Agenda welcome everyone to Cancer Center grand rounds and really pleased to have three various themed colleagues presenting and I, you know, I think if there's one particular theme that I think emerges among many from today's forum is that we have what's really great is the number of talented people across multiple disciplines. Who are making progress on pivotal questions in cancer care in Cancer Research, and I think today’s forum is just you know one very clear of many examples of three individuals doing great work,
each coming from it from a different discipline but working together towards really making a difference for patients for the field and and obviously advancing our research and educational agenda. And I I would, I’ll do. I’d like to do is really. Introduce one of our speakers and ask him to then introduce the other colleague. So let me introduce Kevin Billingslea, who I think frankly in the past. I guess nine months or so really needs no introduction. Kevin, as many of you know, joined us in in or about January.
As our chief medical officer for the Yale Cancer Center and Smilow Cancer Hospital, and is also a professor in the Department of surgery. Kevin is responsible for our clinical enterprise, working with our leaders in nursing and other disciplines, and has really done an extraordinary job and certainly working. You know, arriving here and nothing less stepping into the frying pan with Kovid. And really the need to work collaboratively across so many people to execute on what was heroic.
An extraordinary response on so many parts. Kevin, beyond his success as our chief medical officer, is an international leader in the clinical care and research of patients with a paddle, as well as gastrointestinal ligatures. Legacies before joining us here, Kevin was a professor at Oregon Health and Science University where he was the medical director of the Knight Cancer Institute and the chief of surgical oncology.
and Kevin is going to. Take over with our discussion of evolving multidisciplinary management of colorectal liver metastases, and I'll let Kevin take over and introduce the other great faculty, Kevin, thank you. Charlie, thanks, thank you so much for that really gracious introduction. I'm thrilled to be here. We're going to do kind of a tag team screen sharing here and let me see if I can get going with that. OK, is that working for folks? OK, is that working for folks? I only see you Kevin. OK.
There you go. Got it, how about that OK? Well, you know it’s as Charlie alluded to. I’ve had the pleasure of spending much of my career as hepatobiliary surgical oncologist. And you know, I will share that one of the most gratifying aspects of my time in surgical oncology is participating and witnessing the dramatic advances that we have had in the multidisciplinary care of patients with colorectal liver metastases and one of the things that I was most excited about is I prepared for my transition to the ill Cancer Center in Smilow.
Cancer Hospital was the fact that we truly have. Kind of.
W e essentially have a world class team of experts across disciplines who are contributing to the care of this unique group of patients.
And we have all of the elements here and I want to with that as a jumping off point.
Introduce my two partners in this multidisciplinary grand rounds.
Doctor Michael Cicchini is a seasoned veteran of Yale, he’s a graduate of the Albert Einstein School of Medicine, came here to New Haven for residency,
stayed on for fellowship, and has just continued to rocket to prominence from there. Michael profited as many of our fellows have from the mentorship and guidance of doctor Jill Lacey, who is as most of you know, the Dean of our GI medical Oncologist. Michael has carved out a really unique spot for himself and our organization, an increasingly across the country. In a mix of traditional clinical research and GI medical oncology as well as phase one clinical trial work and drug development.
So delighted to have him with me today and as a clinical partner. Next, doctor David made off is a relatively recent addition to the Yale team. When I was preparing for my move here, he was one of the most people that I was most excited to partner with. David, his essentially written the book on portal vein, embolization, and optimization of the hepatic remnant for in preparation for complex hepatobiliary surgery, he spent much there earlier part of
his career at the MD Anderson Cancer Center, then transitioned back here to the East Coast where he’s at Cornell for a number of years and then more recently we’ve been fortunate to recruit him as the vice chair for clinical research and the section chief of Interventional radiology. And I will say kind of quickly.

Is this side note one of the things that I enjoy most about caring for patients with colorectal liver metastases? Is that it really is a team sport. This multidisciplinary grand rounds does highlight a number of us who are
involved from surgery, medical oncology, Interventional radiology. I do feel little remiss in not having some other folks on a panel who were important contributors such as radiation oncology. And other disciplines, but I know we’ll have other opportunities. So this is a very comprehensive field. We’re not going to cover everything today. Our goal is a team is to kind of give you some broad brush overviews of developments and high points. I will be talking. I’ll be giving an overview and talking about some surgical strategies mainly
focusing on patients with advanced disease.

Doctor made off will be talking about his real area of world class expertise. Which is various techniques to optimize the liver remnant to support complex resection. Role of Interventional radiology and Michael will be updating us on the numerous advances and systemic chemotherapy for the disease. Well, the idea of resecting colorectal metastases is not new. You know surgeons have been doing this for 40 plus years. What is exciting is the developments that have been made in the safety.
00:08:38.831 --> 00:08:40.328 of these operations.
NOTE Confidence: 0.882687389850616
00:08:40.330 --> 00:08:43.162 The number and variety of technical
NOTE Confidence: 0.882687389850616
00:08:43.162 --> 00:08:46.206 approaches and the slow but steady
NOTE Confidence: 0.882687389850616
00:08:46.206 --> 00:08:48.886 increase in long-term survival that
NOTE Confidence: 0.882687389850616
00:08:48.886 --> 00:08:51.939 patients enjoy after these procedures.
NOTE Confidence: 0.882687389850616
00:08:51.940 --> 00:08:54.514 Why would we focus on aggressive
NOTE Confidence: 0.882687389850616
00:08:54.514 --> 00:08:56.820 liver directed therapy for this
NOTE Confidence: 0.882687389850616
00:08:56.820 --> 00:08:58.856 patient with liver metastases?
NOTE Confidence: 0.882687389850616
00:08:58.860 --> 00:08:59.320 Well,
NOTE Confidence: 0.882687389850616
00:08:59.320 --> 00:09:01.620 as many of you understand,
NOTE Confidence: 0.882687389850616
00:09:01.620 --> 00:09:04.100 the liver disease in metastatic
NOTE Confidence: 0.882687389850616
00:09:04.100 --> 00:09:06.580 colorectal cancer often serves as
NOTE Confidence: 0.882687389850616
00:09:06.662 --> 00:09:09.224 as the main source of Morbidity
NOTE Confidence: 0.882687389850616
00:09:09.224 --> 00:09:11.894 and mortality and affect the driver
NOTE Confidence: 0.882687389850616
00:09:11.894 --> 00:09:14.528 demise for folks with this disease.
NOTE Confidence: 0.882687389850616
00:09:14.530 --> 00:09:18.218 And this occurs through a number of pathways.
Patients with bulky disease can experience liver failure more commonly. They suffer from progressive biliary obstruction which is understandable, untreatable, and once this occurs an they're jaundice, it is very difficult to. Provide ongoing effective systemic chemotherapy, and it leads to kind of a downhill spiral.

The good news is that from multiple case series we know that complete resection of colorectal liver metastases patients can enjoy up to and sometimes more of 50% five year survival rate,
yet, there remain significant challenges.

Roughly, only 20% of patients with this disease process are resectable at the time of presentation, and even with aggressive surgical therapy recurrence remains frustratingly high. Often you know 80% at about the five year mark. I don’t want to steal doctor Cecchini’s Thunder here, and I apologize for stepping on his turf, but no self respecting surgical oncologist would talk about progress in this area without some mention of...
the groundbreaking advances that have been made in systemic chemotherapy. I think this timeline kind of tells the story. We’ve gone from the 5F U era, which was the case for many years is. Really, the only chemotherapeutic option in this disease with a 12 to 14 month median survival to our current modern regiments with Folfox, Folfiri and increasingly triplet chemotherapy or patients even without surgery, are enjoying survival of 29 plus months so.
As much as we have,
surgeons congratulate ourselves
on our technical wizardry of big
piece of the progress in the background is effective chemotherapy.
So this is what I is, a surgical oncologist.
Love to see a patient with easily resectable disease,
limited number of tumors,
one maybe two tumors that are peripherally placed not in close proximity to major vascular structures,
and these folks are amenable to an atomic or segmental resection.
The surgical options for manageing folks like this are manifold.
They can be treated well within traditional open operation. Laparoscopic. Liver resection is now in the mainstream, and increasingly we’re used utilizing the robotic platform to address some of these tumors. Now more commonly, what we see particularly at large academic medical centers, such as we work in our patients who have advanced colorectal liver metastases. These are patients with multifocal disease. Often the diseases bilateral on both sides of the liver and often their bulky lesions which are in
So I’m going to share the story of a 48 year old woman who I treated in Portland about eight years ago. She presented with bulky, complex liver disease, Anna sigmoid non obstructed sigmoid primary cancer in place. So not to dwell on too many liver technicalities, but she had a high central liver lesion in close proximity to the vena cava sitting right under the confluence of the three hepatic veins. Should an additional bulky lesion.
NOTE Confidence: 0.835261046886444
00:13:02.625 --> 00:13:05.350 in segment for the liver sitting
NOTE Confidence: 0.835261046886444
00:13:05.350 --> 00:13:08.073 in proximity to one of the pedicles
NOTE Confidence: 0.835261046886444
00:13:08.073 --> 00:13:11.029 in the middle hepatic vein?
NOTE Confidence: 0.835261046886444
00:13:11.030 --> 00:13:13.268 And then she had another bulky
NOTE Confidence: 0.835261046886444
00:13:13.268 --> 00:13:15.443 lesion in segment five and six
NOTE Confidence: 0.835261046886444
00:13:15.443 --> 00:13:17.578 on the right side of the liver.
NOTE Confidence: 0.835261046886444
00:13:17.580 --> 00:13:20.412 So this is a perfect segue into the
NOTE Confidence: 0.835261046886444
00:13:20.412 --> 00:13:22.529 need for multidisciplinary multi
NOTE Confidence: 0.835261046886444
00:13:22.529 --> 00:13:25.173 disciplinary strategies to address
NOTE Confidence: 0.835261046886444
00:13:25.173 --> 00:13:28.643 patients like this with advanced
NOTE Confidence: 0.835261046886444
00:13:28.643 --> 00:13:30.878 colorectal liver metastases.
NOTE Confidence: 0.835261046886444
00:13:30.880 --> 00:13:34.592 And I’m going to talk today in my
NOTE Confidence: 0.835261046886444
00:13:34.592 --> 00:13:37.867 section about 3 strategies to to
NOTE Confidence: 0.835261046886444
00:13:37.867 --> 00:13:40.667 approach this group of patients,
NOTE Confidence: 0.835261046886444
00:13:40.670 --> 00:13:43.430 all requiring the integration
NOTE Confidence: 0.835261046886444
of multiple disciplines. Probably the most common is what we described is conversion chemotherapy, which involves the upfront utilization of multiagent chemotherapy. Usually oxaliplatin based to downstage tumors within the range of respectability. Another approach that is increasingly used at high volume centers around the world is what we call staged habitectomy. This is breaking the surgical treatment up into two sessions with an intervening procedure called portal vein embolization, which leads to optimization of growth of the plant hepatic remnant.
And then the last topic I will touch on briefly is something that many of us around the world are starting to do which is complex parenchymal sparing resections, which allow simultaneous resection of multiple sites of disease.

So the patient I described did go on to have eight cycles of F olfox with bevacizumab Avastin, and she was in the subset of patients who enjoyed a stunning response. As you can see, the central lesion shrunk dramatically.
see a little more space around the dip attic veins. This lesion is now shrunk away from the left portal. Pedicle involves the caudate lobe of the liver which is a bit of a tricky place to operate but now has good clearances. The left pedicle segment for lesion significantly smaller and the right side liver lesion, also smaller. This allowed us to take her to the operating room and one operative setting. Treat her with a left hip. It ectomy a caudate lobe resection segment or section in a sigmoid colectomy.
This was her diseases that appeared in the operating room, stomach, liver, Gallbladder, and the caudate. Lesion shrunken in partially calcified. The segment 56 lesion again nice response partially calcified and what she wound up with his complex bilateral resection, but with plenty of good healthy liver remnant left and I know everyone reports their greatest success. What happened with this lady is she had a single side of recurrent disease about two years after that we treated with a little wedge resection and she is disease free at last.
Follow up about 8 years out.

So what we’ve learned over the years in the French are really led the way in this is that patients can enjoy even after chemotherapy. Conversion can enjoy a very high rate of long-term survival. This is data from Renee. A damn now presented years ago, but makes the point. They looked at their subset of patients from their entire spectrum of liver metastases who are respected after conversion chemotherapy. And although this group of patients who were converted to Resectable
did not enjoy the survival that the primary population did,
33% five year survival in a subset of patients extending out into the eight to 10 year mark as my patient did.
I'd only just you.
While I was there, my partner, Sky Mayo and I took a kind of a new approach to kind of optimizing this approach. We started a hepatic arterial infusion program. As many of you know, this involves the placement of a
chemotherapy pump in a catheter into the hepatic artery to deliver focus chemotherapy with the aim of converting patients. It’s a complex operation involves dissection of the hepatic artery placement at the pump in a subcutaneous pocket with installation of FDR. We did this in combination with systemic chemotherapy with Folfox. A subset for unresectable disease.
Many of these were high risk disease, 36% with the K Ras mutant. All had synchronous disease. All had multiple liver lesions. The point relate relative to this talk that I’d like to point out is that. Of the 13 patients that we were aiming to convert to respectability, a subset we were able to eventually get to the operating room with very extensive bilateral disease, so this is yet another kind of regional chemotherapy strategy to convert patients to Resectable. Another approach that is done
throughout the world that is facilitated by David’s work is a two stage HEPA tech to me.

This is for patients with complex. Lateral disease, they go to the operating room in one session and either have reception of the left liver disease or ablation. Then they go on to portal vein embolization, which leads to hypertrophy of the left liver and the remainder of the disease is respected in a second operation. And this is a strategy that allows us to treat what can be otherwise completely unrespectable disease.
So series from around the world demonstrate that even for patients with advanced bilateral disease, if we can complete the two stage resection, we can provide patients with excellent long-term survival. There is always going to be a subset of patients who dropped out due to progression between the operations or in the course of therapy. And unfortunately, those folks don’t do well, but this is a great strategy to get patients to the operating room. One of the things that I in
number of other surgeons that started to do in recent years, is exploit the concept of the R1 Vascular margin. This is related to the fact that there is going to be a subset of patients like this who have bulky tumors and the diseases in close proximity to a major vein or poorly pedicle. But it is possible if you can get a wide resection margin on the rest of it and get a very narrow margin that’s positive only on the vein to get excellent local Disease Control in that part of the liver and still preserve significant liver parenchyma.
My Friend Doctor Guido Tort
Caelian Milano has been kind of the primary proponent of this,
and I think that this is a strategy that is gaining traction and many HP be centers around the world.
Guido and his team have reported their experience and one of the things that I think his striking is that patients who have you compare their survival.
When you compare R0 resection with R1 resection from the liver parenchyma, there’s clearly decrement in survival. However, the group that have an R1 margin
only on a vessel have a survival. It is virtually identical to those that are R0 resection. I think that this is a great example of a theme that we see across surgical oncology and multiple diseases breast cancer. The most notable here where we overtime have gone to a multi modality approach involving chemotherapy, radiation and much more limited surgery going from radical mastectomy to breast conservation. Now moving towards even eliminating the axillary component of breast cancer surgery. Same in head and neck. Laryngeal preservation,
possibly preservation of the rectum in Rectal carcinomas.

The theme is consistent throughout integration. Multi modality therapy allows a more conservative operation, and I think we’re getting there and liver cancer. This was one of my cases from Portland, not a great picture, but a patient who I took care of. You had multifocal disease in the upper part of the right side of the liver and left liver requiring
reception down on to the hepatic veins and right point medical.

Kind of a wedge resection on the left side, all able to do this in a single operation.
The greatest thing about this is that all of these strategies do require multidisciplinary care.
An integration, as I take off my surgeon hat and put on my CMO hat, all of these strategies come together in the fact that our aim at the Yale Cancer Center through both our care signature effort as well as our multidisciplinary disease teams, is to create a wrap around set of services for our patients.
As I mentioned, it’s not just liver surgery and medical oncology.

An Interventional radiology.

We need to coordinate care for many of these patients, including radiation therapy. Image Ng, including nuclear medicine. Of course, oncology, nursing, pathology, social work, our colleagues in colorectal cancer surgery need to be involved in genetics, and I think that’s the promise. An fun of what we’re doing, so I’d like to hand off now to doctor made off.
00:23:39.580 --> 00:23:40.369 Thank you David.
NOTE Confidence: 0.912310719490051
00:23:42.690 --> 00:23:43.878 I guess I need
NOTE Confidence: 0.900341939926147
00:23:43.880 --> 00:23:46.040 to stop my screen. Share
NOTE Confidence: 0.852466821670532
00:23:46.040 --> 00:23:47.060 my screen here.
NOTE Confidence: 0.788426756858826
00:23:47.760 --> 00:23:54.440 And.
NOTE Confidence: 0.904296815395355
00:24:00.500 --> 00:24:02.920 you will hear me.
NOTE Confidence: 0.904296815395355
00:24:05.810 --> 00:24:08.600 Y es, we can hear you. So what I would
NOTE Confidence: 0.832684814929962
00:24:08.600 --> 00:24:10.826 first like to thank Charlie and Kevin,
NOTE Confidence: 0.832684814929962
00:24:10.830 --> 00:24:13.302 as well as my for giving me the
NOTE Confidence: 0.832684814929962
00:24:13.302 --> 00:24:15.274 opportunity today to speak at the
NOTE Confidence: 0.832684814929962
00:24:15.274 --> 00:24:16.884 El Cancer Center grand rounds.
NOTE Confidence: 0.832684814929962
00:24:16.890 --> 00:24:17.978 As you may recall,
NOTE Confidence: 0.832684814929962
00:24:17.978 --> 00:24:19.610 I didn’t discuss this topic of
NOTE Confidence: 0.832684814929962
00:24:19.675 --> 00:24:21.680 liver regeneration in last December,
NOTE Confidence: 0.832684814929962
00:24:21.680 --> 00:24:23.824 but today I will be focusing on how
these techniques relate to optimizing the anticipated future liver remnant prior to resection in patients, really with only colorectal liver metastases. Very happy to be here in terms of the fact that this is, like Kevin said, this is really in my life’s. Work and passion and having the opportunity is for me very, very nice. So. As you just heard from Kevin, there have been tremendous advances and Pat ability. Every surgical techniques, such that death is now considered rare. However,
complications such as fluid retention,

Cola stasis,

an impaired synthetic function still contribute to prolong recovery times.

An extended hospital stays.

This is particularly true instead of an extent,

but did have a tech to me where 5 or more per node segments are removed,

and in fact,

as you can see,

the mortality in this setting can approach 8 to 10%.

This can be seen from this French study.
and the size of the liver remnant, and this is not in regards to the severity of the overall complications, but really only the complication rate. So at this time there’s really no limit to how smaller liver in.

In order to reduce the morbidity of Petra section at least 20% mushrooming in patients with normal underlying liver that is. For example, patients that have colon cancer Mets to the liver without ever having touch chemotherapy 30% in injured liver such as those that have had extensive chemotherapy or Seattle hepatitis and 40% in those with underlying cirrhosis.
So there’s many preoperative strategies to prepare the liver for resection and. These include Portland Embolization, which was briefly discussed by Kevin radiation lobectomy. There’s an apps procedure that will get into briefly and also something called liberties deprivation. Support and embolization is the original strategy, first described by professional recruiters from the University of Tokyo in 1990. It’s been used to redirect portal blood to the future liver remnant or FLR, and by doing so, initiate hypertrophy of the non embolized.
00:26:45.660 --> 00:26:47.940 segments and by doing this we can reduce
00:26:47.940 --> 00:26:49.792 the number of overall perioperative
00:26:49.792 --> 00:26:51.832 complications and increase the pool
00:26:51.832 --> 00:26:53.649 of potential surgical candidates who
00:26:53.649 --> 00:26:55.647 have what we call marginal anticipated
00:26:55.647 --> 00:26:57.098 future liver remnant volumes.
00:26:57.100 --> 00:27:01.422 Please note that the goal is really
00:27:01.422 --> 00:27:03.347 not to improve the overall survival
00:27:03.347 --> 00:27:05.360 after resection is compared to
00:27:05.360 --> 00:27:07.634 It’s just really to achieve similar
00:27:07.634 --> 00:27:09.616 survival rates to those patients
00:27:09.616 --> 00:27:11.596 who want to undergo surgery.
00:27:11.600 --> 00:27:13.550 It did not actually require
00:27:13.550 --> 00:27:15.500 PV an ultimate until recently.
The general consensus was the PV was the standard of care at most had ability, every centers worldwide or safe and effective generate generation or generation of the FLR. It’s now been over a decade since the first meta analysis of usefulness of PV was published, and in this study they would do 37 publications with over 1000 patients and found a previous states with a low mortality and morbidity rate. Further, 85% of the patients were able to get their proposed surgery. However,
as you can see down here is that there was a substantial group of patients that were not respected and this was due mostly to disease progression or insufficient. I purchased it. I stated previously the goal of PV is to get similar survival rates to those patients who do not require PV. Here we see two actually French studies and pretty old. There actually showed where these outcomes were born out. Now PV E not only causes the
Liberty purchase fee,
but it also results in improved function of the FLR and this has been shown by nuclear medicine studies with alobar function shifted from the embolized than an embolism for after the further in patients with Hilar Cholangio Carcinoma, who had biliary drainage catheters more bile is produced in the non embolized bourbon in the embolized liver and Lastly. We can see that less alterations in liver function tests after resection occur following PV even knows in which P VE. Was not performed. So for decades CT has been the
cornerstone for surgical planning and

when assessing the FL are we do our
calculations based only on the size of
the liver. Remaining siti does directly
measure the future liver remnant and the
total liver volume is not actually measured,
but rather it’s estimated from
the Association between the
liver and patient size.

And this is based on body waiting patients,
body surface area or a larger
patient would need a large deliver.
Smaller patient may need a smaller liver.
The FL R2 total estimated liver volume
can then allow for uniform comparison.
Adefa lower volume parts of resection, whether or not PVE was performed. And this is the formula which is based on a linear regression equation from over 500 Western adults. It’s critical to understand the denominator does not change on the pre and post CT scans because it is an estimate. One must realize that PVE does cause atrophy of the emboli segments that there have been cases where the total liver volume is directly measured. And went down after PVE. Therefore, even if the numerator is unchanged, the FL, our percentage may inadvertently increase,
NOTE Confidence: 0.822804689407349
00:29:58.920 --> 00:30:01.242 giving once a false sense of
NOTE Confidence: 0.822804689407349
00:30:01.242 --> 00:30:03.280 belief that hypertrophy did occur.
NOTE Confidence: 0.822804689407349
00:30:03.280 --> 00:30:05.260 And unfortunately patients have died
NOTE Confidence: 0.822804689407349
00:30:05.260 --> 00:30:07.240 after surgery when this happens.
NOTE Confidence: 0.822804689407349
00:30:07.240 --> 00:30:10.344 So if we look at this patient with
NOTE Confidence: 0.822804689407349
00:30:10.344 --> 00:30:12.102 colorectal liver metastases here
NOTE Confidence: 0.822804689407349
00:30:12.102 --> 00:30:14.796 we see approximately 4 weeks later
NOTE Confidence: 0.822804689407349
00:30:14.796 --> 00:30:17.529 that the FLR grew from 17 to 30%
NOTE Confidence: 0.822804689407349
00:30:17.530 --> 00:30:19.906 or degree of hypertrophy of 13%.
NOTE Confidence: 0.822804689407349
00:30:19.910 --> 00:30:21.358 This patient also had.
NOTE Confidence: 0.822804689407349
00:30:21.358 --> 00:30:23.168 Kinetic growth rate of 3.5%,
NOTE Confidence: 0.822804689407349
00:30:23.170 --> 00:30:25.613 which is a good indicator and this
NOTE Confidence: 0.822804689407349
00:30:25.613 --> 00:30:27.637 will be discussed in much more
NOTE Confidence: 0.822804689407349
00:30:27.637 --> 00:30:29.147 detail in a little bit.
NOTE Confidence: 0.811400353908539
00:30:31.500 --> 00:30:32.403 In recent years,
there's actually been controversy as

and this may depend on the institution

and the formula being used.

In Europe, for example, therapies

uses the cut off for the need for phe.

That said, we showed during my time at MD

And further,

If you have less than percent, FL are,

however, no differences were found.

Once you had more than 20%

of your FL are remaining.

And further,

we wanted to see the impact of
00:31:04.726 --> 00:31:06.719 PV in the patient population in this patient population.
00:31:08.360 --> 00:31:10.418 We found that in those patients that had at least 20%, meaning that they already either had 20% not requiring PV or had 20%.
00:31:12.150 --> 00:31:16.620 and in those days we did it with a higher environment to see if there was any difference, and we compared them to those patients who had less than 20% and actually had at least 20% and did not require PV.
00:31:20.765 --> 00:31:22.805 if there was any difference, we compared them to those patients who had less than 20% and actually had at least 20% and did not require PV.
patient after PV at least 20%

NOTE Confidence: 0.811400353908539

of the future liver remnant,

NOTE Confidence: 0.811400353908539

it really was no difference in

NOTE Confidence: 0.811400353908539

what happened after resection.

NOTE Confidence: 0.811400353908539

So we talked about the brief

NOTE Confidence: 0.811400353908539

hypertrophy a little earlier.

NOTE Confidence: 0.811400353908539

So what is the degree of purchasing?

NOTE Confidence: 0.811400353908539

Well,

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it’s the post PV eff R minus the pre

NOTE Confidence: 0.811400353908539

PV EOFLR which gives you a dynamic

NOTE Confidence: 0.811400353908539

measure of liver regeneration and

NOTE Confidence: 0.811400353908539

this is important because there

NOTE Confidence: 0.811400353908539

is an amount of high purchase that

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is necessary to review.

NOTE Confidence: 0.811400353908539

If you have complications in our study

NOTE Confidence: 0.811400353908539

published in MD Anderson in 2007,
you can see that those patients that have more than 5% degree if I purchase he had significantly less complications that had more than 5% FL.

So here we have a tale of two rivers, one patient with Cirrhosis, and HTC who underwent a right. He protected me here.

We see that the cirrhotic patient had excellent hypertrophy, while the other patient had only 1% growth.
Interesting Lee, the cirrhotic patient, did well after surgery, while the patient that had the normal liver or what we thought was a pretty normal liver actually. Died after their reception. Therefore, if we see that you can use these numbers to see that patients that have at least 20% FLR and at least 5% degree of hypertrophy had a zero percent, 90 day mortality. And like I said, this information can be used when trying to understand whether a patient should be indicated for
their reception after PV.
00:33:10.700 --> 00:33:13.596 So now that we know the floor cut
00:33:13.596 --> 00:33:16.370 off numbers that is 20% for normal liver,
00:33:16.370 --> 00:33:18.890 30% for injured liver from chemotherapy and.
00:33:18.890 --> 00:33:19.883 40% for Cirrhosis,
00:33:19.883 --> 00:33:22.739 and we know that if I purchased the 5%,
00:33:22.740 --> 00:33:24.987 is this enough to really be able
00:33:24.987 --> 00:33:25.950 to predict which
00:33:26.022 --> 00:33:28.447 patients should have their surgeries?
00:33:28.450 --> 00:33:30.907 So we now know that we’ve had
00:33:30.907 --> 00:33:32.899 purchase fees based on the timing
00:33:32.899 --> 00:33:35.425 of the image Ng and that a true
00:33:35.425 --> 00:33:38.089 assessment of the epilogue growth is
00:33:38.089 --> 00:33:40.196 difficult to compare among patients.
00:33:40.196 --> 00:33:42.494 Therefore, we developed a new variable
00:33:42.494 --> 00:33:44.366
called the kinetic growth rate or KJR,
which is the degree of hypertrophy
over the time elapsed from
PV E in the number of weeks.
So here we see three patients
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
with colorectal liver metastases,
each with a degree of hypertrophy,
well within the amount needed for successful,
So when we went back and calculated the kinetic growth rate, the patient that I had only 0.3% per week, while the other two had much higher growth rates. Therefore, when assessing patients which should have surgery, we found that in order to really be safe, that we really need 2% per week. That led to know hepatic insufficiency or 90 day mortality. So, is Kevin stated earlier we can now extend the boundaries for safer section.
by using advanced surgical strategies such as the two stage protecting. The FL, our volumes were calculated to be 16% of PV was performed, and then FLR was then found to be 26%. So the definitive resection was then performed. So to assess the benefit of the two stage separate ectomy.
we reviewed patients who had invented the advanced strategy with extended pack resection and compared those those that did not have tumor in their FL are therefore not really needing second stage. Our results had shown that there was no difference in overall and disease free survival in those patients that required the two stage protect me as compared with those that only required the one stage. And as Kevin showed from our study from MD Anderson in a really highly selected. And she cohort who did complete
the second stage.

We were able to achieve a 60% five year survival, which is really considered amazing. Anything about a decade ago given to buy Alobar nature of the disease. However, there is some concerns regarding team be one of the major concerns is the potential drop out of up to 35% of patients due to an insufficient FL. patients due to an insufficient FL. are or or tumor progression within the four to six week waiting period from the TV to the definitive resection. Therefore, other approaches are needed.
So one issue that has been entertained has been that PV can lead to expedited tumor growth, so to that end the recent data supports that we can use chemotherapy during the waiting period and also can be used within the postoperative period which at one time was thought to maybe limit for generation. However, that has not borne out to be the case. So there are other alternative approaches that we can use. It is Interventional radiologist.
This is a case. This is a study that was performed from Korea where TV did not leave the sufficient regeneration. Anna Korean group found that later performing right, having bane embolization in addition to the PV is shown here actually result in better outcomes. We’ve also used something called radiation lobectomy. This is done by the Transarterial Bar Administration of Y-90 microparticles. She’s now an established means of providing local tumor control within the liver.
That said, there was an unintended phenomenon of contralateral liver I8 and seven in several retrospective studies. Contralateral hypertrophy? A curd from 21 to 47%, and therefore this has been suggested as an alternative to PV with the benefit of local tumor control. And the test of time. So we had talked about this earlier, but nuclear medicine is showing improved liver function after PV E in this small study of 13 patients, with some being colorectal liver.
metastases who underwent some nuclear medicine scintigraphy. They showed that using radiation lobectomy actually can cause changes in regional liver function, and this correlated with the functional liver absorbed doses from Y-90 and then in 2014 a group from France compared 141 patients who underwent right PV with third. 35 patients who underwent radiation at two centers that were matched for criterion known to influence liver regeneration after PVD. The radiation was performed if the authors found the case would be challenging.
00:38:21.260 --> 00:38:23.240 provid PB and to be honest,

00:38:23.240 --> 00:38:25.550 I’m not sure why this would be,

00:38:25.550 --> 00:38:28.078 but when they match the patients they found

00:38:28.078 --> 00:38:29.839 significantly more hypertrophy after PV.

00:38:29.840 --> 00:38:31.772 They concluded that while the hyper

00:38:31.772 --> 00:38:33.060 chicken radiation lobectomy substantial

00:38:33.111 --> 00:38:34.786 and doesn’t minimize tumor progression,

00:38:34.790 --> 00:38:36.440 and I purchased the in radiation

00:38:36.440 --> 00:38:38.402 lobectomy with these therapeutic doses.

00:38:38.402 --> 00:38:40.070 So how do you decide if you should

00:38:40.070 --> 00:38:42.230 use PV or radiation lobectomy?

00:38:42.230 --> 00:38:44.360 The decision should be based

00:38:44.360 --> 00:38:46.010 on achievement intent,

00:38:46.010 --> 00:38:47.618 such as.
Is the patient a candidate for section now and what is the plan resection if the reception should be done now you should just go ahead and perform the P PE. You also need to know what type of malignancy patient has and whether the patient has underlying liver disease. Cases where patients have bottle bar colorectal metastases that require a Tuesday check. Her protect me. There is likely really no role for radiation lobectomy, as you can see, I’m personally not in favor of the radiation lobectomy in this approach,
as you would really need to do 190 of both lobes and it seems appropriate in the setting of HTC with cirrhosis. But I don’t think it really is appropriate in the setting of colorectal liver metastasis. Another approach is Alps, which is short for associating liver partition and portal vein ligation. This approach was proposed to replace pbe with two surgeries. He performed interactive right portal vein ligation followed by completely divest arising. Segment four of the liver and
at the same session is surgeon clears the floor of tumor. The patient is then closed with the tumor bearing liver in place, while the FLL rapidly have Portuguese and then the Sturgeon returns within 7 to 10 days for a second laparotomy to complete the definitive resection. And early reports actually showed very strong tumor growth. I mean, fellow growth and was believed to have a lower risk for tumor progression. When comparing PV 2 apps that were the massive infest or hypertrophy in the Alps Group,
but it came at a much higher cost of major complications and death.

Interestingly, while the kinetic growth rate was found to be higher electron microscopy studies from Japan showed that the hepatocytes were not mature and not really able to handle the increased blood flow to the FL are. Therefore, it was shown that it is not simply regenerating the liver rapidly, but also in a way that allows the hepatocytes maturan function appropriately so interesting.
Lee,

A systematic review and meta-analysis for colorectal liver metastases was performed, confirming the findings of the faster kinetic growth rate with Alps. But with the increased morbidity and mortality, numerous modifications have been proposed, many of which negated distinct advantages of why Alps was proposed in the first place. And lastly, I want to show a new procedure, one that we will now be using at Yale.
PV into Patty being embolization,
Liberty is deprivation is performing PV.
And how do you been embolization
in a single session?
The goal is to shorten and optimize
the phase of liver preparation.
Or surgery without the
aggressive nature of Alps,
and in this early
feasibility study from 2016,
the procedure was found to be safe
in a small patient
cohort of only seven patients,
and then the same group then added
embolization of the middle of having pain
to the right hepatic vein embolization, and they found that by doing so they can get safe and provide the most marketing rapid elevation in hypertrophy and liver function. Unprecedented for an IR procedure, and just soon Kevin and I will be the Copia eyes. Or yell prospective clinical trial. Looking at Libertines deprivation called Dragon One and Dragon 2. Dragon one is a feasibility study, and Dragon 2 actually will compare it to the standard of care which is PV. So in conclusion, liver regeneration is critical to
managing colorectal liver metastases, and, as I hope to have shown, there are numerous strategies that can regenerate the liver, either percutaneously or by surgical means. Currently, the understanding of Liberal generation in this area is really at its infancy. Any apples opportunities do exist for research, so I’m looking forward to working with your team and Kevin on this dragon study and thank you for your attention.
Thank you David, that was awesome.

Thank you David, that was awesome.

Thanks bikini.

Kevin David, can you stop sharing? OK, stop the sharing here, yeah?

Alright, so I’m Michael Cicchini.

I’m a medical Oncologist and I’m going to talk about the chemotherapy in the Peri operative management of these liver metastases for colorectal cancer.

So first I’m going to talk about the molecular profiling. That’s important to decide.

Chemotherapy agents as well as sightedness, which is not truly molecular profiling but certainly hasn’t impacted the chemotherapy selection.
The two types of patients we encounter, the unrespectable patiently up respectable biologics and then some of the damage our agents can do that can complicate the role of complicated surgery so. Molecular profiling for colorectal cancer. What information do I really need to know to make a chemotherapy decision? Wrap the grass in the raft status are very important and they have been so for some time mismatch repair status microsatellite status, repair status microsatellite status, which is analogous to that and then the sightedness has become increasingly important for determining
determining which biologic to use.

So the origin of the primary tumor was at a left sided tumor or right sided tumors.

So to remind ourselves why Rasen rap status is so important.

We need to go back to the EGFR pathway. We have drugs syntax Mammon, Panitumumab two monoclonal antibodies to target EGFR receptor that we add on.
00:44:40.426 --> 00:44:42.186 to chemotherapy, so they’re effective.

00:44:42.186 --> 00:44:44.790 If this pathway is not constituent active,

00:44:44.790 --> 00:44:47.457 blow it.

00:44:45.552 --> 00:44:47.457 So in a rash wild.

00:44:47.460 --> 00:44:52.014 I porra filetype we add on

00:44:52.014 --> 00:44:58.299 Panitumumab Humanized Monoclonal

00:44:58.300 --> 00:45:01.531 Antibody an and or so or sucks Mad A.

00:45:01.531 --> 00:45:04.865 we have to take a different approach.

00:45:06.600 --> 00:45:08.574 Kevin talked about a little bit

00:45:09.943 --> 00:45:11.743 against veg that Jeff Vascular
endothelial growth factor,
and that’s also added on to chemotherapy
be Rapids become important just
in the last couple of years.
Now we have targeted agents for
that and Grafton if insta tox mad,
but for the Intents and purposes
of this stock graph is used as
a negative prognostic.
Mutation and most of those
patients are not can be included
in the consideration of surgery.
So why is the mismatch repair
status so important?
So to answer that,
mismatch repair proteins do.
So Emily age 1:00 PM S 2 Ms H2, and six.
These are the four most most clinically relevant mismatch repair proteins.
Their function is to follow the DNA polymerase machine DNA polymerase machinery along as it undoubtedly makes some mistakes. It fixed these single base mismatches, which are most prevalent in these areas, called microsatellites, which are dynamically Titan tribe nucleotide repeats across the genome. You can imagine this DNA machinery. It’s really caught up on
all this repetitive DNA.

Lots of mistakes are made so we know when these are lost.

Tumors have very high tumor mutational burden that which leads to a lot of Neoantigens.

We’ve known for some time that these are some of the most sensitive cancers to immunostimulatory therapies such as anti PD one and four therapies.

So they’ve been approved in the refractory setting for you for a few years but only recently just a few months ago.

Did we get to see their activity in the first line setting?

You can see very dramatic separation
00:46:37.030 --> 00:46:38.530 of these two curves here.

00:46:38.530 --> 00:46:40.020 Green being Pember Lizum app,

00:46:40.020 --> 00:46:42.684 purple being the chemo arm for a first line.

00:46:42.690 --> 00:46:43.282 Microsatellite instability.

00:46:43.282 --> 00:46:44.170 High collector cancer.

00:46:44.170 --> 00:46:47.440 I mean if we look at the two year mark here,

00:46:47.440 --> 00:46:50.104 you’re seeing 48% of patients that

00:46:50.110 --> 00:46:51.600 are microsatellite instability,

00:46:51.600 --> 00:46:54.272 At at two years versus only 19% with chemo.

00:46:55.460 --> 00:46:56.950 what’s really important to look?

00:46:56.950 --> 00:46:58.410 Actually look at this part

00:47:00.510 --> 00:47:01.710 because that’s where anybody
that’s going to surgery would be.

Maybe early on in their treatment journey and you can actually see Pembroke behavior.

A bit more inferior to chemotherapy.

In this setting in a very rapid drop off,

even with Pam bro,

which obviously has a tail on this curve.

So immunotherapy in the new edge

initially resectable, for example,

is definitely not ready for prime time.

And I think future directions will certainly be chemo immunotherapy,

and hopefully will negate some of the early drop off.

Why is sightedness important?
So we’ve known for some time that high and got the left sided Colon is a different embryologic. Origin in the right right colon so hindgut for left and got for right. Right sided tumors generally worse prognosis, more methylated tumors, higher beer after some degree. Right crass and left side it more than more traditional APC mutations in TP 53 mutations and we know that even if your rash wild type, it matters whether or not you respond to a EGFR antibodies such as anti tumor map or cetuximab.
So it’s really the rash wildtype left sided tumors that we’re thinking about using these drugs in the first line setting. And even if rash while typing right sided data SIM it at this is a map should still be considered.

So what are the drugs that we have at our disposal to help these patients so full F ox? We’ve probably all heard full box, full fury, full F ox series. We when we use in pancreatic cancer here, full fear knocks, but they’re slightly different approaches. So what is folfox? So five fluoro uracil,
which is patented by Charlie Heidelberger. I think in 1957 and is still around and going strong. Is a family space inhibitor so you don’t have time to look around for rapidly dividing cells. Luca born potentiates the activity of five FU. It’s a vitamin that we give along with the chemotherapy. Oxaliplatin is the oxen in full box, that’s in platinum agent that causes DNA addicts and ultimately results in double stranded breaks and are in Attican, which is the IRI. In full fury is.
Ultimately converted into its active form.

About summarize, one inhibitor, SN 38 and ultimately also end result is double stranded breaks, so these are the main agents we have.

We started out again with just 5FU and this is about what we were doing back in the early 90s, so we had about a median survival of 12 year for patients with mosaic answer.

When we started to have doublet chemotherapy’s in full box and full theory, we move this out about the two year mark.

Now we’re really between the two and three, or mark or median overall survival.

For most, for most of our active trials
00:49:40.942 --> 00:49:43.117 with colorectal cancer with folfox theory,
00:49:43.120 --> 00:49:45.479 the triple combination that’s a bit more toxic and reserved for younger patients
00:49:47.534 --> 00:49:49.816 is about a 32 month median survival,
00:49:49.820 --> 00:49:52.835 so we have to ask ourselves at tumor board,
00:49:52.840 --> 00:49:55.178 what does this patient have it with?
00:49:55.180 --> 00:49:56.328 Cash pathway to cure?
00:49:56.328 --> 00:49:58.870 So what our main goals with chemotherapy?
00:49:58.870 --> 00:50:00.545 We’ve heard a little bit about conversion therapy,
00:50:00.545 --> 00:50:01.550 about conversion therapy,
00:50:01.550 --> 00:50:02.886 so converting the unrespectable
00:50:02.886 --> 00:50:04.556 patient to a respectable patient.
00:50:04.560 --> 00:50:06.905 If we have a patient that’s upfront,
00:50:06.910 --> 00:50:08.495 resectable chemotherapy can still be useful to reduce the surgical complexity.
Eradicate micrometastatic disease, which is also hopefully doing for the unrespectable patient and then also assess the biology of the aggressiveness of the disease. Is somebody actually getting a response through chemotherapy, or they just rapidly progressing? That’s not a patient you want to surgery anyway, and if we know that even in the best circumstances the patients never going to get to a surgical option that the treatment is prolonging life, hopefully by controlling disease in improving tumor related symptoms,
so we should think about this as two groups, the unrespectable patient. And the resectable patients. So the upfront resectable patient and just there's no right way to integrate chemotherapy into these patients. By the way, different centers take different approaches, but there's more nuanced than just this slide. But when to consider a front reception? Generally, for fewer liver metastasis, chemotherapy response? Not really. The surgeon doesn’t really think.
00:51:04.337 --> 00:51:06.102 chemotherapy response is going to
NOTE Confidence: 0.749365627765656
00:51:06.102 --> 00:51:08.016 lower the complexity of the operation.
NOTE Confidence: 0.749365627765656
00:51:08.020 --> 00:51:10.639 But when do we do it when there's more
NOTE Confidence: 0.749365627765656
00:51:10.639 --> 00:51:13.377 than four suspicious knodel involvement?
NOTE Confidence: 0.749365627765656
NOTE Confidence: 0.749365627765656
00:51:14.274 --> 00:51:16.360 But again, there’s more nuanced to this,
NOTE Confidence: 0.749365627765656
00:51:16.360 --> 00:51:19.033 so we have to we have to take everything.
NOTE Confidence: 0.749365627765656
00:51:19.040 --> 00:51:21.126 Every aspect of the patient into account.
NOTE Confidence: 0.749365627765656
00:51:21.130 --> 00:51:23.506 Do they have a lot of other comorbidities?
NOTE Confidence: 0.749365627765656
00:51:23.510 --> 00:51:25.596 Where if they if they are not
NOTE Confidence: 0.749365627765656
00:51:25.596 --> 00:51:26.490 tolerating chemotherapy well,
NOTE Confidence: 0.749365627765656
00:51:26.490 --> 00:51:27.682 we’re expecting significant increase
NOTE Confidence: 0.749365627765656
00:51:27.682 --> 00:51:28.874 in liver liver damage,
NOTE Confidence: 0.749365627765656
00:51:28.880 --> 00:51:30.370 which could complicate in operation?
NOTE Confidence: 0.749365627765656
00:51:30.370 --> 00:51:32.380 Is there reason to suspect that
NOTE Confidence: 0.749365627765656
00:51:32.380 --> 00:51:33.720 they have particularly aggressive
00:51:33.781 --> 00:51:35.765 disease and you want to give him the
tincture of time on chemotherapy to
make sure they’re not just rapidly
progressing and you’re going to put
them through an unnecessary operation?
Did they recently received full Fox for?
For management of primary primary,
so could a slight response results
in maybe converting an
open reception to a laprascopic reception.
So what, what chemotherapy do
we typically use? So again,
these are patients that could be respected,
most likely, so full Fox,
a doublet chemotherapy,
perhaps with the biologic bevacizumab

perhaps with the biologic bevacizumab

panitumumab receptors amount,

but the important part is to limit the

number of chemo cycles as much as possible.

These patients that can get to surgery

quickly and should get to surgery quickly,

and we want to do as little

damage is possible to the to

the liver without chemotherapy.

So we should image patients early and

as soon as thought as soon as feasible.

These patients should be taken into surgery.

We generally plan to do six

months total of chemotherapy.

But the rest would be reserved for later.

So what about the unresectable patient?
Now this patient can’t get this surgery without a response, so it’s a different approach, so we talked a little bit about what is undetectable. Perhaps as high as a third of the time that we will get enough cited reduction to convert this patient to respectable? But what regiment is best?
Again, if you look at guidelines, both guidelines are very so. The guidelines don’t really take much of a stand. They say Folfox Folfiri Anna tumor map. But this is a mad. They kind of leave it up to the treating oncologists asthma. On the other hand, takes a more dogmatic approach. It says full flux is the recommendation or for unresectable metastases. Considerable Fox series, so that’s that’s the approach that we would take here, predominantly in the United States.
that most centers would do.

But certainly here at Yale for the younger fit patients, we would do full foxy reeer.

This is a map, but for our upfront, resectable patients we would again just be doing a doublet.

So I’m going to skip through this in the interest of time, especially since Kevin showed especially since Kevin showed some of the slides are ready.

So what about our biologics? So this is another level of nuance.

Again, to do our chemotherapy here.
So we have. We have agents such as bevacizumab. This is a map which is a vascular endothelial growth factor antibody against speculative growth factor, which is created by the tumors and stimulates blood vessel growth. Because the tumor needs increased vascularity, so we know that bevacizumab increases response rates, but it can potentially increase perioperative complications. We see vascular events such as arterial thrombi, vein thrombi, on occasion perforations.
but the big concern is wound healing, so we generally would hold bevacizumab within six weeks prior to any server dream. There is some data that supports it up to four weeks prior to surgery, but but the concern is how you when you hold it preoperatively. So this is actually been looked at. The addition of bevacizumab in systemic therapy for unresectable liver metastasis. So we have a cohort of patients here split up into two groups. These are all kras mutated patients or patients that are
perfect fit for bevacizumab.

So full blocks plus bevacizumab

In arm a in Folfox alone.

In R&B you can see that the reception, the rate of R0 Resection complete resection,

22 verses about 6% without the berbasis matters so very, very big difference about getting to surgery there.

What about progression free survival 9 1/2 median versus about 5 1/2 months favoring Bevis is maben blue here.

Same thing with overall survival.

Less less striking difference about 25 versus 20 months.

Both are statistically significant.
00:55:11.154 --> 00:55:14.016 So bad this is a map should be used

00:55:14.016 --> 00:55:15.948 in the Peri operative management with Folfox 4 correct meeting liver metastases.

00:55:18.250 --> 00:55:20.248 What about the EGFR antibody face?

00:55:20.250 --> 00:55:22.272 These are highly effective therapies for patients that are crashed while type.

00:55:22.272 --> 00:55:24.239 You think we see a similar story here.

00:55:24.240 --> 00:55:26.459 In fact, we're split into chemotherapy, perioperatively before and after surgery with cetuximab.

00:55:26.459 --> 00:55:28.239 In exact opposite, so again, we have two groups here.

00:55:28.240 --> 00:55:30.480 This is a new epoch study, split into chemotherapy, perioperatively before and after surgery with cetuximab.
an without stuck some, and so without cytoxan map is here in blue. Progression free survival curve here so you can see the red group chemotherapy plastic doing inferior to the chemotherapy alone group. Same thing with overall survival. What’s really interesting? If you look at these curves, these are the Times of surgery, so this curve have not separated. They separate later. An obvious explanation to this oh would be an awesome app. Is creating some increase in perioperative complications?
But that’s not the case and the fact that the changes in progression free and overall survival happened later again speaks to. They did that. It’s not an actual increase in proper complications. Frankly, I haven’t seen any good explanation for why this we’re seeing these confusing results, but I think we should proceed with caution when using our bodies in the perioperative setting. I think a lot of my colleagues have not bought into this,
and I again uncertain on the rest of the biological rationale of why we’re seeing this, but it’s a very striking overall survival difference. It’s almost three years. Median overall survival difference without the antibody. So chemotherapy associated liver diseases will close on South are drugs can do damage. That’s why the name that our approach is to limit the number of cycles when feasible, so Oxaliplatin, cut static sinusoidal abnormalities. You can see the dilations here in
light of these sinusoids that directly
from oxide Platt and you can see
nodular regenerative hyperplasia.
This, like lighter pink nodule here.
Crowding out the more healthy
which creates noncirrhotic portal
hypertension, both from Oxaliplatin,
where Uniti Concuss.
Seattle hepatitis so fatty fatty
infiltration and inflammation of the liver.
Here very severe case,
and the less of your case.
But frankly there shouldn’t be fact.
Neither of these images.
So in conclusion, we took the talked about the importance of molecular results. Those are things that need to be sent on every patient so that the medical oncologist can know what treatment approach should be done. The role of sightedness, our approach to the unrespectable in the upfront respectable, and some of the damage our agents can do. Thank you so much. Michael, thank you for high speed yet incredibly comprehensive overview of rapidly evolving and complicated field and. David, I want to thank you as well.
Given the time, I don’t think we have much leftover for discussion, I would just.

Close by saying that this is an incredibly exciting field to work in,

I think the overview that my partners have given gives the audience a sense of the enormous complexity yet opportunity involved for our patients.

And I think for all of us who work together,

it is yet another call.

For an extraordinary level of teamwork,

integration, communication,

all of these clinical services have to be linked together by meticulous communication between us is clinicians as well as
our nurses and administrative Staffs. As we kind of navigate care throughout a very complex system. Charlie, anything to add. Oh, I just want to thank David, Michael and Kevin for really just a brilliant discussion. And thank you for your leadership, your collaboration and building a team around a pivotal area of care, research and thanks everyone for joining us and think giving us a lot to think about and really exciting progress.