a prognostic importance.

And then we also assess at this point whether doing the surgery is worthwhile or not or whether we can save sufficient length of small bowel so that the nutritional requirement of the patient is met without causing major organ dysfunction. And it is systematically done. All the viscera which are involved in the tumor should be resected. In this particular patient, the entire colon has greater omentum, terminal ileum like a big mass cocoon, and this has to be removed. We can see the large bowel being mobilized completely in mass with the spleen in this patient, and we are trying to dissect it off and remove it from the rectum, and that's what's being done, and this will complete this resection of the large bowel. This also included the part of the pelvic peritoneum, which came along with this mass, and I'm going to show it in a minute.

After removal of this, we re-explore, and here is the specimen, the part which includes the small bowel, terminal ileum, cecum, ascending colon, hepatic flexure, and here's the omentum that is involved with the disease, Transverse colon, and there's the omentum, which is shrunken and is riddled with the disease. Mesocolon, attachment of the blood supply of the colon, and here's the spleen, which came along with this because it was involved with the tumor also. Descending colon and sigmoid colon just looks like a big mass. And here is the pelvic peritoneum.

Thereafter, we go back to explore and take out the peritoneum, wherever the disease is. It will involve the removal of the gallbladder, as was done in this gentleman, and removal of the peritoneum from the diaphragm and the site walls of the abdominal cavity.

After this is achieved, at that point, we will start putting in the catheters. Here we are almost removing the right -- the peritoneum from the right surface of the right diaphragm. And here the remaining part of the small bowel, which seemed to be involved in the disease is removed. And at this point we start putting the inflow and the outflow catheters, along with the temperature probe to monitor the temperature constantly. And once this is achieved, we sew the skin in a running fashion, temporarily achieving a watertight closure to prevent the spillage of this perfusing fluid outside. And since it containing the chemotherapeutic agent, we have to be very careful about exposure to the operating room personnel.

Here the catheter is placed, the inflow catheters, the outflow catheters, and they are connected to the perfusion machine, which is the heart/lung machine used in the open-heart surgery. This provides heated fluid, and we start with a 42 degree Celsius temperature, gradually increasing the temperature and monitoring the flow rate and the temperature depending upon the temperature achieved in the peritoneal cavity. This is the machine, and here we are just waiting for the perfusion to complete. And this time we very diligently monitor the patient.

The patient has to be tilted and shaken in order to achieve a uniform distribution of this fluid. And he can be moved from side to side or up and down. And once the perfusion is completed, at that point we start draining the fluid. The peritoneal cavity is again opened, the catheters are removed, and we go back and look into the bleeding site in order to establish the gut continuity achieve complete hemostasis. And if we cannot achieve the bowel continuity at times, we may have to give temporary Stoma to these people, and then close the abdomen.

And that concludes the operation -- in a nutshell, can I have my slides back, please. In a nutshell, this procedure, cytoreductive and hyperthermic intraperitoneal chemotherapy, all the gross disease is removed to the bare minimum, with the intention to get an R-zero, or R-zero resection so that you remove all the gross disease, then treat whatever the microscopic disease that's left behind at a high concentration of chemotherapy to achieve the highest level of tissue concentration, not achieved by the systemic administration and utilize the advantage of localized hyperthermia. Thank you.

Thank you very much, Dr. Saha. That's quite an impressive procedure to watch.

Thank you.

We do have a number of questions from our viewers. But before I get to some of those, I want to just ask you if you could describe a little bit what happens postoperatively? What are some of the common indications that you have to be alert to, and what's the usual postoperative course, and how long is the patient in the hospital following the procedure?

This is a long procedure, and it has got all the complications that comes along with any major abdominal surgery, but besides those, this also has got two unique sets of issues of this surgery, one is that use the hyperthermia and we use the chemotherapeutic agents. And hyperthermia, we have to monitor the temperature of the patient very carefully during the surgery so that he does not have the ill effect of high temperature in the system in the rest of the body, so the rest of the body temperature has to be maintained below 38 or so, so that we do not let the body become heated.

And along with that, it also causes major fluid shift, so we have to monitor the intake and output of these patients very carefully. Besides the chemotherapeutic agents, although we use a high-drug concentration, and since it is a limited time exposure but there is a certain degree of spill, although minimum, so these patients also run the risk of having the toxicity of those specific drugs, and we have to look for that.

These patients usually, after surgery, go to the intensive care unit, remain intubated on the ventilator support overnight, and the following day, they are taken off the ventilator. And once we feel that they are coming back to their -- parameters are getting normalized, then they are sent to the normal routine floor.

Besides those things, the general complication that can happen in any other major abdominal operation like pneumonia, primary embolism, DVT, infection, wound healing has become an issue because we're using chemotherapeutic agent, which has some degree of affect on the wound healing also. So those are the sum things which we have to be careful, and we have to very carefully monitor these patients, and that's why you have to have an appropriate support of staff to monitor these things, and be aware of these complications to be proactive to prevent these complications if they happen, you recognize them and take action.

Right. And the usual hospital stay, average hospital stay after one of these procedures?

Depending upon the extent of the surgery and the general condition of the patient, and if you get into any complication or not, the patient usually stays about 10 to 14 days. It can be longer if they have any. But usually about two weeks. That's with consent of the patient.

Okay. Let me go to a few of the questions that we've had e-mailed to us. The first one is relevant to the patient we're discussing. And I don't know if anyone can really answer this, but the question is, how long did it take this cancer to spread so extensively? Anybody want to take a shot at that, Dr. Fagbemi or Dr. Saha?

Malignant mesothelioma is a cancer that in the beginning is one that grows very slowly. In fact, one option of intervention for those who present with advanced disease is observation, which we just observe them without an intervention. And even in those patients, some of them would live without symptoms for up to 12 to 24 months after we found that they have the disease. So it is quite possible that in a patient they might have the disease for almost a year or longer before it came so extensive. However, the rate of growth coming from the past does not predict the behavior of the disease in the future, and one should keep that in mind.

I think the other problem with a disease like this is that the patient really may not have any symptoms until it has been fairly extensively involving the lining of the abdominal cavity, so it's just difficult to find this disease early, and it's a rare disease, as we have talked about, no good screening approaches to it.

Would you allow me to talk?

Yes.

Allow me to me to make a comment on this. You see that most diseases, abdominal diseases present with either pain or indigestion or swelling or bloating and all of those thing, so this disease has got quite a indolent course, and this is a finding of surprise. Your patient presents with something, and once they get exploratory laparotomy and the tests and they find the result. So the important thing in this is this thing should be in the back of mind, and once you are taking a complete history of the patient, his occupation history and exposure to any toxic agents and things should be the part of it. And if a patient has a history of exposure to asbestos because that's one agent that has been implicated to that; that should be in the back of your mind.

One thing, it's a paradox that any operative intervention initially kind of limits the chances of a better outcome. And once you are doing the biopsy or paracentesis, it should be suggested that it should be there as for possible in the midline, so even if something happens, then you can dissect that area along with that. But it's a surprise finding.

Yeah. Okay. Another question relevant to this disease in the patient we're talking about. Is the bowel put back in? If not. How does the patient digest and move their bowels afterwards. So you might want to just talk about bowel continuity and what was left out.

Yeah. That's a very important question, and that comes to the point when I talked initially that you have to assess at the very beginning of the disease everything is resectable, but once you resect it whether he will have a worthwhile life and lifestyle, that has to be conceded, and all these issues have to be discussed with the patient up front. Our aim is to maintain at least a minimal length so that nutritional needs of the patient is met. Yes, you cannot put the bowel back. There's no way, like in some kidney diseases, kidney stone disease and some renal cancer cases, they do the bench nephrectomy and put the things back again. That's not possible in this disease.

Yeah, okay. We have a lot of questions that are related to this procedure in this patient, but we have one question, let me just switch gears for just a moment to Dr. Gerndt. And

the question was, how many of the chemoembolization procedures can you carry out in a single patient? What's the usual number? And can you give us a little information about that?

Sure. The simple answer is that there's no set limit. Because the toxicity to the rest of the body is limited to the doxorubicin dose, we're really not subject to the limitations that the systemic or IV chemotherapy has. So we can continue to treat as long as it's working, you can still get the catheter where you need it to get, so there's no set limit on the number of treatments.

Okay. So as long as the patient is tolerating things and anatomically you can get there.

Yes.

And the patient is benefitting from the treatment.

There are cases where we are able to halt treatment and watch and only treat again if there was progression of disease. This particular patient has had a three-month hiatus between this treatment and his previous set, and we hope to have at least another three-month hiatus now. So there are often points where you can pause and let them go back to their life and not be spending time in the hospital.

Yeah. And his quality of life in these treatment breaks is reasonably good?

After the first two weeks, I think he would say it's pretty good. Some treatments are harder than others, and sometimes the recovery is a little bit longer than two weeks. So there is some effect of decreased tolerance when you get into the higher. We try to space them out as much as we can without giving up the advantage that we've gained.

Okay. All right. Let me switch back to HIPEC again. And here is an important and somewhat complex question. During the intraoperative phase, and you actually alluded to this a little bit, can you elaborate on the safety, handling, and disposal of the chemotherapy agents used by the HIPEC and the surgical team?

That's a great question. And to establish a hyperthermic intraperitoneal chemotherapy you have to have to look into the institution, whether you've got capability and supportive staff who understands the implications and the spillage and the effect of the chemotherapy and all. We follow the OSHA guidelines and the guidelines which are there for the disposal chemotherapeutic agent. We use special gloves, usually double glove, and protect ourselves and other support staff which are there, the operative nurses, the circulators, perfusionist, anesthesiologist, and the whole team. And we have those protective gloves, masks to be -- the people who are in the immediate vicinity like the surgeon and the circulator and the nurse assisting in the case, they have to be gowned and gloved up to the -- completely, and that's what needs to be done. There are specific certain guidelines to disposal of these products, and each and everything after we started the chemotherapeutic agent are treated with special precautions. Those instruments that we use, they go for a special wash, and those things are adhered to.

Okay. Thank you. This is actually part two to the question. Although it's about a little bit different subject. Although there are many world reports of clinical studies for pseudomyxoma peritoneii with favorable results for HIPEC, it still seems ambiguous whether or not treatment should include HIPEC. Can you identify those studies a health-care provider should consider reviewing? What resources do you recommend? Somebody

obviously interested in learning more about the role this procedure would play, and it maybe relates a little to something that we've talked about in terms of this procedure having more prominence on the other side of the Atlantic, at least up until now, that it has in the United States.

That's a great question, and I just do not have the list of the things right now. But one good monogram that a surgical clinical North America has issued as an issue on the hyperthermic intraperitoneal chemotherapy and the peritoneal surface malignancy, that's a good area to review, and it has reviewed the application of this technology and the different -- all possible scenarios I should say all possible scenarios.

It is kind of interesting that this procedure was done mainly in the United States and Dr. Sugarbaker in Washington, D.C., he has done the groundbreaking, and he is the pioneer in this technology, and he's probably got the largest experience. But it was applied more effectively in France, and they did many more studies, and in certain instances, it has become a standard of care, and they've got, you know, 35 centers to do that. It is now catching up in the United States. When I was in my fellowship, very few places were doing this procedure. But now there are many more, and I think each state has got two or three centers where this can be done. But as for the research center is concerned, that is the best point.

Okay. Good. Another question. How many of these cases, and I think we're talking, again, about the mesothelioma, were found incidentally versus elective? I think we've sort of talked about that already, related to an earlier question. If elective, would a pre-operative bowel propose any additional risk? What prophylactic antibiotics are used? It sounds like a surgical person asking a question here? And here is an interesting question, can laparoscopy be applied for the initial debulking?

Laparoscopy is being investigated. In certain situations it can be done. But that is being done where there is a minimal disease, where you don't have to do a lot of resection of the organs and a lot of resection of the peritoneal cavity with the minimal disease. And it's being done, especially across the Atlantic. They have done this in France, Spain, and other countries. Italy they have done it. But I am not aware that any one of us are doing laparoscopy perfusion here in the United States.

Okay.

And that's where the question of bowel prep comes in. You follow the same principles of bowel prep as you do in any major abdominal surgery, and the same set of antibiotics are used, but we have to give intraoperative dose depending upon what antibiotic you're using, you have to do intraoperative dosing if you think that you're going beyond the life of that drug.

Because of the long duration of this procedure frequently.

Usually we give once you have about four to six hours of surgery and once you are concluding surgery.

Okay. We've got just a couple more here we'll try to get through, and then we'll, I think, bring our program to a close. Here's a fairly quick question. Do you expect a white blood cell nadir with the chemotherapy, that is, do you expect the white blood cell count to fall after the intraperitoneal chemotherapy?

Sometimes you see it and you have to carefully monitor the white cell count and the platelet counts and the coagulation parameters after the surgery.

\Okay. Let's make this maybe the last question, because we are running a little overtime. What are the five-year survival rates for patients undergoing HIPEC?

Wow. You know, the HIPEC is done in so many diseases, and each disease has got its own outcome. The best outcomes I have seen are in the pseudomyxoma peritonei, and in the colorectal cancer without hyper -- there was one randomized trial done by a Dutch Institute, National Cancer Institute of Netherlands, and they are probably the only one who could do this randomized study in the patients with systemic chemotherapy versus systemic chemotherapy and hyperperitoneal perfusion. The median survival was about 22 months in the hyper group, whereas just chemotherapy group, it was 8.3 months.

So there appeared to be a significant survival in that study. Okay. Okay. Well I think we better bring our program to a close at this point. I hope that you have found our program informative this evening. I want to, again, express a special gratitude to our patients who have allowed us to share their stories with you this evening, and I want to express my thanks to our expert panel, who have done a wonderful job this evening of expounding on these interesting approaches. Thank you again for joining us. We're coming to you from Marshfield Clinic in Saint Joseph's Hospital in Marshfield, Wisconsin. Thank you, and goodnight.

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