It is. My name is Pam Koons. I’m a GI medical oncologist and the director of the Center for GI Cancers. It’s my great pleasure to get to introduce Doctor Kiran Taraga as today’s speaker and welcome to those in person and everybody online. So Doctor Traga is a professor of surgery and the division Chief of Surgical Oncology in the Department of Surgery and the Assistant medical director for the Clinical Trials Office. At Yale Cancer Center,
he joined Yale in fall of 22, and I'm from the University of Chicago, where he was vice chief of the section of General Surgery and Surgical Oncology and director of the surgical GI Cancer program. He is considered a national, international thought leader in the management of Oligometastatic disease and is an expert in regional perfusion, including hyperthermic intraperitoneal chemotherapy or hypec. This is a technique that delivers chemotherapy intrapararete mealy following resection of visible tumors and his research focuses in
00:01:08.100 --> 00:01:10.525 this space specifically on clinical
NOTE Confidence: 0.928752571428571
00:01:10.525 --> 00:01:12.950 trials exploring the interface of
NOTE Confidence: 0.928752571428571
00:01:12.950 --> 00:01:15.261 immunotherapy and liquid biopsy and
NOTE Confidence: 0.928752571428571
00:01:15.261 --> 00:01:17.376 the surgical management of cancers.
NOTE Confidence: 0.928752571428571
00:01:17.380 --> 00:01:19.424 I can say personally it’s been really
NOTE Confidence: 0.928752571428571
00:01:19.424 --> 00:01:21.100 just wonderful to have you here,
NOTE Confidence: 0.928752571428571
00:01:21.100 --> 00:01:23.095 Karen and he is a fantastic
NOTE Confidence: 0.928752571428571
00:01:23.095 --> 00:01:24.275 collaborator for the scientists
NOTE Confidence: 0.928752571428571
00:01:24.275 --> 00:01:26.379 in the room and in the zoom room
NOTE Confidence: 0.928752571428571
00:01:26.379 --> 00:01:28.660 I’m putting in a plug that he is
NOTE Confidence: 0.928752571428571
00:01:28.660 --> 00:01:29.892 looking for potential partners.
NOTE Confidence: 0.928752571428571
00:01:29.892 --> 00:01:30.676 So I’m.
NOTE Confidence: 0.928752571428571
00:01:30.676 --> 00:01:31.460 So Karen,
NOTE Confidence: 0.928752571428571
00:01:31.460 --> 00:01:32.618 thank you for joining us today,
NOTE Confidence: 0.9064422666666667
00:01:38.680 --> 00:01:41.104 but thank you Doctor Koons and
NOTE Confidence: 0.9064422666666667
thank you everyone for coming today.

I took the liberty to of sharing some slides which have some of our research interests.

And so forgive me if it seems like there's just so many topics we're covering it just we'll hopefully share with you how excited I am about this field and how much I would love to get all of you excited about it as well.

Renee, do you know if I can turn some of the lights down around this space here?

Because I think I have some videos I was running here.

So I am a surgeon and it is
lunchtime and I do apologize.

I'm going to show some pictures.

I tried to kind of reduce the number of pictures I have.

I do consult for I've just done some consulting for Mark, but it's not anything I'm going to speak about today.

So in 2016 there was this news frenzy that I'm sure most of you probably didn’t even see, but it said a new organ has been discovered.
the peritoneum and the mesentery.

And so for all of us surgeons in the room we laughed because you know this is something people have known for thousands of years. But I think what you’re seeing in this schematic over here is you’re seeing the the colon. So you can see in C here, you can sort of see how the mesentery kind of wraps around the colon. And I tell patients the peritoneum...
NOTE Confidence: 0.9301902
00:03:16.612 --> 00:03:18.670 is just sort of like a membrane,
NOTE Confidence: 0.9301902
00:03:18.670 --> 00:03:20.866 which is essentially like Saran wrap.
NOTE Confidence: 0.9301902
00:03:20.870 --> 00:03:23.264 It’s essentially as thin as Saran wrap,
NOTE Confidence: 0.9301902
00:03:23.270 --> 00:03:24.986 but it has some remarkable functions.
NOTE Confidence: 0.9301902
00:03:24.990 --> 00:03:26.550 It it has, you know,
NOTE Confidence: 0.9301902
00:03:26.550 --> 00:03:29.126 it clears a lot of endotoxins,
NOTE Confidence: 0.9301902
00:03:29.126 --> 00:03:30.494 bacteria, there’s macrophages,
NOTE Confidence: 0.9301902
00:03:30.494 --> 00:03:33.230 there’s some T cells in that.
NOTE Confidence: 0.9301902
00:03:33.230 --> 00:03:35.370 It has very important roles
NOTE Confidence: 0.9301902
00:03:35.370 --> 00:03:36.654 in cellular adhesions.
NOTE Confidence: 0.9301902
00:03:36.660 --> 00:03:38.256 And so it’s a very interesting thing.
NOTE Confidence: 0.9301902
00:03:38.260 --> 00:03:39.755 And as surgeons we notice
NOTE Confidence: 0.9301902
00:03:39.755 --> 00:03:41.250 this because cancers when they
NOTE Confidence: 0.9301902
00:03:41.309 --> 00:03:43.019 spread to the peritoneal lining,
NOTE Confidence: 0.9301902
00:03:43.020 --> 00:03:45.420 they rarely cross the peritoneal barrier.
NOTE Confidence: 0.9301902
So it’s a very interesting phenomenon that such a thin membrane can actually restrict tumors within this membrane. And so it’s a very exciting sort of space to think about. And you know the biggest question is always you know, where do peritoneal surface malignancy stand and should we club all of them together like. Is the phenotypic expression of metastasis as the peritoneal metastases, is that more important or do we think of cancer is more like gastric cancer, pancreatic cancer, liver cancer?
And so is it more Histology specific in terms of where they start or the phenotypic expression? And I would argue that it is a combination of both. So I think clearly you have to recognize Histology specific, you have to think about the somatic mutations, you have to think about what the primary tumor is. The tumors that spread to the peritoneum are somewhat bound by some general common principles, which is that they tend to spread.
in a very different way than hematogenous or lymphatic spread. So they rarely spread, you know, beyond sort of these spaces and they spread by almost contact. It’s a very bizarre phenomenon when we open the abdomen and we look. It’s always in spaces which are sort of sequestered where the flow of peritoneal fluid gets stopped. So the right diaphragm for instance or by the ligament of trite, so just a very mechanical sort of a problem that we see. And in this talk when we’re talking
about peritoneal metastasis, you know generally we’re thinking of secondary peritoneal tumors, so tumors that have started at another site and then spread to the peritoneum even though there are primary peritoneal malignancies like mesothelioma or plastic small round cell tumors. That occur in the peritoneum itself. Now the question is how do we estimate the incidence of this? Is this a big problem or is this a very small problem? And the answer is we don’t exactly
know how big the problem is.

But I would contend and we’ve done

the math on this and we’ve kind

of looked at this annually there’s

probably about 100 to 150,000

patients with peritoneal metastases

that are diagnosed every year.

If you add up everyone that’s a lot,

that’s about three times the number of

new pancreas cancer diagnosis every year.

So it it is something phenotypically is a

very large but heterogeneous population

and I’ve shown this slide many times.

So those of you that have heard this talk,

you know or heard some version of my

talk have seen this slide, but I don’t,
I won’t apologize for it because I do think this was a very important part in my life in deciding how and why to do paranew metastasis. And this was a young patient who had colon cancer and had clean scans and presented with a bowel obstruction. And I explored his abdomen over here and for you know, those of you in the room, what we’re seeing here, you know, this is the liver, this is the head of the patient. You can see the graphic there, the liver right.
there, the transfer of stolen

And the sheet of Elmer's glue,

that was his peripheral metastasis and.

And it was very unfortunate that we just could not help this young patient who then succumbed to this cancer in a few months after this.

we just could not help this young patient who then succumbed to this cancer in a few months after this.

So it's a, it was a very thought provoking problem.

that I have dedicated my career to.

And so First off,

I would just say that peritoneum metastases are much more common than we think they are.

So. So it's a, it was a very thought provoking problem.

that I have dedicated my career to.
And and why is that?
Well, think about it this way if you cannot.
Detected on CT scans or PET scans or MRI's,
you cannot actually measure it.
So in this, in this graphic that one
of our residents made many years ago,
we just looked at all the
different sort of sources of
incidence only seems 2% or 3%.
But if you actually look at autopsy series, which are dominated by patients probably who die of different reasons, the incidence of metastasis is as much as 20%. And this is only for colon cancer. So I imagine 135,000 new colon cancers a year, and you have 20% of them with peritoneal metastasis. And if they’re mucinous tumors, it’s 40%. So it’s a much higher incidence. But the problem is we don’t know where the reality is.
measure pertinal metastasis.

So that’s one of the big problems and challenges that are there.

I think the second is that these patients don’t have clinical trials for them often. Why?

Because we can’t measure it. If you can’t measure it, there’s no drug company that’s willing to give you a drug to put these patients on clinical trials because you don’t have measurable disease. So how do you know if your drug is working or not? And that’s the biggest challenge we all face.
And in fact, this is one of the papers that one of our fellows had looked at many years ago. In which we saw that for colon cancer, there were 46,000 patients at that time point who had been enrolled in clinical trials of which only 600 had some version of peritoneal disease and there was no outcomes reported for these folks. So a very excluded population of patients, a very big population of patients, but excluded from clinical trials and excluded from a lot of treatments. And the problem then becomes those that do get enrolled on clinical
trials or those that have widespread disease or very measurable disease, they have big tumors, lumpy tumors. And so we look at these graphs and we're very nihilistic. We're like, ah, pertinent metastases. It's, you know, not something that we would take care of and these patients should just go to Hospice. And I think palliative care is very important in the management of these patients, but but just being very nihilistic about this disease is not fair to these patients either.
And in fact, so much so that almost five or six years ago, in fact, when I started and when I had that graphic, none of the surgical textbooks had a chapter about peritoneal metastasis. It’s remarkable. Now we do have many chapters because of our constant advocacy work. And then finally, you know, when you think about sort of this nihilism around peritoneal metastasis, the question is why? Why are these patients dying? Are they dying of cancer, cataxia? Do they die because these patients have this sort of overwhelming interleukin
00:09:47.186 --> 00:09:49.070 response that they can’t eat or
00:09:49.070 --> 00:09:50.786 drink and they kind of waste away?
00:09:50.790 --> 00:09:52.596 Is this a catabolic phenomena like
00:09:52.596 --> 00:09:55.070 that or the are they just dying
00:09:55.070 --> 00:09:57.070 because they have bowel obstructions?
00:09:57.070 --> 00:10:01.228 it’s like if someone had renal failure and
00:10:01.230 --> 00:10:01.788 you don’t put them on dialysis and they die,
00:10:01.788 --> 00:10:04.600 you wouldn’t say,
00:10:04.600 --> 00:10:06.315 renal failure is such a horrible problem
00:10:06.315 --> 00:10:07.830 you don’t have treatment for it,
00:10:07.830 --> 00:10:10.126 but if someone has a bowel obstruction
00:10:10.126 --> 00:10:12.560 and and you are unable to fix it.
00:10:12.560 --> 00:10:14.520 You know is that is that truly
more the nature of the disease or
is it the biology of these tumors.
And so one of my colleagues at
the University of Chicago,
who’s one of the world leaders in in
the thought process of oligo metastasis
actually coined the term oligo metastasis.
And when you look at sort of
colorectal and this is colorectal
metastasis with liver tumors,
there’s a completely differential
expression of micro RNAs.
And they published a lot of subsequent
work looking at immune rich profiles
which seem to do really well.

These patients.

If you look at the X axis on the survival curve over here, it's 10 plus years, almost 15 years and you have about 40-40 to 60% of patients actually living that long when you have this sort of appropriate expression of of your tumor. And and this is one of those experiments where you know in this specific case they looked at micro RNA200C and you basically have vial type versus those that express it. And of course you can see an oligo
metastatic phenotype which is eligible for surgical therapies, radiation or ablation, ablative therapies versus those patients that have Poly metastatic phenotypes. And similarly when you essentially reduce the expression of these micro RNAs you can actually see sort of some of these will have oligometastatic disease some of these will have polymetastatic disease. So clearly there is a differential phenotype of patients that can be cured. So not all stage 4 cancer is the same
is is sort of where I I I would try to say these three slides or what what I wanted to convey.

And so you know, how do we as surgeons approach a problem like this? You know, very often we would see patients with peritoneal metastasis. So you can see the livers down here, it’s a large amount of peritoneal metastasis is the phals form ligament. And very often surgeons would come out of these cases saying, oh gosh, we cannot do anything for these patients. But we’ve subsequently developed techniques called peritoneectomies.
I tell patients it’s like peeling the wallpaper off the walls. Essentially you’re not destroying the walls, but you’re actually taking disease out. Here you can sort of see what it looks like, it’s that Saran wrap which is underneath our instruments right here and the same patient you can actually strip or clean out that entire peritoneal layer by keeping an intact peritoneal SAC so that you can actually remove all of this in its entirety. So it is something that is
interesting and surgically would become more aggressive at it.

But right now this is a very aggressive approach. You know you can see this is a big laparotomy incision. The head of the patient is on one side, the feeder on the other. And after we remove all this cancer, we put heated intrapartitial chemotherapy. The the concept is that you know you have application of chemotherapy at high doses which has low toxicity.
to systemic absorption is very low,

you can actually enhance the penetration of the drug.

You know these tumors are very hypovascular,

so you can kind of enhance the vascularity during that period.

But again it’s a little bit also controversial because you know how does one application of chemotherapy work so effectively versus multiple applications that we do in the systemic setting.

And clearly you know now we do these laparoscopically as well in selected
patients when we find disease early, so we can deliver heated chemotherapy that way. And then also now what is very hot in Europe and Asia is intrapertinal aerosolized chemotherapy where you can actually distribute the drug a lot better across the entire pertinal cavity. This is called pipec and over 10,000 procedures have already been done in the world for these technologies. And as you would imagine a lot of these patients require very close management as a team,
the team that consists of physicians. Which consists of nurses and dietitians and program and only when you do that you’re able to achieve you know, good outcomes. And so this is sort of where you know, we were before I left the University of Chicago, we did about 180 procedures a year. We were able to reduce the length of stay for patients from 10 days to six days, the benchmark programs being MD Anderson and Wake Forest and readmission rates of 8%. So it took a lot of effort for us to bring this program together.
For patients that had peritoneum metastases, but the biggest question is well, is it helping these patients, are they living longer? Is it worthwhile to do these aggressive approaches for these folks and this is what happens when patients get selected patients with good performance status get systemic chemotherapy, that’s the reference survival data right here. And then of course those that had cytoreductive surgery, this was our own data for
00:14:53.016 --> 00:14:54.200 how these patients did.
NOTE Confidence: 0.943723035714286

00:14:54.200 --> 00:14:56.195 Only about 20% of our high grade
NOTE Confidence: 0.943723035714286

00:14:56.195 --> 00:14:58.039 patients live 10 years or longer.
NOTE Confidence: 0.943723035714286

00:14:58.040 --> 00:14:59.632 So if you look and remember the graph
NOTE Confidence: 0.943723035714286

00:14:59.632 --> 00:15:01.386 that I showed earlier for those that
NOTE Confidence: 0.943723035714286

00:15:01.386 --> 00:15:03.054 enrolled in NCT and clinical trials
NOTE Confidence: 0.943723035714286

00:15:03.054 --> 00:15:04.599 that were good performance status,
NOTE Confidence: 0.943723035714286

00:15:04.600 --> 00:15:05.980 patients got systemic chemotherapy.
NOTE Confidence: 0.943723035714286

00:15:05.980 --> 00:15:08.440 No one lived more than five years.
NOTE Confidence: 0.943723035714286

00:15:08.440 --> 00:15:10.099 So you do have the select population
NOTE Confidence: 0.943723035714286

00:15:10.099 --> 00:15:11.440 of patients that you can help.
NOTE Confidence: 0.943723035714286

00:15:11.440 --> 00:15:13.240 But the question is where do we go from here?
NOTE Confidence: 0.943723035714286

00:15:13.240 --> 00:15:14.800 How do we make this better?
NOTE Confidence: 0.943723035714286

00:15:14.800 --> 00:15:17.144 And this is really where I think it’s
NOTE Confidence: 0.943723035714286

00:15:17.144 --> 00:15:19.400 important for all of us to think about it.
NOTE Confidence: 0.943723035714286

00:15:19.400 --> 00:15:20.340 So the first question we
NOTE Confidence: 0.943723035714286
00:15:20.340 --> 00:15:21.280 want to ask ourselves is,
NOTE Confidence: 0.943723035714286
00:15:21.280 --> 00:15:23.180 can you actually prevent
NOTE Confidence: 0.943723035714286
00:15:23.180 --> 00:15:24.130 peritoneal metastasis?
NOTE Confidence: 0.943723035714286
00:15:24.130 --> 00:15:25.890 And I’ll show you some science behind this,
NOTE Confidence: 0.943723035714286
00:15:25.890 --> 00:15:27.635 but something that is very
NOTE Confidence: 0.943723035714286
00:15:27.635 --> 00:15:29.380 interesting is that a recent
NOTE Confidence: 0.943723035714286
00:15:29.444 --> 00:15:31.472 trial that was just looking at
NOTE Confidence: 0.943723035714286
00:15:31.472 --> 00:15:33.675 patients that had T4 colon cancers,
NOTE Confidence: 0.943723035714286
00:15:33.675 --> 00:15:35.650 nothing has spread outside and.
NOTE Confidence: 0.924771571111111
00:15:58.700 --> 00:16:00.275 On that patients actually have
NOTE Confidence: 0.924771571111111
00:16:00.275 --> 00:16:01.535 better local regional control.
NOTE Confidence: 0.924771571111111
00:16:01.540 --> 00:16:02.975 If you apply intrapertinal chemotherapy
NOTE Confidence: 0.924771571111111
00:16:02.975 --> 00:16:05.367 at the time of a primary cancer
NOTE Confidence: 0.924771571111111
00:16:05.367 --> 00:16:07.175 resection without pertinal metastasis,
NOTE Confidence: 0.924771571111111
00:16:07.180 --> 00:16:08.800 can you actually,
can you actually reduce that?
And so if you think about it
and this is something I will, I will tell you is is
very interesting science.
done by one of my colleagues
at the University of Chicago.
Where we’re thinking about
the intestinal microbiome,
I think many of you might might
have heard about the important
role of the microbiome and thinking
about carcinogenesis as well
as development of metastases.
And clearly in a Peri operative event
we change the microbiome of the intestines. And so the hypothesis for their experiments were to look at what happened if you took a Western diet. So essentially the experiments were in mice you basically resected the colon, put colon cancer cells inside it, and then you gave them a collagenolytic bacteria called Ephycallus with the hypothesis that collagenolytic bacteria cause increase in astomatic leaks.
So this is their work.
NOTE Confidence: 0.924771571111111
This has been their life’s work
NOTE Confidence: 0.924771571111111
on this and it’s remarkable and
NOTE Confidence: 0.924771571111111
there’s lots of experiment that
NOTE Confidence: 0.924771571111111
support that it causes this.
NOTE Confidence: 0.924771571111111
But what was interesting to me.
NOTE Confidence: 0.924771571111111
Is when you actually look at this,
NOTE Confidence: 0.924771571111111
these anastomosis.
NOTE Confidence: 0.924771571111111
So once you’ve cut the mice,
NOTE Confidence: 0.924771571111111
you put them back together and you
NOTE Confidence: 0.924771571111111
inject collagenolytic bacteria and
NOTE Confidence: 0.924771571111111
then you put colon cancer cells in there.
NOTE Confidence: 0.924771571111111
All the all the tumors that developed
NOTE Confidence: 0.924771571111111
were on the serosal surface and
NOTE Confidence: 0.924771571111111
not on the mucosal surface.
NOTE Confidence: 0.924771571111111
So all of them came on the serosal surface.
A lot of these mice ended up dying of peritoneal metastasis. It's a very interesting credence to the theory that perhaps there may be a microbial alteration that is occurring in these primary cancer resections that is leading to these patients getting peritoneal metastases. And what is very funny is that one of our colleagues in Belgium said maybe the reason mitomycin which is our intraperitoneal chemotherapy works is that it is also an antibiotic. And again it’s not been proven, but it’s just a very thought.
provoking way of thinking about.

Where the microbiome lies as we think about why patients get hurt in metastasis,

but if we can find these tumors and we can actually detect them early and we can treat them,

these patients beat the survival curves.

So this is the survival of patients that if they were found early and had surgery,

you can look at the X axis is five years and you can see that 90% of these patients are alive at five years.

So really a,

can you prevent them and B,

can you find them if they're very early and then treat them.
That is sort of really where we need to move the needle and that’s really where I would love for us to think about it, about it together. And so the problem is conventional cross-sectional imaging. This is a CT scan on a coronal view of a patient and on a cross-sectional imaging, the peritoneum is incredibly difficult to image. So the imaging of the peritoneum, if you can see my cursor, which you cannot, is actually this line that kind of goes along the colon. It’s this sort of little little fun time.
stuff here. This stuff right there,
NOTE Confidence: 0.946962453333333

that’s the first name right there.
NOTE Confidence: 0.939212499655173

And so it is, it is very difficult for
NOTE Confidence: 0.939212499655173

us to believe that our radiologists
NOTE Confidence: 0.939212499655173

are going to be able to tell us that
NOTE Confidence: 0.939212499655173

a patient has peritoneal metastasis.
NOTE Confidence: 0.939212499655173

It is just not feasible.
NOTE Confidence: 0.939212499655173

You can certainly tell if someone
NOTE Confidence: 0.939212499655173

has liver metastasis or not,
NOTE Confidence: 0.939212499655173

but it’s very difficult to tell
NOTE Confidence: 0.939212499655173

if they have peritoneal meds.
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And so we’ve played with this
NOTE Confidence: 0.939212499655173

along with many,
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many other groups and there’s a lot of
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radiomics work that folks have done.
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We’ve done our own radiomics work.
We did some work with our physics group at the University of Chicago and try to kind of pick up better ways of looking at the pertinum. You can look at panel B, you can sort of see how you can actually enhance the pertinum better by kind of playing around with contrast agents and how do you give it later? How do you give it earlier and how does that kind of make a difference? I think the other thing that we’ve very been very interested in is study of circulating DNA,
whether it’s cell free or whether it’s circulating tumor DNA. And clearly we know as surgeons that it’s very prognostic. What do we do with that information is still something we’re all trying to figure out. But we know that if they’re, if they don’t have cell free DNA prior to surgery and you operate or at least vary in cell free DNA before surgery you operate and they stay negative. These patients will do really well, whether it’s GI cancers of different types or other types of cancers. And so this is some of our work.
that just got published as well and was one of the plenary sessions. Some of you have heard this before. But really what we did was we took patients who had peritoneum metastases. We did surgery for these folks and then we studied them and followed them at CTDNA. We said can we actually figure out a better way of identifying these tumors early and the answer was yes, CTDNA did work for us. This is a small sample size with numerous assessments. It’s not 100% sensitive.
It was only about 90% sensitive in this cohort and it did have a false negative rate.

So patients who did have undetectable CTDNA, 1/5 of them still had peritoneal metastases.

And in fact if you look at cohorts of different technologies, many times you have florid peritoneal disease and they shed almost no CTDNA.

In fact one of our research fellows were run in the back has just submitted an abstract where if you have a single solitary liver metastasis your CTDNA is super high. But if you have a full abdomen full of peritoneal metastases,
you have almost no CTDNA in the range of like point some MTM per ML. So it’s a remarkable phenomenon that the burden of tumors this is almost the same or even many fold more, but it doesn’t shed it. It gives credence to the belief that maybe local regional treatments like surgery, intravertinal chemotherapy may have a role in in these sort of metastatic settings and then as expected if they shed DNA they do worse. If they don’t shed DNA, they do a lot better and that’s sort of what we saw in this.
And the biggest question was we saw these patients you know three months before they showed up on scans and you know ceas and things like that. But really the bigger question is what are we going to do with that information and how do we make it practical for our patients. And so you know some of our research has been focused a lot on looking at epigenetic modifications and why this is important is because right now, we need a large amount of DNA to actually do CT DNA, to do other types of cfDNA.
can we actually extract DNA at very low levels without the bisulphite conversion so that it doesn’t destroy a lot of the DNA in the blood and then look at alterations in a cheap sort of reproducible way? And so this is where we work with one of our chemists, Schwan hey, who actually came and gave chemistry grand rounds not long ago at Yale. And a phenomenal colleague and collaborator, but you know basically looking at HMC and now we’re looking at 5 MC modifications. So we have different sorts of
modification profiles and his lab has already shown and this is I think published in cellular science. But looking at sort of the five HMC distributions of patients and you can identify patients who have cancer versus controls, you can look at adenomas versus controls, adenomas versus cancer and then what we found was peritoneal disease versus no peritoneal disease. We also had understanding of the mechanistic underpinnings of peritoneal metastasis and you know I've identified some epithelial meas and camel
transition markers that potentially could be part of our signature to identify peritoneal disease better.

So switching gears a little bit, you know what I hope I’ve emphasized in this first few minutes of my talk is that peritoneal metastases. Maybe a heterogeneous group of things. There may be a population of patients that are treatable with local regional therapies. We struggle to figure out how to identify these patients, whether it’s with cross-sectional imaging, radio omics, or whether this type of work or whether
it’s with cell free DNA work,

although there’s promising avenues in both of these.

So the question comes to how can you actually think about treating these patients?

Are there things we can do differently?

In clinic,

we often see patients coming and saying I stopped having sugar because I was told I have cancer,

I’ve told sugar feeds these cancers and really what happens to these tumors. We believe that these tumors are hypoxic.

We believe that the peritoneum has very little vasculature as compared to say the liver and other sort of solid organs.
like the lungs and we all know that.

You know tumors as they develop metastatic potential, they rely more on anaerobic pathways, but they also still have location specific metabolic needs specifically around oxidated phosphorylation.

And so the question is, where are these tumors getting their fuel from?

And so we did a couple of trials with one of my colleagues, Ernst Langel over there where we gave patients sort of tracer.
labeled glucose and kind of studied tumors and and clearly they go along more anaerobic pathways. You see a lot more lactate in these tumors and they kind of use different metabolic substrates as they’re kind of getting it. But what was very interesting is the omentum, which is the commonest site of peritoneum metastases. And we don’t know why it does have a very rich source of fuel with it which is adipocytes. And and in these experiments what basically Ernst Group showed was that when you actually control
for Fab BP4 which is associated integrally with adipocytes, you can actually reduce the amount of in vivo metastasis in mice and so essentially it is somehow. You know, lending critics to the theory that the momentum and the adipocytes that are in the momentum are providing fuel as opposed to a lot of the vasculature which provides fuel to these pertinent metastases. Very interesting preliminary work. It’s again not meant for you know like inpatient in patient care right away,
but I think very interesting for us to think about how do we take care of these patients and perhaps how do we think about alteration of adipocytes. And the other thing we’ve been very interested in is how do we actually enhance the effect of intraperitoneal chemotherapy, how do we leverage this to enhance the care of these patients. So these are patient panels where we had patients with high grade unresectable tumors, where we did multiple applications of intraperitoneal chemotherapy only, no surgery and we actually developed complete pathological...
00:26:09.314 --> 00:26:11.642 responses as you can see in panel

00:26:11.642 --> 00:26:13.546 C for these patients that had very high grade disease that we would not have routinely offered surgery for.

00:26:13.546 --> 00:26:15.519 And they lived exactly the same as those that we did open big cytoreductive surgeries and hypex for.

00:26:15.519 --> 00:26:16.944 But what was more interesting was that a lot of these tumors actually developed and I don’t have that data here, but they all had alterations in their P, DL1 expression, their C, PS,

00:26:20.928 --> 00:26:22.788 cytoreductive surgeries and hypex for.

00:26:20.928 --> 00:26:24.638 But what was more interesting was that a lot of these tumors actually developed and I don’t have that data here, but they all had alterations in their P, DL1 expression, their C, PS,
an intravertinal chemotherapy plus immunotherapy for these patients that are otherwise cold tumors. These are incredibly cold tumors. If you look at the TCGA Atlas, a lot of these GI tumors actually have a lot of you know sort of hot immune signatures. When you actually go to giving these folks checkpoint inhibition or do any sort of conventional immunotherapy, they don’t respond as well unless they’re MSI high or they have specific characteristics. And so with intrapartinal chemotherapy we believe that you can actually change some of the immune profile of these tumors.
And so I think in the last, you know maybe 5 or 10 minutes of this of my talk. You know I just wanted to tell you that there are numerous unanswered questions in the management of peritoneal metastasis. Numerous I will tell you that we don’t even know the basics of the immune environment of the peritoneum. It’s fascinating. I was talking to Steve Rosenberg once and I asked him, I said do you understand the immune environment of the peritoneum and and the bottom line is for some
You know many of the labs many, many animal models look at intrapertinal tumors. But we actually don’t understand what the native immune environment of the peritum is. How is T cell trafficking happening over there? What is the repertoire of T cells that are present in the peritum. We understand what happens when there’s peritonitis. We certainly know that when someone has inflammation, what happens to these tumors and how do they, the inflammatory processes.
But we don’t actually understand what happens to these clinically. How we see this is many times our patients are dying because of the inflammatory response. They die of bowel obstructions because the tumors create the significant inflammatory response, it causes mesenteric fibrosis and then we’re unable to fix these bowel obstructions that these patients have. And so we don’t understand this. The other work that is very interesting is that we all know that the vent beta ketenin pathways are...
activated in a lot of these GI tumors

that cause peritoneum metastasis.

But what we have also seen is

the conventional bad actors,

the B RAF mutant tumors.

They don’t do as poorly when

they have peritoneal metastasis.

They actually do almost exactly the same.

And indeed it’s the big three CA

pathways that are mutated that

seem to predict differently.

So they do differently based on sort

of what they’re signaling pathways.

And we don’t understand that.

We don’t know why that is the case.

And then finally,
there's a lot of science about pharmacokinetics of drugs and novel drug delivery.

We know that if you give someone systemic chemotherapy by the time it crosses the plasma peritoneal barrier, the concentration of the drug depending on the molecular size of it is one by two to the 10th, so 1 by 1000 and 24th of the serum concentration of this chemotherapeutic and that is a remarkably low dose of systemic chemotherapy when it comes to the peritoneum. The question is how do you...
How do you actually change that such that your drug substrate substrates are able to actually enter the peritoneum? And how do you think about the pharmacokinetics? I'm just, I just have two like sort of quick slides for for folks to look at. And this is the work that was actually done by one of our medical students. All the work that I've shown today, most of it has been done by either our lab or one of our collaborator labs. And it's all been driven by medical students, residents,
undergraduate research students, fellows.

And so I, I,

we truly have been very hungry for for young,

you know smart minds to come work

with us to help figure out how do we

actually make a difference in this.

And this is just the work looking at

the number of pathways that are altered

for patient with pertinum metastases.

And you know of course the APC pathways

are always affected in a lot of these

GI tumors here as about half of the time.

But the big three kind is which we

thought was the most important pathways

in particular metastasis only about
and of course mad for 11% and then this sort of you know and again done by one of our medical students. So, so remarkable sort of work and then this is something where we’ve been looking at microparticles and how do you actually deliver microparticle based. Packlet axle, 2 tumors and what we discovered is that these microparticles are just bound by mucin. So mucin just kind of binds it and doesn’t let it distribute within the peritoneal cavity. And so this is just sort of some of the other work that’s coming out
right now when we’ve been working with one of our pharmacologists to try to figure this out and really finding that, you know, it really binds our nanoparticles and microparticles that we’re introducing in the peritoneal cavity. So just kind of a very tough space. But that exactly that is why it makes it exciting. That’s why we’re Yale because, you know, we don’t, we don’t address simple problems. We want to take on the tough problems. And I think that’s where having
all of you smart folks here is, is so important and exciting to me. And so my pitch for all of you would be that it’s a poorly studied field, but it has a large impact. There’s a huge population of patients that would benefit tremendously. From improvements in the management of peritoneal metastasis. So, so I welcome all of you if you’re interested. There’s lots of tissue. We do laparoscopies for these patients. We take out tons of tissue. Sometimes my tissue specimens go across the alphabet,
which means I have more than 26 specimens per case. So lots of tissue to be drawn. Most of these patients are very generous. It is not infrequently once a month or once twice a month I get an e-mail of someone who wants to donate their body to science research. And that is probably the most generous gift that any human being can ever make. But we don’t know what to do with that. Like what do we do with that. We don’t even have a mechanism of actually studying that or making use of it. It’s a nice window of
opportunities environment. We're able to give chemotherapeutics. We're able to give Immunotherapeutics to patients. We do laparoscopies, get biopsies, go do surgery. 2 weeks later, we can actually show you and get you tissue for how these patients will do afterwards as well. I think these patients have a significantly tough time, not only with the disease, the lack of knowledge of the disease. 90% of patients who would come to my clinic were told they were going to live less than three months, 90% we actually,
we actually did a survey and we asked people in our waiting room and they had been told by some healthcare provider who did this. We did a lot of education around this. We have lots of processes of working together. Jen Capital is here and we were just chatting about this. But how do we cointegrate palliative care into our into our clinics so that we make sure that we’re, we’re taking care of the human being as a whole and not just you know pertinent metastases or not just GI cancer,
but we’re taking care of our, our patients and appropriately transitioning when we’re not able to provide them with therapeutic options. And how do we build clinical trials in this space you know how do you advocate for pharma companies. To get allow these patients to get onto clinical trials, because right now we cannot put these patients on clinical trials. Many times you have ascites that’s not enough. Or if you have tumors which are very small, don’t even fit the 1 centimeter category, you can’t put them on a clinical trial.
So there’s a big, big initiative at the Coke Institute at MIT where we’re trying to get together to try to figure out how do we, how do we fix this. But I think it’s a great space to build a career. That is what I will tell you when I started as a surgical oncologist. You know, every surgical oncologist, for those of you that may not know what we do, we want to do the big liver pancreas operations. That is sort of the sexy thing.
for us to want to do. And that’s what I wanted to do. I wanted to do robotic whipples. That’s what I went and trained and I became an expert in that. And I said I published the first series of how to do robotic whipples and I said this is what I’m going to make my career on. I had the right people to work with.
I had good mentors and that was the best decision of my life. But they said, oh, you know, you can do sort of liver and pancreas, but why don’t you do this stuff? And I started doing it. And I love my patient population and I love what I did. It was a tough problem. No one else wanted to do it. And so I got to write the book chapters, to be coming and doing all of this stuff. And here look at me, I'm.
I'm division chief of surgical oncology, one of the best divisions in the world. So it is a remarkable space and not much has changed. Yes, some has changed, but I think it's a great opportunity for those of you that are excited to build your careers on this because there's not those many people that want to do this stuff or can do this stuff really well. So I would say we were looking lots of partnerships and feel free to reach out. I do have to acknowledge this is
obviously not a comprehensive group,
but this is some of my group
that we’ve worked really closely on for understanding
a lot of our chemistry work.
A lot of our fellows and residents that I, I have not acknowledged,
but I have some of their work in the
slides that have really been very helpful and a lot of funding that
we’ve had over the years that have
we’ve had over the years that have supported our research.
So with that I’m going to stop.
I know it’s a little early but but
I’d welcome any questions or comments
and love a good discussion on

So thank you again for your attention today.

Laura. So

I think this talk

kind of group

together the context of like a

legal mess that you need for.

A lot of life, and normally we obviously

haven’t used either reduction a lot

without a care of intent in MGI center.

And I’m hoping you could weigh in on

your perspective on the difference

of what your new goals are when
00:36:16.210 --> 00:36:17.810 you’re working in this space,
00:36:17.810 --> 00:36:20.730 whether you’re considering it,
00:36:20.730 --> 00:36:22.550 no matter whether you’re considering
00:36:22.550 --> 00:36:24.982 it like a rapid process or if
00:36:24.982 --> 00:36:26.650 that matters and try to discuss
00:36:26.650 --> 00:36:28.050 that with people as well.
00:36:28.760 --> 00:36:29.768 Yeah. No, great question.
00:36:29.768 --> 00:36:32.092 And I I I would say that one of
00:36:32.092 --> 00:36:33.604 the things that we’ve tried to
00:36:33.604 --> 00:36:35.480 do quite deliberately is we’ve,
00:36:35.480 --> 00:36:37.655 so I think when we use the word
00:36:37.655 --> 00:36:39.395 reduction from say debulking,
00:36:39.400 --> 00:36:41.656 So I think when we use the word
00:36:41.656 --> 00:36:43.080 debulking we’re talking about
00:36:43.080 --> 00:36:44.680 enhancing quality of life.
So those, those are not very frequent settings, but we would do debulking procedures if patients have large amounts of mucinous societies or large amount of mucin. Those are the bulking but non curative intent procedures. For the curative intent procedures, we call them site reduction and we have very specific goals of what we want to achieve, which is a CC0 site reduction, which means there’s no visible cancer with oncological principles of surgery. So no longer are we satisfied with,
we just go pluck a little something out and feel like we’ve done a great job.

We have to be oncologically precise in the way we’re doing our surgical techniques, just like we are when we’re doing liver resections, pancreas resections or things like that. The drawback is we can’t image it. So we don’t know what a good, you know, good or bad job we’ve done. And so one of the big things we’ve been doing is making sure our laparoscopy pictures, our surgical pictures are actually in the chart and we can review,
review it with the patients because many times they don’t even know what’s going on, right. They look at the scan and they’re like, oh, there’s just cancer everywhere. And so, so we’re very specific in our intent. And in my ideal world with our palliative care physicians for the three visits, but really the first visit is where I kind of give people hope because
most of them have already been told, you know, three months they’re going to live and die and whatever. And I tell them, hey, listen, this may not be quite the same. Let’s assess it and evaluate it. The second visit is where we really just go through the numbers and again, you know that very nice essay by the evolutionary biologist of like how median is not the mean and, it’s not the message and. And you know,
it's very hard for patients to wrap their heads around it, but I do think it’s important for them or their caregivers to at least understand what the reasonable expectations are. What is our survival data that we have? What is sort of best case scenario, what is worst case scenario? And are we using the hitchhiker model, like are we trying to keep people alive like a diabetes chronic disease type model and saying, hey, we’ll look for this next disease site or are
we saying we’re going to go for a cure or not.
And that’s where we really have a lot of conversations about goal matching and how are we doing the right thing.
And then the third visit is just much more specific around the surgical procedure and what does involve and everything else.
So, so you know we’ve tried to take a very deliberate approach,
but I will tell you that having another physician or another team member in this conversation that may not be a surgeon, you know, very often obviously our
medical oncologist we were Co, you know, seeing patients or palliative care physicians was really helpful for patients.

Because, you know, I’m an optimist and I can sell things different ways, right.

I mean I could say, oh, surgery is no problem. It’s a big no, it’ll be fine versus, you know, Oh my God, it’s a tough surgery and you’re going to do poorly.

So as surgeons, we have a lot of power in how we can actually navigate this conversation and having a sounding
NOTE Confidence: 0.914861194285714
00:39:35.783 --> 00:39:37.890 board for the patients to talk to
NOTE Confidence: 0.914861194285714
00:39:37.890 --> 00:39:41.340 someone who is perhaps not quite,
NOTE Confidence: 0.914861194285714
00:39:41.340 --> 00:39:41.968 you know,
NOTE Confidence: 0.914861194285714
00:39:41.968 --> 00:39:44.264 as narrow minded or or as focused
NOTE Confidence: 0.914861194285714
00:39:44.264 --> 00:39:45.350 I should say.
NOTE Confidence: 0.914861194285714
00:39:45.350 --> 00:39:47.132 Has helped I think generally our
NOTE Confidence: 0.914861194285714
00:39:47.132 --> 00:39:48.603 patients make the right decisions
NOTE Confidence: 0.914861194285714
00:39:48.603 --> 00:39:50.655 and I think for all of us to also
NOTE Confidence: 0.914861194285714
00:39:50.710 --> 00:39:52.366 internalize the fact that you know
NOTE Confidence: 0.914861194285714
00:39:52.366 --> 00:39:54.703 to make sure that we’re not pushing
NOTE Confidence: 0.914861194285714
00:39:54.703 --> 00:39:57.310 therapies on our patients and especially
NOTE Confidence: 0.914861194285714
00:39:57.310 --> 00:39:59.702 you know when we’re not seeing a
NOTE Confidence: 0.914861194285714
00:39:59.702 --> 00:40:01.390 good sort of outcome on the end.
NOTE Confidence: 0.914861194285714
00:40:01.390 --> 00:40:03.110 So I think it’s a very complex thing.
NOTE Confidence: 0.914861194285714
00:40:03.110 --> 00:40:05.340 I mean I think and I’m sure all of us
NOTE Confidence: 0.914861194285714
face it in our clinics every day and what I’m saying is probably not unique, but I think what has helped me.

Is being deliberate about it and also it has helped our team.

You know, I will tell you, we go through cycles of despair even as, you know, physical teams like our, our nurses, physicians, everyone who takes care of these patients. Because you see people that look like you could be your friends, neighbors, colleagues who are dying a very miserable death. And you know, we took care of all these patients
all the way through Hospice. So it is, it is a very difficult thing to kind of be part of the process. And so I think it rejuvenates to have other physicians, providers and then of course having a clinic that’s balanced because you have 20 people that are doing great and you have you know maybe three or four that are not. So we’re so thrilled you’re here. I think you’ve heard me say that many times and I’ll repeat it again.
So I'm going to build on the conversation that you were more curious. Just on into patients that come to desiring this therapy aren’t a yearly candidates that or maybe it wants to decide not to pursue the decide on productive therapy. And then the other related to that is he talked about the recovery from that surgery. So what what does it look like? Yeah, so I think what when we’ve looked at our own data I would say about 67% of our patients had. You know, at least a diagnostic laparoscopy and about 50% of our
00:41:31.566 --> 00:41:32.604 patients who came through our doors
00:41:32.604 --> 00:41:33.979 ended up having cytoreductive surgery.
00:41:33.980 --> 00:41:36.020 So 50% didn’t have it.
00:41:36.020 --> 00:41:37.352 So as you can tell, we are selective,
00:41:37.352 --> 00:41:38.816 but we track our whole cohort.
00:41:38.820 --> 00:41:40.408 So we’re not just saying, oh,
00:41:40.408 --> 00:41:41.724 we’re going to just look at those
00:41:41.724 --> 00:41:42.910 that we’ve done surgery and say
00:41:42.910 --> 00:41:44.220 this is how well we’re doing it.
00:41:44.220 --> 00:41:46.060 The second comment is it,
00:41:46.060 --> 00:41:48.097 it really dependent on the surgery itself.
00:41:48.100 --> 00:41:49.819 So it’s a, it’s a whole gamut of things.
00:41:49.820 --> 00:41:51.260 When we do a laparoscopic hyspec,
00:41:51.260 --> 00:41:52.376 they go home the same day.
00:41:52.380 --> 00:41:54.236 I tell them they can do their normal
physical activities like the next week.

So that's what when we just do a laparoscopic one,

when we do these big monster open side reductions, hynex 812,

you know, 14 hour cases right now our median hospital stays about 5 to 6 days.

But I tell them they feel about 80% of normal in six weeks and they feel 110% of normal at three months because now the cancer is better,

so they feel better.

But this is all generally sort of what things are.
during discussion of surgery is not so much mortality because our mortality rates, as you saw, are very low. It’s more about loss of autonomy and functional independence. So you know there’s an 8% risk of having failure to thrive. Which is a difficult problem. You know then you are on TPN, you’re getting drains, you have this and that and I think that is the the most stressful part of these. But we’ve tried to integrate sort of quality of life initiatives,
00:42:44.500 --> 00:42:46.464 you know fertility management,
NOTE Confidence: 0.91974477875
00:42:46.464 --> 00:42:47.937 young patient care,
NOTE Confidence: 0.91974477875
00:42:47.940 --> 00:42:49.560 obviously palliative care and advanced
NOTE Confidence: 0.91974477875
00:42:49.560 --> 00:42:50.856 direct advanced care planning.
NOTE Confidence: 0.91974477875
00:42:50.860 --> 00:42:52.452 So you know the goal is to have
NOTE Confidence: 0.91974477875
00:42:52.452 --> 00:42:54.029 a more comprehensive way that
NOTE Confidence: 0.91974477875
00:42:54.029 --> 00:42:55.899 patients get the most information.
NOTE Confidence: 0.893702826363636
00:42:59.610 --> 00:43:02.122 I know that this is a slowly evolving
NOTE Confidence: 0.893702826363636
00:43:02.122 --> 00:43:03.842 deal with what we discussed,
NOTE Confidence: 0.893702826363636
00:43:03.842 --> 00:43:06.850 but has it been evaluated from a racial,
NOTE Confidence: 0.893702826363636
00:43:06.850 --> 00:43:09.850 ethnic standpoint as far as incidents
NOTE Confidence: 0.893702826363636
00:43:09.850 --> 00:43:11.810 of care communities along with
NOTE Confidence: 0.904163572
NOTE Confidence: 0.904163572
00:43:13.106 --> 00:43:15.410 So I mean, I think we have, you know,
NOTE Confidence: 0.904163572
00:43:15.410 --> 00:43:16.580 obviously our own cohorts and our
NOTE Confidence: 0.904163572
00:43:16.580 --> 00:43:17.769 own data that we’ve looked at.

92
And in Chicago about 17% of our patients were African American and I think about, you know, maybe another 15% were other ethnicities and everyone else was white. I think the, we found that our African American patients were less likely to do advanced care planning, they were less likely to look in clinical trials. They were usually presented with a higher PCI score, with a higher pertinal index, but actually recovered remarkably the same from cytoreductive surgery procedures. In fact you know at some level I would
00:43:54.015 --> 00:43:56.205 say that are at least in Chicago
NOTE Confidence: 0.904163572
00:43:56.205 --> 00:43:57.832 or African American population had
NOTE Confidence: 0.904163572
00:43:57.832 --> 00:43:59.644 better social structures than some of
NOTE Confidence: 0.904163572
00:43:59.644 --> 00:44:00.890 our white populations of patients.
NOTE Confidence: 0.904163572
00:44:00.890 --> 00:44:02.641 And I think it’s a very selective
NOTE Confidence: 0.904163572
00:44:02.641 --> 00:44:04.369 cohort because I think the the
NOTE Confidence: 0.904163572
00:44:04.369 --> 00:44:05.630 African American patients who were
NOTE Confidence: 0.904163572
00:44:05.630 --> 00:44:07.058 didn’t have the means or lived in
NOTE Confidence: 0.904163572
00:44:07.058 --> 00:44:08.428 food deserts or things like that,
NOTE Confidence: 0.904163572
00:44:08.430 --> 00:44:10.230 they probably never made it to our clinics.
NOTE Confidence: 0.904163572
00:44:10.230 --> 00:44:11.686 So I think you know I’m very
NOTE Confidence: 0.904163572
00:44:11.686 --> 00:44:12.310 cognizant of that.
NOTE Confidence: 0.904163572
00:44:12.310 --> 00:44:14.263 But those that did make it to our clinics
NOTE Confidence: 0.904163572
00:44:14.263 --> 00:44:15.830 actually had remarkable social support,
NOTE Confidence: 0.904163572
00:44:15.830 --> 00:44:17.666 so much less rates of post
NOTE Confidence: 0.904163572
00:44:17.666 --> 00:44:19.227 operative depression or you know
00:44:19.227 --> 00:44:20.597 so they did pretty well.

00:44:20.600 --> 00:44:21.764 From a survival standpoint,

00:44:21.764 --> 00:44:22.637 I don't know.

00:44:22.640 --> 00:44:23.417 Vrun probably left,

00:44:23.417 --> 00:44:24.971 but I don't think we've seen

00:44:24.971 --> 00:44:26.480 a significant difference.

00:44:26.480 --> 00:44:28.272 But I don't think our cohort is big

00:44:28.272 --> 00:44:30.118 enough to make that conclusive.

00:44:32.920 --> 00:44:33.998 There are a couple of questions in

00:44:34.000 --> 00:44:38.040 the Q&amp;A and the chat. Ask for Nas

00:44:38.040 --> 00:44:40.434 feeding

00:44:40.440 --> 00:44:43.160 So Nick, Nick says.

00:44:43.160 --> 00:44:44.732 Is there any consistency in localization

00:44:44.732 --> 00:44:46.440 in terms of where the metastasis

00:44:46.440 --> 00:44:47.960 form in the peritonema momentum?
I’m wondering if it’s random or if it’s in proximity to lymphoid tissues. Nick, you know this is a phenomenal question and I will tell you that in our minds as surgeons there is very remarkable consistency like we see it on the right diaphragm. We think it’s because there’s Milky spots on the diaphragm, big channels. We always see it in the momentum. So those are very common sites. Mechanistically, we see it by the ligament of triads as a very common site. And then in the pelvic peritoneum,
especially on the left side,

in fact,

you'll see many of these peritoneal

patients will have bowel obstructions

and they obstructed the pelvis as

the sigmoid colon is turning down.

And in those cases,

stents don’t work very well.

And so that’s usually the thing.

I don’t think it’s particularly

close to lymphoid tissues,

but I think that’s where hopefully

we’ll send you some specimens and

you can help us figure it out.

And then I think Guillermo,

Hi Guillermo it’s good to see you
as one of our colleagues from Mexico who says what are your thoughts on the debate for drug combinations on hyper protocols. I think we just need to do better. I think mitomycin is like a 60 year old drug and we've just got to figure out better ways of doing it. So people are looking at intrapartinal immunotherapy now on different versions of cytotoxics. Do you ever analyzed CTD and A? We don’t but we are.
other groups that have looked at it and certainly it is more sensitive than serum CT DNA. But on the flip side it’s logistically impractical. So you know you have to leave a catheter in there and measure it and stuff. So I think that’s the headache with that.

Great, ohh, very good. Thank you so much. Thank you all for your attention.