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 intraparate mealy

following resection of visible

tumors and his research focuses in
this space specifically on clinical
00:01:10.525 --> 00:01:12.950 trials exploring the interface of
00:01:12.950 --> 00:01:15.261 immunotherapy and liquid biopsy and
00:01:15.261 --> 00:01:17.376 the surgical management of cancers.
00:01:17.380 --> 00:01:19.424 I can say personally it’s been really
00:01:19.424 --> 00:01:21.100 just wonderful to have you here,
00:01:21.100 --> 00:01:23.095 Karen and is he is a fantastic
00:01:23.095 --> 00:01:24.275 collaborator for the scientists
00:01:24.275 --> 00:01:26.379 in the room and in the zoom room
00:01:26.379 --> 00:01:28.660 I’m putting in a plug that he is
00:01:28.660 --> 00:01:29.892 looking for potential partners.
00:01:29.892 --> 00:01:30.676 So I’m.
00:01:30.676 --> 00:01:31.460 So Karen,
00:01:31.460 --> 00:01:32.618 thank you for joining us today,
00:01:38.680 --> 00:01:41.104 but thank you Doctor Koons and
thank you everyone for coming today.

I took the liberty to of sharing some, 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 the panel C, 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.
00:04:39.547 --> 00:04:41.750 in a very different way than
NOTE Confidence: 0.9301902
00:04:41.750 --> 00:04:43.554 hematogenous or lymphatic spread.
NOTE Confidence: 0.9301902
00:04:43.560 --> 00:04:45.400 So they rarely spread,
NOTE Confidence: 0.9301902
00:04:45.400 --> 00:04:46.320 you know,
NOTE Confidence: 0.9301902
00:04:46.320 --> 00:04:47.982 beyond sort of these spaces and
NOTE Confidence: 0.9301902
00:04:47.982 --> 00:04:49.560 they spread by almost contact.
NOTE Confidence: 0.9301902
00:04:49.560 --> 00:04:51.762 It’s a very bizarre phenomenon when
NOTE Confidence: 0.9301902
00:04:51.762 --> 00:04:54.100 we open the abdomen and we look.
NOTE Confidence: 0.9301902
00:04:54.100 --> 00:04:55.750 it’s always in spaces which are
NOTE Confidence: 0.9301902
00:04:55.750 --> 00:04:57.487 sort of sequestered where the flow
NOTE Confidence: 0.9301902
00:04:57.487 --> 00:04:58.937 of peritoneal fluid gets stopped.
NOTE Confidence: 0.9301902
00:04:58.940 --> 00:05:00.560 so the right diaphragm for instance
NOTE Confidence: 0.9301902
00:05:00.560 --> 00:05:02.140 or by the ligament of trite,
NOTE Confidence: 0.9301902
00:05:02.140 --> 00:05:04.276 so just a very mechanical sort
NOTE Confidence: 0.9301902
00:05:04.276 --> 00:05:06.300 of a problem that we see.
NOTE Confidence: 0.9301902
00:05:06.300 --> 00:05:08.316 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 decimal 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
00:05:34.968 --> 00:05:36.516 know how big the problem is.

00:05:36.520 --> 00:05:38.445 But I would contend and we’ve done

00:05:38.445 --> 00:05:40.624 the math on this and we’ve kind

00:05:40.624 --> 00:05:42.562 of looked at this annually there’s

00:05:42.623 --> 00:05:44.373 probably about 100 to 150,000

00:05:44.373 --> 00:05:46.345 patients with peritoneal metastases

00:05:46.345 --> 00:05:48.810 that are diagnosed every year.

00:05:48.810 --> 00:05:50.810 If you add up everyone that’s a lot,

00:05:50.810 --> 00:05:52.875 that’s about three times the number of

00:05:52.875 --> 00:05:54.890 new pancreas cancer diagnosis every year.

00:05:54.890 --> 00:05:58.218 So it it is something phenotypically is a

00:05:58.218 --> 00:06:01.368 very large but heterogeneous population

00:06:01.370 --> 00:06:02.850 and I’ve shown this slide many times.

00:06:02.850 --> 00:06:04.433 So those of you that have heard this talk,

00:06:04.450 --> 00:06:06.242 you know or heard some version of my

00:06:06.242 --> 00:06:08.454 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
NOTE Confidence: 0.944027375
And the
NOTE Confidence: 0.893257136
sheet of Elmer’s glue,
NOTE Confidence: 0.893257136
that was his peripheral metastasis and.
NOTE Confidence: 0.893257136
And it was very unfortunate that
NOTE Confidence: 0.893257136
despite our best treatments and the
NOTE Confidence: 0.893257136
best surveillance and the best scans,
NOTE Confidence: 0.893257136
we just could not help this young
NOTE Confidence: 0.893257136
patient who then succumbed to this
NOTE Confidence: 0.893257136
cancer in a few months after this.
NOTE Confidence: 0.893257136
So. So it’s a,
NOTE Confidence: 0.893257136
it was a very thought provoking problem
NOTE Confidence: 0.893257136
that I have dedicated my career to.
NOTE Confidence: 0.893257136
And so First off,
NOTE Confidence: 0.893257136
I would just say that peritoneum metastases
NOTE Confidence: 0.893257136
are much more common than we think they are.
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 of peritoneal metastases. And if you look at the NCCN text, which comes from randomized trials which require resist measurable tumor, which means you should be able to measure the tumor, the 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, but when you look in that, 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. Because we don’t know how to
00:08:05.436 --> 00:08:06.129 measure pertinal metastasis.

00:08:06.130 --> 00:08:08.167 So that’s one of the big problems

00:08:09.650 --> 00:08:09.650 and challenges that are there.

00:08:09.650 --> 00:08:12.242 I think the second is that these patients

00:08:12.242 --> 00:08:14.886 don’t have clinical trials for them often.

00:08:14.890 --> 00:08:15.136 Why?

00:08:15.136 --> 00:08:16.366 Because we can’t measure it.

00:08:16.370 --> 00:08:17.090 If you can’t measure it,

00:08:17.090 --> 00:08:18.494 there’s no drug company that’s willing

00:08:18.494 --> 00:08:20.509 to give you a drug to put these

00:08:20.509 --> 00:08:21.794 patients on clinical trials because

00:08:21.794 --> 00:08:23.449 you don’t have measurable disease.

00:08:23.450 --> 00:08:24.626 So how do you know if your

00:08:24.626 --> 00:08:25.450 drug is working or not?

00:08:25.450 --> 00:08:27.850 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 drink and they kind of waste away? Is this a catabolic phenomena like that or are they just dying because they have bowel obstructions?

00:09:55.070 -- 00:09:57.070 It’s like if someone had renal failure and you don’t put them on dialysis and they die, you wouldn’t say, Oh my God, you know, renal failure is such a horrible problem because

00:10:01.228 -- 00:10:01.788 you don’t have treatment for it, but if someone has a bowel obstruction and you are unable to fix it. 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, Ralph Wexselbaum, who's one of the world leaders 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. There's very different profiles and. 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 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 phal’s 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 peritonectomies.
I tell patients it’s like peeling the wallpaper off the walls. So essentially you’re not destroying the walls, but you’re actually taking disease out. And so 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 that is
interesting and surgically would become more aggressive at it. But right now this is a very, you know it is an 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 intrapartial 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 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
00:13:30.059 --> 00:13:31.943 patients when we find disease early,

00:13:31.950 --> 00:13:33.725 so we can deliver heated

00:13:33.725 --> 00:13:34.790 chemotherapy that way.

00:13:34.790 --> 00:13:36.582 And then also now what is what

00:13:36.582 --> 00:13:39.114 is very hot in Europe and Asia

00:13:39.114 --> 00:13:40.392 is intrapertinal aerosolized

00:13:40.392 --> 00:13:42.419 chemotherapy where you can actually

00:13:42.419 --> 00:13:44.465 distribute the drug a lot better

00:13:44.465 --> 00:13:46.179 across the entire pertinal cavity.

00:13:46.179 --> 00:13:48.580 This is called pipec and over 10,000

00:13:48.639 --> 00:13:50.279 procedures have already been done

00:13:50.279 --> 00:13:53.709 in the world for these technologies.

00:13:53.710 --> 00:13:55.852 And as you would imagine a lot

00:13:55.852 --> 00:13:57.606 of these patients require very

00:13:57.606 --> 00:13:59.830 close management as as a team,
the team that consists of physicians. Which consists of nurses and dietitians 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 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.
00:14:29.560 --> 00:14:31.320 For patients that that
NOTE Confidence: 0.943723035714286
00:14:31.320 --> 00:14:32.640 had pertinum metastases,
NOTE Confidence: 0.943723035714286
00:14:32.640 --> 00:14:34.116 but the biggest question is well,
NOTE Confidence: 0.943723035714286
00:14:34.120 --> 00:14:35.800 is it, is it helping these patients,
NOTE Confidence: 0.943723035714286
00:14:35.800 --> 00:14:36.900 are they living longer?
NOTE Confidence: 0.943723035714286
00:14:36.900 --> 00:14:38.994 Is it worthwhile to do these aggressive
NOTE Confidence: 0.943723035714286
00:14:38.994 --> 00:14:41.208 approaches for these folks and this
NOTE Confidence: 0.943723035714286
00:14:41.208 --> 00:14:43.152 is what happens when patients get
NOTE Confidence: 0.943723035714286
00:14:43.152 --> 00:14:45.137 selected patients with good performance
NOTE Confidence: 0.943723035714286
00:14:45.137 --> 00:14:46.837 status get systemic chemotherapy,
NOTE Confidence: 0.943723035714286
00:14:46.840 --> 00:14:47.815 that’s the reference
NOTE Confidence: 0.943723035714286
00:14:47.815 --> 00:14:49.115 survival data right here.
NOTE Confidence: 0.943723035714286
00:14:49.120 --> 00:14:50.530 And then of course those that
NOTE Confidence: 0.943723035714286
00:14:50.530 --> 00:14:51.235 had cytoreductive surgery,
NOTE Confidence: 0.943723035714286
00:14:51.240 --> 00:14:53.016 this was our own data for
NOTE Confidence: 0.943723035714286
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
want to ask ourselves is, can you actually prevent peritoneal metastasis? And I’ll show you some science behind this, but something that is very interesting is that a recent trial that was just looking at patients that had T4 colon cancers, nothing has spread outside and. On that patients actually have better local regional control. If you apply intraperitoneal chemotherapy at the time of a primary cancer resection without peritoneal metastasis, can you actually,
can you actually reduce that?

And so if you think about it

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. 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. This has been their life's work on this and it's remarkable and there's lots of experiment that support that it causes this. But what was interesting to me. Is when you actually look at this, these anastomosis. So once you've cut the mice, you put them back together and you inject collagenolytic bacteria and inject colon cancer cells in there. All the the tumors that developed were on the serosal surface and not on the mucosal surface. 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. So 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,
that’s the first name right there.
And so it is, it is very difficult for us to believe that our radiologists are going to be able to tell us that a patient has peritoneal metastasis. It is just not feasible.
You can certainly tell if someone has liver metastasis or not, but it’s very difficult to tell if they have peritoneal meds.
And so we’ve played with this along with many, many other groups and there’s a lot of radiomics work that folks have done. 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, 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 metastasis.

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 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. And so the question is,
00:22:10.550 --> 00:22:12.454 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, who actually came and gave chemistry
grand rounds not long ago at Yale.

00:22:35.016 --> 00:22:35.706 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 So what I 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 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, that 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, 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 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, 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 almost developed complete pathological...
responses as you can see in panel C for these patients that had very high grade disease that we would not have routinely offered surgery for. And they lived exactly the same as those that we did open big cytoreductive surgeries and hyoex for. 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, scores to the to the factor where we have now a clinical trial for adding
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. But 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 the bottom line is for some
you know many of the labs many animal models look at intrapertinal tumors. But we actually don’t understand what the native immune environment of the pertinum is. How is T cell trafficking happening over there? What is the repertoire of T cells that are present in the pertinum. 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, what happens to the the diseases and 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 medenteric 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
alter that pharmacokinetics? 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 and it’s all been driven by medical students, residents,
undergraduate research students, fellows. And so I, we truly have been very hungry 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, 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, 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, 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.

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, we get biopsies, we 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, 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 clinics so that we make sure that 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 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.

And I got a job offer from Milwaukee,

which changed my life

forever and I had a job offer

from Mount Sinai and Milwaukee.

And I chose the job offer in Milwaukee,

even though it paid less, just because

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 can do sort of liver and pancreas, but why don’t you do this stuff? And I said, oh, OK 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, I got to write be at the podiums, I got 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 for collaborations, 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, 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

this and of course this is

this is my cell phone and e-mail.

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
you’re working in this space, whether you’re considering it, no matter whether you’re considering it like a rapid process or if that matters and try to discuss that with people as well. Yeah. No, great question. And I would say that one of the things that we’ve tried to do quite deliberately is we’ve, we’ve separated the term cycle reduction from say debulking. So I think when we use the word debulking we’re talking about 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 that is debilitating or large ovarian metastasis that is making it difficult. 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, the doctor said I don’t have much cancer and you look inside and 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 that 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, you know, 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
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 --> 00:39:44.264 you know, as narrow minded 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 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.
00:40:33.515 --> 00:40:34.810 all the way through Hospice.
00:40:34.810 --> 00:40:35.515 So it is,
00:40:35.515 --> 00:40:37.160 it is a very difficult thing to
00:40:37.219 --> 00:40:39.163 to kind of be part of the process.
00:40:39.170 --> 00:40:41.090 And so I think it rejuvenates
00:40:41.090 --> 00:40:42.370 to have other physicians,
00:40:42.370 --> 00:40:43.765 providers and then of course
00:40:43.765 --> 00:40:45.160 having a clinic that’s balanced
00:40:45.209 --> 00:40:46.868 because you have 20 people that are
00:40:46.868 --> 00:40:48.485 doing great and you have you know
00:40:48.485 --> 00:40:50.250 maybe three or four that are not.
00:40:50.250 --> 00:40:50.730 So
00:40:52.210 --> 00:40:53.330 we’re so thrilled you’re here.
00:40:53.330 --> 00:40:55.388 I think you’ve heard me say that
00:40:55.388 --> 00:40:57.647 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. So what does it look like? 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
patients who came through our doors ended up having cytoreductive surgery. So 50% didn’t have it. So as you can tell, we are selective, but we track our whole cohort. So we’re not just saying, oh, we’re going to just look at those that we’ve done surgery and say this is how well we’re doing it. The second comment is it, it really dependent on the surgery itself. So it’s a, it’s a whole gamut of things. When we do a laparoscopic hypec, they go home the same day. 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, hypex 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. You know then you are on TPN, you’re getting drains, you have this and that and I think that is 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.
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, 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, so higher pertinal index, but actually recovered remarkably the same from cytoreductive surgery procedures. In fact you know at some level I would
say that are at least in Chicago

or African American population had better social structures than some of our white populations of patients.

And I think it’s a very selective cohort because I think the African American patients who were didn’t have the means or lived in food deserts or things like that, they probably never made it to our clinics. So I think you know I’m very cognizant of that. But those that did make it to our clinics actually had remarkable social support, so much less rates of post operative depression or you know
so they did pretty well.

From a survival standpoint, I don’t know.

Vrun probably left, but I don’t think we’ve seen a significant difference.

But I don’t think our cohort is big enough to make that conclusive.

There are a couple of questions in the Q&A and the chat. Ask for Nas feeding.

So Nick, Nick says. Is there any consistency in localization in terms of where the metastasis 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. We think it’s because there’s Milky spots on the diaphragm, big channels. 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

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 you know mitomycin is like a 60 year old drug and you know we've 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.