

[MUSIC PLAYING]

M. HAROON A. CHOUDRY: The topic of the presentation today is regional peritoneal therapies, rationale for cytoreductive surgery and HIPEC and novel therapeutic strategies. The presentation outlined for today includes definitions. I'll be defining peritoneal surface malignancies, especially from a surgeon's perspective. I'll define cytoreductive surgery and HIPEC, and I'll define hyperthermic intraperitoneal chemoperfusion.

Then, I'm going to discuss some concepts related to CRS and HIPEC, for peritoneal surface malignancies. We'll discuss appropriate patient selection for CRS-HIPEC. We'll then talk about some of the clinical and oncologic outcomes data, for peritoneal surface malignancies after CRS and HIPEC. And finally, we'll talk about some novel therapeutic strategies, specifically focusing on patients with appendiceal and colorectal cancers.

So, moving on to definition. From a surgeon's perspective, and otherwise, peritoneal surface malignancies refer to tumors that are disseminated within and are confined to the peritoneal lining of the abdominal cavity. So if you look at this CT scan on the right, it is an axial image of a CT scan of a patient with appendiceal mucinous cancers, or pseudomyxoma peritonei. This grayish material is all tumor that's basically filling and expanding the abdominal cavity. All this gray stuff is tumor, and then it's compressing all these organs in the abdominal cavity.

And so that's what peritoneal surface malignancies will look like. And there can be two main varieties. There's primary peritoneal surface malignancies. These are tumors that originate from within the peritoneal lining of the abdominal cavity. And these can be tumors like malignant peritoneal mesothelioma or primary peritoneal cancers.

And then there are secondary peritoneal surface malignancies. So these are tumors that have originated somewhere else in a different organ and then have spread to the peritoneal cavity-- for example, tumors from the breast or the lung or from the liver, and then they spread into the abdominal cavity.

Moving on to the definition of cytoreductive surgery and HIPEC. So important to remember that these two procedures are done together during the same operative procedure. Cytoreductive surgery basically refers to the surgical removal of all visible macroscopic disease from within the abdominal cavity-- so whatever the surgeon has to do to remove everything that is visible in the abdominal cavity. And then during that same operative procedure after having done the cytoreductive surgery and HIPEC, the surgeons place in-flow and outflow catheters and temperature probes into the abdominal cavity of a patient, and then using a machine, heated high dose systemic chemotherapeutic drugs are then circulated into the abdominal cavity. And the concept behind this is that the high dose heated chemotherapy then kills any microscopic or invisible tumor cells that have been potentially left behind after the cytoreductive surgery.

So what are the rationale and concepts behind CRS and HIPEC? So concept number one is that cytoreductive surgery is feasible because the abdominal cavity is enclosed by a natural barrier called the peritoneal membrane. So if you-- once again, if you look at this picture of a patient with pseudomyxoma peritonei, this grayish material is all tumor that's expanding within the peritoneal cavity and causing the organs to get compressed. And so, keeping that in mind, the peritoneal cavity is actually in-- the abdominal cavity is actually enclosed by a peritoneal membrane. This peritoneal membrane is shown by this purple line here. It basically covers the abdominal wall on the inside, the retroperitoneum on the inside, and it also covers all the organs.

So the lining along the peritoneal wall in the retroperitoneum is the parietal peritoneum, and the lining along the organs is the visceral peritoneum. But you can see that this is an enclosed cavity or an enclosed space. And so on the one hand, it's bad because when tumors, for example, if they penetrate through an organ or they rupture an organ, they get into this space and then they can disseminate throughout the abdominal cavity and that is obviously bad. But on the other hand, it is good because surgeons use this peritoneal membrane as a plane of dissection. So if the surgeon stays outside this peritoneal lining, they can use this to completely remove any and all tumor that has coated the inside of the peritoneal cavity. And so it's a nice plane of dissections that surgeons used to do a complete resection.

And so if you use that concept, patients that are not good candidates for cytoreductive surgery and HIPEC are those that have significantly breached this peritoneal lining. So patients who have extensive involvement of the abdominal wall, who have extensive involvement of tumor into the retroperitoneum, for example, the involvement of the lymph nodes or the major vessels of the ureters, or patients who have breached the peritoneum membrane and systemically spread, for example, to the liver parenchyma or to the lungs, or to the bones. Those are patients who generally are not good candidates for cytoreductive surgery and HIPEC. Patients who are the good candidates are the ones in which it's confined within this peritoneal space.

Concept number two is that cytoreductive surgery involves a systematic and comprehensive removal of all visible disease. This is not a cherry-picking operation, since surgeons use very specific visceral peritonectomy procedures in order to remove all the disease. And so this is what we want to achieve. This is a patient before having undergone cytoreduction, and this is a patient after having undergone cytoreduction.

And so if you look at this top picture, this is a picture of the inside of the abdomen. In the right upper quadrant, you can see the liver over here, you can see the gallbladder, you can see the duodenum, and this is the retroperitoneum where the kidney sits, and this is the diaphragm. And so you can see all these little miliary tumor nodules that are basically speckled all over these surfaces.

And once the surgeon removes all this by doing a peritonectomy procedure, you end up with this. You can see the liver capsule has been stripped. There's still a little bit of disease in the gallbladder that will be removed. You can see that this kidney is nicely visible with no tumor on it. You can see the duodenum is nice and visible with no tumor on it. The diaphragm on the right side has been completely stripped, and so you can get a complete macroscopic resection of all the tumor by doing it, but they're doing a very comprehensive operation.

Concept number three is that HIPEC is feasible because the peritoneal membrane, or barrier, allows us to give very high doses of chemotherapy into the abdomen while minimizing systemic toxicity. So this is a graph of a patient who has given intraperitoneal Mitomycin C. Mitomycin C is a commonly used drug for HIPEC. The y-axis here represents the concentration of the drug, the x-axis represents the time or the duration during which the drug is present in the abdominal cavity.

And so the top solid line here is the concentration of Mitomycin C over a period of 90 minutes. And you can see we can maintain a very high concentration of drug during 90 minutes of perfusion. The solid line at the bottom is the concentration of drug that gets into the systemic circulation, so into the plasma. And as you can see, a very low amount of the drug is getting into the systemic circulation. And then some of the drug that does get into the circulation is old and excreted out the kidneys through the urine.

And so this is what you want to achieve, a high intraperitoneal concentration, a low systemic concentration, and good excretion of any drug that gets out of the peritoneum. And so when we choose drugs, these are the concepts you're looking for. You want a drug-- and generally, this means drugs that are high in molecular weight, they're ionic, that are hydrophilic, and so they have a high area under the concentration time curve. And at the same time, we also want drugs that are either augmented by heat so that they have a higher efficacy when they're heated up. And so these are other concepts that you want to keep in mind when choosing drugs to give intraperitoneally.

Concept number four is that the intraperitoneal delivery of drug during HIPEC, has limited tumor penetration, and therefore, cytoreductive surgery is very important. And so I'm going to explain this in a couple of graphs here. So this top, top picture basically is a schematic picture of a tumor nodule. So these are two-- this is an experiment done in a rat model of intraperitoneal colon cancer. And these rats were then treated either with IP, or intraperitoneal, or IV, intravenous cisplatin and these tumor nodules within removed from the peritoneal cavity and the concentration of drug was checked at different levels of these tumors after being removed from the animals.

So this is a picture of one of these nodules. And if you look at the left side here, this is the surface of the tumor nodule. And on the right side, this is the depth of the tumor nodule down to about 2.25 millimeters. And so you can see, this solid line represents the concentration of drug as it passes through this tumor nodule and so you can see an exponential decrease in the concentration of drug as it passes from the surface of the tumor nodule to about 2.25 millimeters deep into the nodule. And this is because the drug either doesn't penetrate the tumor nodule because of high interstitial fluid pressure, or because it becomes metabolized by these cells or it gets absorbed into the systemic circulation. And so there's a limit to how far a drug will penetrate.

And this is what was found when the cisplatin levels are checked in these nodules. The solid line at the top is the concentration of cisplatin measured when given intraperitoneally, and the dotted line at the bottom is the concentration of cisplatin when given intravenously. And as you can see, the intraperitoneal delivery was much better than the intravenous delivery, only up to about 2.25 or 2.5 millimeter depth. After that, there was really no difference. And so that's the whole concept behind cytoreduction. When surgeons talk about removing all visible disease, or minimal disease down to less than 2 and 1/2 millimeters that's the concept. We want to get as much tumor out as possible so that these little tumor nodules that are left behind can then be penetrated by the IP chemotherapy to mop up any microscopic disease that's left behind.

Concept number five is that heat kills cancer cells directly, and augments chemotherapeutic effect. So the use of heat to kill cancers has been around for generations, and this concept is then applied to HIPEC as well. So this is an in vitro experiment. These are fibrosarcoma cell lines and they were exposed to heat plus cisplatin for a period of up to 200 minutes. And the temperature was increased from 37 degrees centigrade, all the way up to 43 degrees centigrade. And when you treat cells with heat, there's an initial stunning phase where the cells get stunned, but after a while they-- after enough heat is given, and for enough duration, they go into an irreversible cell death. And in the presence of chemotherapy, that optimum temperature is around 42 degrees centigrade, where you get irreversible cell death and cells obviously can't then recover.

And so that's the concept behind HIPEC, where we use these drugs at a temperature of about 42 degrees centigrade for about 100 minutes, and this is something to keep in mind. Because you need enough time to make these cells go into irreversible cell death. And that's one of the big criticisms to some of the modern randomized trials that have been done in Europe, where they're using much shorter time periods and therefore not seeing-- potentially not seeing the effects that we may expect to see with HIPEC.

Concept number six is that the impact of uncontrolled peritoneal metastases is severe and catastrophic. And this is what you want to try and avoid in patients, with patients presenting with very significant amount of disease volume that becomes very difficult to actually remove. And the concept here is that if you compare a metastases to the liver versus the peritoneal cavity, in the liver a tumor starts to grow, but it doesn't really cause organ failure or much problems from a quality of life perspective to patients until it's very large or takes over a lot of the liver.

As opposed to this, tumors that spread into the peritoneal cavity, each tumor itself then disseminates further. And these tumors lead to obstructions of the bowel, they can lead to ischemia of the bowel, and lead to, eventually, to inanition or inability to eat. And it's a very difficult quality of life issue, and therefore early control of peritoneal disease becomes very important, because once this occurs where you have bowel obstructions and perforations, then obviously you're not amenable to any kind of therapy. And so the earlier you can get to these peritoneal diseases and keep them under control, the better. And that's the whole concept behind cytoreductive surgery and HIPEC.

Concept number seven is that cytoreductive surgery and HIPEC can be performed with acceptable perioperative morbidity, mortality, and quality of life. And these two data fields that are put in-- you're not supposed to be able to read these-- but the crux of these multiple studies that are listed here, is that the average morbidity or complications after cytoreductive surgery is somewhere between 20% to 30%. These are severe morbidities, and the average mortality rate after cytoreductive surgery and HIPEC is about 3%. And this is no different to what you would see after other major surgeries, for example, after pancreatic or duodenectomies, or after esophagectomies. And so while these are not minor, they're obviously associated with significant risks to patients. But they can generally be done safely with low mortality rates, and so once you get over that acute phase of these operations you can have potential for long term survival.

So having gone through the rationale and the concept behind cytoreductive surgery and HIPEC, how do we select patients? What is the appropriate patient selection for these kinds of procedures? And when we look at trying to select patients, we look at what are the major prognostic variables that affect outcomes. And this is based on obviously a lot of research that's been done from multiple different institutions nationally and internationally and basically, it comes down to tumor-related factors, patient-related factors, and surgery-related factors. So when you look at tumor-related factors, the main variables are things like histology, grade, the burden of disease, which is called peritoneal cancer index, presence of lymph nodes or not, and other such tumor-related factors.

When you look at treatment-related factors, you're looking at things like completeness of resection-- can you get a complete resection, or do you leave residual tumors behind, then post-operative complications, can you do these operations safely, and get patients through these operations safely, and other things like response to chemotherapy, or whether these are primary presentations or repeat surgeries.

And finally, patients have to be able to tolerate these procedures. So it's very important to know what the performance status and what the comorbidities of patients are before you do these operations. And so in general, no matter what studies you look at, or from what institution, you'll find that certain cancers do better than others. For example appendix cancers will generally do better than colon, or gastric cancers. Patients that have lower-grade disease, as depicted by grade one appendix cancer here, will generally do better than patients with high-grade disease, as shown here.

Patients who have low volume or tumor burden, shown here in blue, will generally do better than patients who have a large volume of disease as shown here in red and patients in which you can get a complete resection, removal of all macroscopic disease will generally do better than patients in whom tumor is left behind after the surgery. So no matter what studies you look at, you'll generally see the same trends when you're looking at survival. And then in the end, obviously you want patients who do not have extra-peritoneal disease, because that's a contraindication to cytoreductive surgery and HIPEC in general.

So moving on to what the data is out there, for cytoreductive surgery and HIPEC-- so there are potentially multiple indications for this procedure. And as you're aware, there's a wide spectrum of peritoneal surface malignancies. So there are malignancies for which CRS and HIPEC is generally considered standard of care, and I would include appendix cancer and malignant peritoneal mesothelioma in this group.

Then there are malignancies in which it's still somewhat controversial, but there's more and more data to support its use. And under that category, colorectal cancer and ovarian cancer can be placed, because there's a lot more and more data that's coming up showing the benefits of cytoreductive surgery and HIPEC. And then there's the groups of patients in which it's still considered experimental and should not be done except under a protocol or trial. And these are patients who have gastric cancer with peritoneal metastases, or other upper GI malignancies that may have spread to the peritoneal cavity.

So just briefly-- obviously, these are large topics, so I'm going to very briefly talk about some of the data. So starting with appendiceal mucinous neoplasms, or pseudomyxoma peritonei, this is an entity where CRS-HIPEC is considered standard of care. So just to briefly introduce you, clinically pathologically describing PMP. PMP is characterized by mucinous ascites and mucinous tumor nodules that have spread throughout the abdominal cavity of the peritoneal cavity. And they almost exclusively arise from mucinous appendiceal neoplasms. And again you've seen this picture before, but this is what it looks like with this gray tumor that has basically spread throughout the abdominal cavity.

What is the natural history of this tumor? They tend to start as these unruptured mucinous neoplasms of the appendix. This is a picture of the appendix that's basically filled and become dilated with mucus. They can be low-grade varieties called a LAMN, and they can be high-grade varieties called mucinous adenocarcinoma. As time goes on, this mucinous neoplasm then ruptures, and it can spew out this mucus looking, or gel-like material, which then spreads throughout the abdominal cavity. And this is what you end up with. You have this mucinous ascites that spreads within the abdominal cavity, and you have these mucinous tumor nodules that basically coat the internal organ surfaces of the abdominal cavity. And so this is what patients will often present with when we're faced with this disease. And once again, you can have a low-grade variety and you can have a high-grade variety. The low-grades tend to do well, and the higher-grade tumors are a little more aggressive and harder to treat.

And so what is the data? This is some of the recent data out of the University of Pittsburgh. This is a survival curve. You're looking at the survival of patients over time. This is overall survival, and as you can see, the blue line here is Grade 1, or the lower-grade tumors, the green is the Grade 3, or the high-grade, and the red line is the intermediate, or the Grade 2 tumors.

Overall, patients do very well. The overall median survival is almost 10 years. Grade 1 survival is over 10 years. The Grade 2 survival is around five years on average-- these are all average numbers-- but Grade 3 tumors are still hard to treat, with an average median survival of about 20 months. When you come to disease-free survival, that still remains a problem.

Despite having quite significantly improved overall survival with these therapies, we still have a large number of patients that recur. For the lower-grade tumors, the average time to recurrence or progression free survival is almost five years. For Grade 2 it's about, almost two years, and for Grade 3 it's about a one-year progression-free survival. So there's still a big problem, despite these aggressive surgeries, especially in the higher-grade tumors. But compared to systemic chemotherapy alone, we have made a lot of progress by adding CRS-HIPEC into the mix of the treatment for these patients.

Moving on to malignant peritoneal mesothelioma. Once again, just a brief introduction to this disease, as we all know malignant peritoneal mesothelioma is characterized by ascites and whitish, plaques, or tumor nodules that disseminate within the peritoneal cavity. It'll often look like this, you can see all these tumor nodules that coat the abdominal-- the peritoneal cavity on the inside. And this is what it can look like on a CAT scan, you can see the ascites, you can see these tumor nodules that are quite substantial. And there are a variety of subtypes of peritoneal mesothelioma.

There are the borderline, or the very low, considered borderline, or low malignant potential mesotheliomas, which have an excellent prognosis. They have a well-differentiated papillary in the multicystic subtypes. There's the epithelial subtype, which has an intermediate prognosis, and does well with cytoreductive surgery and HIPEC. And then there's the very high-grade tumors, the sarcomatous and the biphasic. And these patients have a much poorer prognosis, and you have to be very selective when offering cytoreductive surgery and HIPEC for such patients.

So what are the outcomes for cytoreductive surgery for peritoneal mesothelioma? So this is just one paper that I'm going to show you. This is by the Sugarbaker Group at Washington Hospital, a big name in cytoreductive surgery and HIPEC. He reviewed his patients over 20 years and selected 129 of the patients with malignant peritoneal mesothelioma. These are a highly selective group of patients,, so he only selected patients who had epithelioid subtype, who had low-grade features, and who had a complete either CC0 or a CC1 resection.

And he divided the group over time, into cohorts that-- the initial cohort that only underwent CRS-HIPEC, a later cohort in which he added EPIC-- EPIC is Early Post-operative Intraperitoneal Chemotherapy-- and then the most recent group, where he included EPIC as well as NIPEC, which is Normothermic Intraperitoneal Chemotherapy Long Term. So he did the surgical procedure, then did post-operative intraperitoneal chemo, and then long term post-operative intraperitoneal chemotherapy, and he looked at his survival.

And this is the graph on the right. This is 10 years here. So as you can see from the graph, the green represents his most recent cohort of patients that got all three therapies. And you can see a very good long-term survival in these patients, and even in the patients who got the other two alone, you can see median survivals over five years. So you can make a huge impact in patients' lives with adding CRS-HIPEC. And this is in contrast to systemic chemotherapy alone, where survival is generally less than 12 to 18 months.

Moving on to colorectal peritoneal metastases, again just highlighting some of the more recent data. So if you look at the role of modern systemic chemotherapy, obviously a very important part of treatment of colorectal cancer is systemic chemotherapy. This is data from the ARCAD database, this is a database in Europe, it looks at randomized trials, first-line chemotherapy-- for patients with colorectal metastases in general. And they looked at their data and they split it into patients who had liver-only metastases, lung only metastases, or peritoneal only metastases, and they looked at their overall survival over time. And from this graph, you can see, that you can get reasonable median survivals for patients.

So liver only, about 19 months, lung only, 24 months, but for peritoneal metastases, you can see that the survivals are not as good. So there's data to show that the peritoneum is not as responsive to systemic chemotherapy. But despite having relatively good median survival, the problem is long-term survival. So if you look at peritoneal metastases, it is very rare patients that live five years, with peritoneal only metastases. And so that's the problem, we've made a lot of progress with systemic chemotherapy, but we have not been able to have a big impact in long-term survival in patients.

Now moving on to what's the role of CRS-HIPEC in these patients. This is the most recent randomized controlled trial that was done in France. This is only an abstract form at the moment, but the actual publication has not come out, but it was presented at ASCO in 2018, called the PRODIGE 7 study. So this is patients with peritoneal metastases from colorectal cancer, they were not highly selected, so they took 265 patients. They had no extra-peritoneal disease, but their PCI or tumor burden was up to 25. And they had to get a complete macroscopic resection or tumors less than 1 millimeter residual left behind after cytoreductive surgery. They had to get systemic chemotherapy for a total of six months. This was either given preoperatively, postoperatively, or perioperatively, and they couldn't have had HIPEC before.

So they took these patients, and they randomized them to either cytoreductive surgery, plus HIPEC, or cytoreductive surgery alone, without HIPEC. So this was a trial looking at what the benefit of additional HIPEC is to cytoreductive surgery. If you look at the two groups, they were well matched. The PCI on average was 10 and it was similar between both groups. And also, the ability to get an adequate resection was very similar between the two groups. And here's the crux of the data. The median survival for both groups was about 40 months, and the five-year survival for both groups was about between 36 and 39 months.

So you can see from here, that in this randomized trial of patients with colorectal peritoneal metastases, HIPEC did not add anything in this particular study. It was a negative study, but cytoreductive surgery obviously has a significant impact, and can give long-term survival in patients. It obviously comes at a cost. There was a higher degree of complications in patients who got HIPEC compared to those who did not have HIPEC, and the major morbidity rate was about 14%, and there was a slightly longer hospital stay. Now obviously this to me, and to a lot of experts here in the US at least, does give credence to the fact that cytoreductive surgery does have an important role to play in patients with colorectal peritoneal metastases. The question of whether HIPEC has a role is still under consideration.

There are a number of criticisms to these studies that have to be thought of when you look at this study. I won't go into the details, but one of the main ones is the fact that in Europe, and specifically in this trial, they often use oxaliplatin as their intraperitoneal drug, and they only gave it for 30 minutes, at 42 degrees centigrade. And if you think back to the concept and rationale that I presented earlier in this talk, there is really no preclinical data that demonstrates efficacy at only 30 minutes. You need to give this intraperitoneal chemo-- heated intraperitoneal chemo for at least 90 minutes to get a good effect, and here at UPMC we use about 100 minutes. And then there's obviously other criticisms about the use of oxaliplatin because often these tumors are resistant since they've seen a lot of systemic oxaliplatin. And there are also some design issues with this trial. But in the end, regardless, this is an important study, an important trial, and it shows a benefit to adding cytoreductive surgery to patients with colorectal peritoneal metastases.

Moving on to ovarian peritoneal metastases, I just want to show two studies that are out there. This is the more recent study by van Driel, out of Netherlands, published in 2018. This was a randomized trial of patients with stage 3 epithelial ovarian cancer, and these are selected patients, so these were patients who had high tumor burden, who were eligible for neoadjuvant chemotherapy. Or patients who had an attempted cytoreductive surgery or debulking, or resection but were aborted, or could not get to less than 1 centimeter residual disease, so they had a lot of residual disease left behind.

These patients then went on to perioperative chemotherapy, and either cytoreductive surgery alone, often after chemo, or cytoreductive surgery and HIPEC. And in this trial, you can see from these graphs on the side, this is the overall survival and the recurrence-free survival data. Both recurrence-free survival and overall survival were better in patients who got cytoreductive surgery plus HIPEC, compared to those who got cytoreductive surgery alone, showing that there is a potential benefit to CRS-HIPEC for patients with, at least, certain disease states for epithelial ovarian cancer, maybe the patients with a higher disease burden after neoadjuvant therapy.

And the second randomized trial for ovarian cancer was by the Spiliotis group. This one is another randomized trial from Greece, they looked at stage three epithelial ovarian cancers, and this was for recurrent epithelial ovarian cancers, after patients had had a complete response to primary therapy in the past. And patients were then randomized to CRS alone, or CRC plus HIPEC, with systemic chemotherapy. And even in this recurrent setting, there was a benefit to addition of HIPEC to CRS, showing reasonable long-term survivals in these patients with recurrent disease, 27 months versus 13 months. Another important thing to see in the study is that they did not see a difference in patients who had either platinum-sensitive or platinum-resistant disease. And so there is data out there, suggesting that there is a role for CRS-HIPEC in well-selected patients with ovarian cancers.

Finally, just moving on to gastric peritoneal metastases-- as I mentioned earlier, this is still experimental, should really only be done on a trial, or on a protocol. But this is what data we do have. This is a recent study published out of France. So this is a multi-institutional study called the CYTO-CHIP study. And they basically compare databases from their two groups. One is the RENAPE group, and one is the FREGAT group. The RENAPE group is the peritoneal metastases group that does CRS and HIPEC, and the FREGAT are the upper GI surgeons that don't use HIPEC. And so they compared outcomes of CRS-HIPEC done by the RENAPE group versus CRS alone by the FREGAT group. And so this is 277 patients, they compared these two databases, they propensity match scored to do this comparative study, and they compared CRS alone, to CRC plus HIPEC.

As you can imagine, they weren't well-matched, and therefore they did the propensity score matching. However, at the end of the study, after this adjustment they found that the patients who had the HIPEC did do better than those who did not have HIPEC. And it's important to remember that in this study, the patients who did get the HIPEC, or in the RENAPE group, did have more advanced disease, and still did better. There was however significant morbidity and even a mortality of about 8%. And so there is some data to show that there may be a benefit. However, there may be significant morbidity, and so this must be kept in mind when approaching such patients.

There are currently a couple of randomized trials going on, the PERISCOPE II study going on in the Netherlands. This is for high risk, so T3T4 lymph node positive patients with gastric cancer, with a PCI less than seven, so well-selected or cytology only. And these patients are being randomized to either chemo alone, or chemo plus gastrectomy with cytoreductive surgery and HIPEC. So obviously, this is a very important study that we'll be keeping an eye out for. And the other important study is the GASTRIPEC study. This is a German randomized controlled trial. So this is for patients with macroscopic gastric peritoneal metastases, being randomized to either cytoreductive surgery alone, or cytoreductive surgery plus HIPEC, with systemic chemotherapy. And so this again, will be an important study to see what the role for CRS-HIPEC is for gastric peritoneal metastases.

Moving towards the end of this talk, I'm going to just go through some novel therapeutic strategies, and talk about the rationale and some ongoing clinical trials for these novel therapies that are up and coming. So the first novel therapy I want to mention is mucolytic therapy. And most of these trials that I'm going to-- these novel therapies that I'm going to talk about right now, are specifically related to appendix and colorectal cancer.

So mucolytic therapies-- the rationale here is that as we mentioned before, these mucinous neoplasms produce excessive amount of mucus in the abdominal cavity. And this causes a significant amount of compressive organ dysfunction, and also this extracellular mucus forms a protective barrier around these cancer cells, so that systemic chemotherapy does not affect them as well because it just can't reach the cancer cells. And so to put that in perspective, these pictures, I put these pictures up here, this is what we find in the abdominal cavity of patients. You can see this is all mucinous tumor. And so if you look at this under an electron microscope, this mucus forms this lattice structure, as you can see here, and these four sizes within the lattice structure are in the range of nanometers. So extremely small, and so that's why it's so hard to penetrate these tumors and so hard to have effective therapy against these tumors.

And so based on that, our group and Dr. Morris' group in Australia, have been working on this combination of mucolytic drugs. So drugs that actually dissolve or disintegrate mucus. And so we've been using a combination of bromelain. Bromelain is a protease, and it's extracted from pineapples. And then N-acetylcysteine is a well-known cysteine bond breaker, that is extracted from onions. And so mucus itself is made up of a lot of proteins and a lot of cysteine bonds, and so that's the rationale behind using this combination of two drugs.

And so this is data from my lab, this is mucus or a sample of mucinous tumor that was taken out of a patient with pseudomyxoma peritonei. This is untreated mucus, you can see this gel-like material, which is highly viscous. It's all aggregated together in the form of a gel, and this picture on the end shows two hours of treatment with bromelaine plus N-acetylcysteine, and you can see the entire tumor is dissolved into liquid. And so obviously, very promising, and very exciting data that we could potentially just dissolve the mucus so that we can have better effectiveness of systemic chemothera-- or intraperitoneally delivered chemotherapeutic agents.

And so this is also some more data from my lab, using the same drug combination, but in an animal model. So we made an animal model in which we take mucinous tumor from patients, and we put it into the peritoneal cavity of nude rats. And then we treat them intraperitoneally every other day, for about five weeks with this combination therapy. The column on the left is the untreated rats, and the column on the right is treated rats. This is a picture of an inside of a rat, once we have sacrificed them, and you can see all this mucinous tumor that's basically coating the organs. And on an MRI down here, you can see all this whitish material is actually tumor. This is after five weeks of treatment, you can see most of it, 90% of it is now liquid, and can still see a little bit of mucinous tumor. And on an MRI, you basically don't see much tumor at all. So there is a significant effect of this drug, even in an animal model.

Now Dr. Morris in Australia has actually already performed an early phase clinical trial on patients with pseudomyxoma peritonei. So he conducted this trial, and he's recently published it. It's a first in-human trial of bromelain plus N-acetylcysteine in patients with pseudomyxoma peritonei. What he does is, or did was, either catheters were placed directly into pockets of mucinous tumor or catheters were placed into the abdominal cavity, and then this combination was given over short periods of time.

So the row up here is pre-treated tumors, and CT scans, and the rows down here is after treatment. So this patient here had a pocket of mucinous tumor down deep in the pelvis, you can see a large amount of mucus. A catheter was placed in, the patient was treated with this mucolytic combination, and you can see a significant reduction in the size.

This is a patient with tumors seen here in the abdominal wall, and after treatment, you can see that means this tumor has pretty much gone away. And so there's good evidence to support the use of this mucolytic therapy. And this isn't a patient given directly into the peritoneal cavity, you can see this mucinous, grayish material that's lining or coating all these organs, and after treatment, you can see most of it has dissolved and disappeared.

So very exciting data, and based on this data, there are two trials that are going to be starting in the United States very soon. Dr. Morris is bringing in the same trial that he ran in Australia, to the United States, and hopefully should be opening up pretty soon. It'll be catheter-based, either a catheter will be placed directly into tumors, or into the peritoneal cavity. But it's short-term therapy so it'll be one, or a few treatments, looking at tumor response, and toxicity with treatment.

In addition, we at UPMC will be opening a similar but different trial. We'll be using the same drug combination in a Phase I/II-- so an early-phase trial. But we'll be doing long-term therapy, so we will be placing a catheter into the abdominal cavity of patients. These are patients who are unresectable. And then we'll be giving treatment every other day for up to six weeks. So it's long-term therapy to look at response of tumors as well as toxicity. And so these are two exciting studies that hopefully should be starting either more towards the end of the year or early next year.

Moving on to the second type of novel therapy is molecularly targeted therapies. The rationale here is that most tumors, or tumors in general, have genetic and molecular abnormalities that drive cancer cells. And what we found is that these mucinous appendix tumors, or appendix tumors in general, tend to be different from colon cancer. So they have different genetic abnormalities. For example, mucinous tumors tend to be much more commonly KRAS mutated, GNAS mutated, TP53 mutated, and so they have a different genetic background, compared to other colon cancers, for example. And that's consistent across most tumors.

And so talking specifically about appendix colon cancers, there are currently two trials that are currently recruiting patients. One's out of the NCI, one's through Genentech. These are Phase II trials, so tumors from patients are taken, they are genetically sequenced, the genetic abnormalities are assessed, and then based on these specific genetic abnormalities for which we do have targeted drugs, patients can then be enrolled in these trials to try and treat them.

Moving on to the third novel therapeutic strategy-- what is immunotherapy? We've all heard of immunotherapy, and this is also the news now for intraperitoneal therapies. So the rationale here is that we're harnessing the patient's own immune system to fight cancer cells. And so if you look at a patient with mucinous appendiceal neoplasm, or pseudomyxoma peritonei, you can see this tumor, this is all mucus here, this is the neoplastic cells.

All these blue cells are lymphocytes, so we know that there is a lymphocytic reaction to these tumors, but the problem is they don't do what they're supposed to do. And so the theory behind immunotherapy is trying to harness, or activate, these immune cells to actually do their job. And so there are four main prongs to immunotherapy. There's vaccines, which is mostly in a preemptive phase, but then there's therapeutic immunotherapy, and that can be either immune checkpoint inhibitors, or oncolytic viral therapy, or adoptive cell therapy.

And so talking about immune checkpoint inhibitors, obviously it's a very complicated topic, but I'll be highlighting a few features of it. Basically, the rationale here is that immune cells, for example, T cells-- their activity is controlled by various molecules and pathways that either activate them, or inactivate them. And so, for example, we've all heard of T cell activation inhibitors like CTLA-4, and PD1, PD-L1. And then there are T cell activators, for example, ICOS and OX40. And so if you inhibit the inhibitors, or if you activate the enhancers of these cells, we could potentially improve the immune system's ability to fight cancers. And based on this, there are a couple of random-- sorry, a couple of trials that are currently ongoing.

This first trial is out of the University of Pennsylvania. It's a Phase II trial, that's looking at CTLA-4 and PD1 inhibitors, or a combination of ipilimumab, and pembrolizumab. These are for patients with appendix and colon cancers, with peritoneal metastases. And the second one is from GSK, GlaxoSmithKline, it's a Phase I study of intravenously delivered ICOS or OX40 receptor antibodies. These are activators, with or without immune checkpoint inhibitors. So again, this is immunotherapy given intravenously, for peritoneal metastases from colon-- including patients with colon and appendix cancers, but their early phase trial is looking at efficacy and safety.

The next immunotherapy that's up and coming, and being tested for peritoneal surface malignancies, are adoptive cell therapies. So the rationale here, is that cytotoxic T cells can be taken from patients, and then they can be re-engineered to fight cancer more effectively. And so one of the adoptive cell therapies that we've all heard about, is CAR-T cell therapy, or chimeric antigen receptor T cell therapy.

And the concept behind here, is that we can take T cells from patients, we can then re-engineer them to better target cancer cells, we can expand them outside the human body, and then we can give them back to patients with the hope that they're much more effective against cancer. And so this is just a picture of that, that we take a T cell, we add a chimeric antigen that helps these T cells be more effective, and then we give it back to the patients.

And so this is data from Dr. Katz, who's a surgeon, a surgical oncologist who works with immunotherapy, and he developed an intraperitoneal delivered CAR-T cell, that targets CEA. And obviously, CEA is often a molecule seen on colon and appendix cancers. And so he used a mouse model of intraperitoneal colon cancer, and this is just some of the data from one of his publications.

And so if you look at the graph on the left here, this is mice that were not treated with any immunotherapy. This is mice with intraperitoneal colon cancer treated with IV delivered CAR-T cell. And this is mice treated with IP-CAR-T cell. And this y-axis basically shows the amount of tumor in these mice. And you can see a significant reduction in the burden of tumor in these mice.

The second graph shows the same thing, except with immune checkpoint inhibitors. So this is IP-CAR-T cells alone, and then these three are IP-CAR-T cells with different types of immune checkpoint inhibitors. And again, you can see a significant reduction in the burden of tumor inside these mice, which you can see here in a picture, this is untreated mice, this fluorescence is basically tumor inside the abdominal cavity of a mouse, and at this end you have the CAR-T cells with immune checkpoint inhibitor, that you basically sort of see no fluorescence, showing that you can have a significant impact on the amount of disease.

And based on that, Dr. Katz has a Phase I study that's currently ongoing, he's giving intraperitoneal CAR-T cells that are labeled with CEA, and he's looking at, basically, early phase outcome measures, like maximum tolerated dose and safety, and so this is a trial that's ongoing currently. And there are obviously other trials that are also ongoing.

Finally, moving on to oncolytic viral therapies. So the theory behind here is that we can use genetically engineered viruses, that can then destroy cancer cells either directly, or indirectly, by activating the immune cells. Viruses have been used for a long time to try and target cancer cells and these are genetically engineered to specifically target cancer cells. And so this is some of the data from Dr. Bartlett, who's another big name in cytoreductive surgery and HIPEC and a big name in immunotherapy. He developed an intraperitoneally delivered vaccinia virus-- this is a genetically modified vaccinia virus-- that expresses a membrane-bound interleukin-2. And interleukin-2 is a well-known cytokine used to fight cancers.

And he tested this again in a mouse model of intraperitoneal colon cancer. This is just a picture of this vaccinia virus IL-2 gene. And so if you look at these gene construct-- and so if you look at this picture on the left, this is a graph of the mouse model treated with this therapy. And this is survival, percent survival of mice over time. This is an intraperitoneal model of MC38, which is a kind of colon cancer. And if you just look at the green and the red lines here, this is survival.

The red line is the vvDD of the vaccinia virus IL-2, and the green is a similar vaccinia virus IL-2. If you compare this to untreated, which is the blue line, or the vaccinia virus on its own without the IL-2, the black line, you can see a significant improvement in survival of these mice. And then this graph on the right is the same type of treatment, except immune checkpoint inhibitors were added, and you can see here in the red and the blue, where the vaccinia virus expressing IL-2 with immune checkpoint inhibitors was given, and you can have long-term survival of these mice.

Showing very promising data, preclinical data. And based on this, there should be a trial opening soon at the University of Pittsburgh using the same vaccinia virus expressing membrane-bound IL-2, and we're going to be looking at unresectable patients with either colon cancer or mesothelioma, and then treating them intraperitoneally with this oncolytic viral therapy. Again, looking at safety and efficacy of this therapy.

Another novel therapeutic strategy that's being tested, is this pressurized intraperitoneal aerosolized chemotherapy, also known as PIPAC. Of note, this is mostly being used in Europe, and in other countries, but not in the United States at the moment. The rationale here is that it has a similar concept to cytoreductive surgery and HIPEC, except it's done laparoscopically, and the drug that's given, is aerosolized, so it's delivered into the peritoneal cavity under high pressure, so that it becomes aerosolized, and is not given under heat.

And so the concept behind this is that by giving these drugs under high pressure, you're improving the penetration of drugs, and you're improving the distribution because you're giving it laparoscopically into the peritoneal cavity. And by doing that, you can give lower doses of drug, and because you're doing it laparoscopically, you can do this multiple times. And so there are a number of reasons why this may be a good way to approach patients with peritoneal metastases.

So based on this, there are multiple trials. They're all outside the United States. They're still early phase trials and a variety of different peritoneal metastases, looking at the efficacy and the safety of this PIPAC procedure for patients with peritoneal metastases.

Finally, I'll talk about EPIC. EPIC is basically giving intraperitoneal chemotherapy following surgeries, so after having completed surgery, the patients recover, and then in their first five post-operative days, a catheter is left behind in the abdominal cavity, and then chemotherapy is administered into the peritoneal cavity, with the hope that any microscopic disease left behind can be targeted. And so there's an ongoing randomized trial at Memorial Sloan Kettering, that's run by Dr. Garrett Nash, it's a Phase II trial, and he's comparing CRS-HIPEC versus CRS plus EPIC, and this remains ongoing as another potential trial that patients can get enrolled in.

The final one that I'll mention, is there are other novel strategies that are being, or have been considered, for patients with peritoneal metastases. And one of them is called NIPS-- it's Neoadjuvant Intraperitoneal and Systemic chemotherapy. So the rationale here is that we're trying to improve the response and reduce systemic toxicity by combining both systemic therapy and intraperitoneal delivery of chemotherapy so that we can reduce toxicity in patients. And so this is a trial being done by Laura Lambert in Utah. It's a Phase I early-phase trial, in which instead of giving all three standard drugs intravenously, two of the drugs irinotecan and 5-FU is given intravenously, whereas oxaliplatin is given intraperitoneally. And so they're looking at the combination of intraperitoneal and systemic chemotherapy, to see if patients can tolerate this better, and at the same time have good tumor response.

So I'll stop there. Obviously, that's a lot of information. We've gone through a lot of different concepts and a lot of different upcoming therapies. And I would be happy to take any questions at this point, thank you.