Posed for today.

We have two talks, one from Doctor Boffa and then the second from doctor Chang.

Doctor Boffa will go first.

Let me make a brief introduction of Dan. Doctor Boffa is a professor of thoracic surgery and division newly appointed in recent months. Congratulations who received his medical degree from the University of Chicago’s Pritzker School of Medicine and completed residency at New York Presbyterian Hospital.
Weill Cornell Medical Center and his fellowship at Cleveland Clinic. Dan specializes in oesophageal and lung cancer. Achalasia gastroesophageal reflux disease, Adel hernia, oesophageal diverticula am and hyper hydrosis. All things you don’t want to have as a highly skilled looking doctor Barber performs the majority of his surgeries with minimally invasive procedures. Committed to increasing the survival rate of cancer patients, doctor Boffa has focused his clinical
research on the prevention of tumor metastases and the early detection of lung cancer and on a personal note, I've just been thrilled to be working with Dan for almost a decade now. Here, as we've taken an already great top and made it even better, so Dan, so happy to have you today. The floor is yours alright. Thank you very much. So I have one disclosure. I have a couple of disclaimers. For the interest of time I'm going to present some data without much in the way of methods.
afterwards and I’ll even make a pretty egregious statement without any data.
And I also have a disclaimer. This is a very emotional topic, and it’s one that is fraught in quite a bit of. It makes people quite uncomfortable, and so I just want to give you that as a heads up. So surgical safety? Why is this even important? Why is this worth talking about? Um? So I’m going to give you what I think is a mind blowing perspective. So surgical deaths occur in patients who are likely to be cured because that’s who we operate on.
Had they not died, they would have lived a long time. Therefore, when you, when a surgical patient dies, they forfeit a considerable amount of survival. So if you look at survivorship that’s lost each year from cancer surgery mortality’s, it’s a big number, even though there’s only thousand patients that have died from surgical mortality’s, they would have lived many years collectively, in fact. It is, it is very similar to what you
would see if you took all stage four patients and stop giving chemotherapy to three out of four.

An I can go into detail about how we came up with these numbers, but it’s a huge amount of survivorship that’s lawston, so this is just giving some perspective. So cancer surgery outcomes are quite variable and they vary based on factors related to patients surgeons. But they also very relating to variables that relate to the hospital. So this is a classic study birkmaier put out almost 20 years ago where
he showed that as you increase the surgical volume at a hospital, the mortality decreases.

The numbers at the extremes are quite different. Going from a 20% chance of dying from surgery to 8% and this is 30 day mortality. 90 day mortality is generally twice these numbers, so it’s a huge amount of variability.

The question is how does a patient pick the best hospital? Well, one way is to use mainstream media, an US news and World Report is probably the most common that people talk about,
and that patients engaged when they're making these decisions. And there's some data that actually it is a pretty reliable way to find a safe, high quality hospital. The IT does create a unique situation though. The hospital name is associated with the hospital's reputation for quality and safety. That becomes their brand. Top ranked hospitals have a strong brand. These top ranked hospitals have been increasingly forming affiliations with hospitals and communities and during those affiliations they share that brand. So here's an example.
Here's Hellman’s Pella Clinic.

I made this up.

It’s famous, it’s trusted.

It’s respected in its top ranked.

It, there’s Middlebury Hospital,

I made this up as well.

And they form an affiliation,

And then Asterix is the affiliation.

Could be part ownership.

It can be just a monetary based relationship,

but there’s a whole range

of affiliation means,

but during that affiliation,

the Middlebury adopts the brand of Hellman,

Pella Clinic, and the question is,
what does that mean?

So the first question is what would patients think of that?

Well, we conducted a survey. This is a public survey, so it’s not patients.

It’s the general population we use GfK, which allows you to conduct nationally representative surveys.

And we had a study that looked at 1000 patients.

We had a response rate of just under 60% and we asked.

We asked people what do you think the likelihood of dying from surgery
when you consider a top ranked hospital or a hospital in the community that is affiliated with a top ranked hospital and we describe this as a complex cancer operation. So of the thousand patients. Um?

Just over 1/4 felt that you were more likely to die at an affiliate versus the top ranked hospital. 4% felt you actually more likely to die at the top ranked hospital. But 69% felt that it was the same at a top ranked hospital and the affiliate that shares its brand. The so once this affiliation has formed,
once you add the name of the hospital to the hospital community, 69% of people think the safety is the same. That’s very different to when they don’t have the brand to hospitals that are not affiliated. 85% of people preferred and be cared for. The top ranked hospital. When you actually talk about the effectiveness of care, how often patients would be cured of cancer, half the respondents thought that the safety and the effectiveness of care is the same. At top ranked hospitals and the community hospitals or hospitals in the community.
that share the top ranked brand.

And we wanted to know is this true?

So we started with a study in Medicare patients,

so these are people over the age of 65

and we looked in the Medicare database

and we looked at top ranked hospitals

and those were hospitals that had been ranked at least once between 2012 and 16,

and because some hospitals come in and out of the top ranked.

Cohort you end up with 59 hospitals,

so we started with 59 hospitals.

We used the American Hospital Association survey to look to see if they had an affiliation recorded
and that was 640 hospitals. But then we did an Internet search and looked for hospitals that were actually hospitals in the community, the affiliates that were advertising that affiliation in their brand presence, something that the public and patients would see just for our nomenclature, we call the top ranked hospitals parents. And the affiliates children? It’s just. It makes it easier to talk about. We don’t imply maturity or seniority or anything like that. It’s just helps us conceptualize.
And I will use that terminology a little bit later.

So we looked at complex cancer surgery and these were the procedures we looked at. There were 17,000 patients that had surgery at top ranked hospitals and 12,000 affiliates.

Other than a little bit difference in the age, most of the associated demographics were actually pretty similar. When you looked at the case mix, meaning, what types of procedures the affiliates were doing compared to the top ranked hospitals,
you see that most of the surgeries were colectomies at affiliates so 60.

3% of all the complex surgeries they were doing were colon based.

Where is the top ranked hospitals that was just a third and when

Whipples made up a very small percentage of what was happening at affiliates, but a reasonable percentage of what happened at top ranked hospitals.

And there is a sense of regionalization within these networks,
But if you look at the type of surgery and say where are all colectomies being done, more than half of all colectomies are happening at affiliates, whereas for Whipples only 18% of Whipples are happening in affiliates. So it does seem that the more dangerous operations in this, Mix are happening at the top ranked hospital as appeared the affiliates.
so if you look at the beds it’s 200 versus 700. If you look at other things that have been associated other attributes that have been associated with quality that you affiliates. There’s a big difference there for Commission on cancer accreditation. The affiliates are less likely. They are far less likely to be a teaching hospital in the annual volume is much lower. If you look at the use of minimally invasive techniques and leapfrog standards. It’s far and away. Favors the top ranked hospital, so we looked at 90 day mortality
and we looked at.

We first use an aggregate approach which meaning we took all the patients that had surgery at the top ranked hospitals and we compared him to all the patients who had surgery at the affiliates.

The dark blue bars are the top ranked hospital and the lighter ones are the affiliates.

The different procedures are on the X axis, and a taller bar means a higher 90 day mortality. And for everything the affiliate has a taller bar.

When you look at it in an adjusted way, this is a logistic regression.
Looking at 90 day mortality and it’s listed here for each of the procedures. But when you look at all the procedures, its mortality was 1.4 times higher and affiliate hospital versus the top ranked hospital. We did not include in our adjustment hospital factors because patients don’t consider those typically when they are making decisions. They look at a top ranked hospital. They look at the brand. They’re not looking at teaching status or ciocie accreditation or annual volume. We now looked at a family approach.
where we took each parent and looked at all of their children. So we took one top ranked hospital and compared it to all of their affiliates combined. And we use the standardized mortality ratio, which is similar to what CMS uses to create its star rating system. Here the Orange of the top ranked hospitals and the blue are the affiliates collectively and anything to the right means it’s less safe than anything to its left. So here you can see the orange dots seem to be to the left and the
blue dots seem to be right saying showing there’s a higher adjusted mortality at the affiliates. And when you look at all of them combined, 83% of the time the blue bars were to the right of the orange bars, so 83% of the time the affiliates were less safe than the specific top ranked hospital. So in summary, the chance of dying from complex surgery an affiliate is about 40% higher than it is at the top ranked hospital. An 83% of the time. So it’s not just a couple.
of top ranked hospitals
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that are the issue,
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and we’ve done sensitivity analysis.
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Looking at does it matter where
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in the top 50 you fall we have
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adjusted for things like volume
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and hospital attributes and it does
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not eliminate this differential.
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So we wanted to look at
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this in a different way.
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We looked in the National Cancer
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database because this allowed us to
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look at all ages an with a lot more
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patients and better staging information.
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For those of you that aren’t familiar
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with the National Cancer database,
it’s contributing to the National Cancer database is compulsory for all COC accredited hospitals. It ends up capturing about 70% of the cancer care in the United States. So we looked between 2012 and 16. We expanded the number of cancers that we were looking at and ended up with 120,000 patients, 80,000 at top ranked hospitals and 40,000 affiliates. This is again unadjusted mortality, so the blue bars are the affiliates. The orange bars at the top ranked in for every one of them.
The Blue Bar is taller, meaning there's a higher unadjusted mortality at the affiliates. When you look at a 90 day mortality in an adjusted model, the odds ratio of 90 day mortality was actually 1.7 times higher. So your 70% more likely to die from your cancer surgery at an affiliate hospital compared to the top ranked hospital. We wanted to look at long-term survival as well. So if you look at Unadjusted Stage 3, colon cancer, the red line is the top ranked
00:15:13.873 --> 00:15:15.030 hospital survival.

00:15:15.030 --> 00:15:18.040 The blue line is the affiliate survival, and so this is just for Stage 3 colon cancer.

00:15:22.340 --> 00:15:24.490 It's significant for Stage 1, two and three colon cancer.

00:15:26.640 --> 00:15:29.220 We also looked at lung cancer, and we really only did those two cancer types because in this way, because the numbers were low.

00:15:32.920 --> 00:15:35.667 the for the other cancer types, so we just looked at stage stratified, colon and lung and it was significantly higher at the top ranked hospital versus the affiliate after cancer surgery.

00:15:51.980 --> 00:15:54.170 And we landmark these outside
the 90 day mortality.

So it wasn’t just that you were having fewer surgical deaths,

even if you just looked at people that survived their cancer surgery.

The survival was higher.

We also looked at this in an adjusted way. We use gamma models and time ratios, so a time ratio just means relative to the survival at the top ranked hospital.

So this is the plot of the adjusted survival.

So anything to the left of the yellow line means that they had less survival than affiliates had less survival that top ranked hospitals.

So overall, all of the procedures.
The survival was less at the affiliates versus the top ranked hospitals, so overall the after surgery the patients at affiliate hospitals only lived about 3/4 as long as patients that had surgery at top ranked hospitals. So in that that data was adjusted for volume as well and it did not change the significance of the findings. So the summary of that this research is that the public believes that brand sharing equals quality sharing that surgical mortality is 1.7 times higher. If you have surgery at a affiliative,
00:17:25.030 --> 00:17:27.982 a top ranked hospital compared to
NOTE Confidence: 0.84117377
00:17:27.982 --> 00:17:30.850 the actual top ranked hospital.
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00:17:30.850 --> 00:17:33.124 And that the survival is shorter
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00:17:33.124 --> 00:17:35.077 at the affiliate compared to
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00:17:35.077 --> 00:17:36.927 the actual top ranked hospital.
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00:17:36.930 --> 00:17:39.234 So affiliation does not in and
NOTE Confidence: 0.84117377
00:17:39.234 --> 00:17:41.530 of itself equal care equality,
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00:17:41.530 --> 00:17:44.946 despite the fact that that a large
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00:17:44.946 --> 00:17:48.758 proportion of the public believes it does.
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00:17:48.760 --> 00:17:52.162 So is this the problem or is
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00:17:52.162 --> 00:17:53.620 this the solution?
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00:17:53.620 --> 00:17:57.309 So we actually believe that the network
NOTE Confidence: 0.84117377
00:17:57.309 --> 00:18:00.505 infrastructure can be leveraged to be the
NOTE Confidence: 0.84117377
00:18:00.505 --> 00:18:04.607 solution to a lot of the gaps in cancer care.
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00:18:04.610 --> 00:18:08.215 And it really provides three key things.
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00:18:08.220 --> 00:18:08.813 Connectivity,
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00:18:08.813 --> 00:18:10.592 accountability and ability.
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00:18:10.592 --> 00:18:13.557 So from the connectivity standpoint,
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00:18:13.560 --> 00:18:17.320 if you look at the current cancer surgery
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00:18:17.320 --> 00:18:20.917 market share a lot of hospitals have a piece
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00:18:20.917 --> 00:18:24.979 of the pie and they’re totally disconnected,
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00:18:24.980 --> 00:18:26.884 and it’s very difficult
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00:18:26.884 --> 00:18:28.788 to share best practices.
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00:18:28.790 --> 00:18:30.694 The there’s privacy issues.
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00:18:30.694 --> 00:18:33.074 There’s competition among the hospitals.
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00:18:33.080 --> 00:18:35.455 There’s the lack of compatibility
NOTE Confidence: 0.84117377
00:18:35.455 --> 00:18:36.880 between their systems,
NOTE Confidence: 0.84117377
00:18:36.880 --> 00:18:38.568 so as a result,
NOTE Confidence: 0.84117377
00:18:38.568 --> 00:18:40.256 it’s very difficult to
NOTE Confidence: 0.84117377
00:18:40.256 --> 00:18:42.230 do quality improvement.
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00:18:42.230 --> 00:18:43.445 Across these hospitals.
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But you gotta keep in mind that there's a connection between the top ranked hospitals and their affiliates. That eliminates these barriers. It turns out that the these networks around the top ranked hospitals, they have a huge piece of the pie. It's not a one out of three complex surgeries actually happens within these networks and every year their market share is increasing, so it's eliminating the barriers that prevent a lot of quality improvement within These Top Rank networks. And they are major players in the complex cancer surgery.
Domain. Accountability.

So for instance Yale. I has multiple sites within the state and we have. These are multiple affiliates and all of the networks around top ranked hospitals have a similar map of different states. They are comprised of very different hospitals. And the temptation is to identify with one of the hospitals that people at each of their hospitals feel that they had. But the reality is. The network is our identity and we have
to embrace that and we should have one set of expectations for safety, effectiveness, and timeliness and the patient experience should be the same across the entire network.

And there are bodies that are starting to look at networks as individual entities to be accredited. So while I think there’s a moral obligation to match outcomes and care with public expectations, there’s likely going to become some oversight that will look at how well in the way in which care is delivered across these networks.

The last is the ability
giving hospitals the ability to provide excellent care, so excellent care is comprised of three domains. First is infrastructure which are the resources in the support. And for this quite simply, the scenario has to match the hospital environment. If the hospital is not equipped to care for big surgery and the complications of surgery or stem cell transplants, that’s not where it should take place within the network. But there are other opportunities,
so regionalization within a network I think is important. Process needs to lead to consistent outcomes, but it also needs to be adaptable to the individual nuances. And I think the best way to think of process is to think of the user. So from the patient’s perspective, and there’s no better user perspective in my opinion than the users of Amazon. It’s single access. It feels like it’s one big store, although it’s a whole bunch of different stores in different structures that are participating, it feels like it’s close to home,
but it’s almost never close to where you live, and it does allow for the public to make an informed choice, and I think that’s important is to allow people to have a choice that where they want to be cared for, and be informed as to the implications. Great network, feels like a great team and that includes not just surgeons but medical oncology and radiation oncology, but also the nurses and the therapists you have to. You have to expand by programs.
It’s not just a à la carte expansion through affiliation. You really have to program build throughout a network. And finally, Clinical Excellence. In my opinion, Clinical Excellence in staff is comprised of three things. The knowledge, skill, and judgment. And you need to have experts. So here is an example of experts. This is the division of thoracic surgery at Yale. But you have to keep in mind that there are experts out of outside of New Haven and we have to recognize.
and partner with these experts and give them what they need to be clinically successful. And we can’t just have physician experts. It’s gotta be experts at every every touch point with patients, there has to be content expertise across the domain. Process may be our signature. But excellent people are our margin and we have to give people what they need to be successful. So when you think of a network. We have to take great care patients. There’s no doubt,
but we also have to be a great place to work. Every decision we make, we have to think about what are the implication on our patients and our ability to provide care. But we also have to think of the implications on the people who are working here, because if it were not, these two things simultaneously, it’s not a sustainable model. I thank you and I’d be happy to take questions for 2.5 minutes. Thanks Dan, that certainly was stimulating and brings up a lot of issues. Let me ask the first question.
as questions are coming in so it's sort of a two parter one.

When you operate at Bridgeport or at New London, is that an affiliation or is that as if you're operating at the same center?

So the we have the same expectations for outcomes, but the people that are involved in the care are we have any Mace who spends time at both campuses, spends time at tumor board at this campus and uses a lot of the shared infrastructure so that the intake process is driven through.
Here the Park Ave.

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Cure model is the same care as it is in New Haven,

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so different people,

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but people that are tightly integrated into the New Haven infrastructure so that we believe we deliver a very similar level of care.

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We just don’t do the same things there.

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There are complex cases,

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we just don’t do there.

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Thanks, I’m hurting.

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Chow asks from the VA.

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Is it possible that patients who ended up going to the community hospitals had fewer resources,
an worse socioeconomic status?
And that was the reason for the difference?
The so when you adjust for so the NCD has income by zipcode, but the.
When you look at when you just for race, adjust for income.
Adjust for education.
These factors still exist,
so I think that those are certainly things that influence choice and.
We have a lot of research in a separate vein as to why patients choose the hospital that they do.
And in a separate survey looked at barriers to traveling for safer care.
because it’s pretty well known that people prefer safer environments, but they have barriers that cannot prevent them from coming.

We found that about 75% of people that wanted to come. Two, the flagship in a hypothetical model, had a barrier. The interesting thing is when we looked at facilitators, it was almost always a low cost facilitator, meaning it was a ride or it was a night to stay or parking, or but it wasn’t a huge thing that was keeping them from being able to.
Jetta come we are our new line of investigation is looking on the impact of Medicaid expansion on cancer care and so. I think that’s also ties into that, so we should have more for you on that front. In the future we have time for one more question. The questioner asks this time of affiliation overtime lead to improved outcome. Also for the Children’s Hospital and I’ll just add you showed a slide where you compared expertise at the main center and then you showed care center physicians. But you were showing surgeons in one picture.
and medical oncologists in the other.

So is this hold for all disciplines or is this just for surgery? Little confusing. I think it I think that. So.

I will say TuneIn on Friday to surgery grand rounds where I have an hour and I’m going to go into a lot of this.

We had 144 affiliations that took place during our study period. We look the year before and after just to see does affiliation make things better, but top bar the dark one is pre affiliation. The lighter one is after affiliation.
So and then these are just the affiliates. And then we also look at non affiliates and see what happened. So if you look at the hospital beds they got a little bit smaller. If you look at the OC accreditation they picked up more of the affiliates gained accreditation, but you also saw an effect like that in the non affiliates. When you look at the number of complex surgeries the affiliates got busier after. And that didn’t happen in the non affiliates, so the affiliation increased.
their market share.

But if you look at 90 day mortality before and after affiliation, there's a big drop, so the affiliates got safer after affiliation, so that was really encouraging unfortunately, however.

And the non affiliates also dropped during that time period. And when you look in a difference model, there actually really the change overtime is very similar.

We could find no effect that affiliation made hospitals better.
It seems that the top ranked hospitals choose to affiliate with better hospitals, so affiliates are better than non affiliates. But the active affiliation in these 144 hospitals did not make anything better. OK, well, that will have to be the last word. Certainly we need to come to some more of your lectures and talk about this more, but you know, certainly this is vitally important for patients and physicians like to understand these data. Thank you, Dan. Thank you.
OK, well we have a second talk today and.

I'm also a colleague and friend, Veronica Chang, Professor of neurosurgery who's going to talk to us about challenges in brain cancer metastases management.

I have a little blurb here also from Renee for her. Doctor Chang is a professor of neurosurgery and radiation oncology and director of stereotactic radiosurgery and the Gamma Knife Center. She received her medical degree from the University of WA and completed her residency at Yale School of Medicine.
Her fellowship at Johns Hopkins.

Veronica leads in a row surgical arm of the brain metastasis program at Yale. This is a program that’s comprised of Multidisciplinary Physicians in the specialty areas of medical oncology, radiation oncology, neurosurgery, radiology, pathology, neurooncology. This is the nationally ranked unique program specifically dedicated to coordinating clinical management of patients with brain metastases as well as the performance of brain science of science, basic science, translation and clinical trials.
She’s an active member of our long sport.

Saronic, it’s a pleasure to have you here.

Today we started a few minutes late.

So I won’t cut you short at the end.

We’ll make sure we have time for questions as well. The floor is yours.

OK, does that look alright?

OK, so thank you Roy for that introduction.

That was very kind so. I’m going to.

My talk is going to be a little bit different than dance today.

And before I start, these are my disclosures.


OK, does that look alright?

OK, so thank you Roy for that introduction.

That was very kind so. I’m going to.

My talk is going to be a little bit different than dance today.

That’s not at all that would be uncomfortable.

And before I start,

these are my disclosures.
So as you all know, brain tester sees code about 20 to 40% of patients with metastatic cancer. And so you can see on the left back when I started treating brain metastases, we only thought that a few types of cancer really went to the brain. This is obviously changed over the years, and so you can see on the right now that pretty much almost any cancer type can go to the brain because while about 10% of brain metastases can be found at initial diagnosis of cancer, by far the vast majority, so 90% developed later in the course of
cancer and as patients are living longer, I think the brain metastasis problem is becoming more prevalent. And so over the last two decades, then significant changes have occurred in the management of brain metastases. And while there have been an increasing number of successes in treatment and want to concentrate today on some of the challenges that have arisen from these changes in paradigm. And so the biggest change in brain metastasis management has been the move from whole brain radiation therapy with or without surgery, which was supported by the petrol studies.
in the 1980s to the incorporation of brain radiosurgery first as salvage, then for a few lesions as first line treatment and then for radiosurgery to pretty much everything and now to a combination of CNS penetrating drugs in combination with radiosurgery. And I know that many of you are familiar with radiosurgery. But for those of you who are not, gamma knife is the machine that we use here at our institution for the delivery of brain radiosurgery. For the majority of our patients, gamma knife still requires the
application of an immobilizing headframe that then allows the placement of each metastasis in the middle of the radiation beams, which enables the delivery of a very accurately targeted high dose of radiation in a single day to single fraction to target lesions almost anywhere in the brain.

And also sorry. And so, with all our radiosurgery capable machines, how about we now also have mask based capability?

And so, while accuracy of treatment and long treatment tolerability is still best in the frame,
the mask is further extent expanded. Our capability to treat patients like this one. And so this is a 64 year old lady who was just recently diagnosed with lung cancer. Some of you may remember her. And this patient would previously have had whole brain radiation therapy because of the large number and size of lesions. Today what we can do is break the radiosurgery up into three to five days. So on the first day, the frame is applied and all the smaller lesions are treated so you can see that there’s quite a few lesions.
that are less than 3 centimeters in diameter, and all of these are treated in single fraction as they would be for most of their other patients. Then a plan is made for the larger lesions in the first of three or five fractions can be administered in the frame, and the patient comes back for more treatments than performed in the mask to only the larger lesions. And so it’s gotten very complicated from a planning standpoint, but this often allows us to avoid whole radiation therapy altogether. And it means that radiation can be completed usually within a week.
And so this may seem a little crazy on our part, but parallel to our institutional practice, the national use of radiosurgery has grown exponentially as well. As you can see from these grants from the National Cancer database, not only is radiosurgery being used as first line treatment for patients living longer, and often undergoing second and third treatments with radiosurgery.
and so its use is escalated or around the country. And so not only then do we increasingly see treatment plans that look like this one on the left, where the blue dots are the first treatment, yellow dots, the second treatment, and so each time the patient comes is more lesions treated, but to the right you can see in every increasing number of radiosurgery capable machines being developed, and so on. The top is the cyber knife, which was the first iteration outside the gamma knife in the middle of picture is Linux based radiosurgery machines.
So they look very much like our standard. Radiation machines then on the bottom is the ZAP. Which is the newest self shielded machine that you might start seeing coming on the market? And so the question arises then, as radiosurgery becomes increasingly available. Many lesions is too many to treat with radiosurgery. And so, based on survival literature which we’re realizing now is not great for us, large popularity population data.
suggests that there is no upper limit to when to consider radiosurgery since there are groups that show that median overall survival durations can be in the order of 18 months in patients with greater than 30 metastases treated at one sitting. From the neurocognition outcome standpoint, which is where we’d like to be without data, there is no guidance here, since the largest randomized study involved only patients with one to three brain metastases, and this study only showed that whole brain radiation therapy was bad for cognition. And so the only data that we have...
to go on is this small study that was done which tried to correlate the number of lesions with how much dose the whole brain might achieve received in a single day of treatment. And so we believe that for greyhole rain dose, which is marked on the left axis correlates probably about 25 lesions, which is the current upper limit of safety. Unfortunately, there’s very little other data to guide us, and so it’s important not only to remember that number of lesions treated needs to be taken in context of patient.
expected survival and cognitive reserve. But also, patient ability to tolerate, delete the treatment and so treat in 25 lesions, translates into three hours of physics planning while the patient sits and waits with the headframe and then an additional three more hours of having one's head locked in the machine for treatment, making it a 7 to 8 hour minimum treatment day. And obviously the time is spent is worth it if the results are good, but. It's not for everybody.
So for many patients who still live less than a year after diagnosis of brain metastases, though radiosurgery still remains the first line treatment. And so on the bottom you can see here a volume change overtime graph that we published quite a while ago, now showing that if you live only nine months there is that initial shrinkage of the radiosurgery treated lesion. As you can see all the way to the left and then the volume remains stable over the course of your lifetime. If however, you live longer than that,
then there is an increasing chance that you could run into this phenomenon that you see around the 12 to 18 month mark where the lesions start to grow, and so as radiosurgery has become more popular, the rate of this phenomenon has significantly increased, and so this is a phenomenon that is unique to radiosurgery, does not occur after a whole brain radiation alone, and it’s becoming increasingly problematic. And so when we first encountered this phenomenon,
it was assumed that regrowth was due to tour, 'cause that’s what it was when things regrew after horn radiation therapy. But in fact, we know now that 50% of radio graphic regrowth. Can be due to post high dose radiation, inflammatory phenomenon known as radiation necrosis, which you can see on the right, and so is images show perivascular infiltration associated with the and intra parenchymal T cell necrosis and Astra Cytosis. and Vascular Highlanders issue
that you see following radiation. While we do not really understand the pathophysiology still behind the development of radiation necrosis clinically, we have relied on experience that suggests that if disease is progressing in the body, then regrowth in the brain is likely to be tumor. On the other hand, what we’ve learned is that patients who are doing well in the body and have been successfully treated with immunotherapy or have received repeat radiation for presumed tumor, regrowing in the brain and more.
likely to develop radiation necrosis. Unfortunately, even with these clinical predictors were not always right, and so we turned to image Ng to try to help us. And over the years, many imaging sequences have been proposed, including those listed here. The latest favorite is more profusion and so to the right is an example of how wrong we can still be with these images though. So this is a patient who had his right temporal and then right cerebellar
lesion treated nine months ago.

The lesion started to regrow an on Mr Perfusion.

Blue areas are considered low blood flow whereas green to red areas are considered higher blood flow and so where there’s less blood flow, we think it’s less likely to be Moran. More blood flow more likely to be tumor.

The right temporal lesion was red’s tumor and the right cerebellar lesion was read as radiation necrosis. Both lesions ultimately needed resection for symptomatology, and in fact, the pathology was the exact opposite.
And so unfortunately today the gold standard for differentiation differentiating tumor from radiation remains surgical. One imaging modality that has been reported to be more helpful in Europe is amino acid PET. The traditional amino acid compound that has been most studied and used, his radio labeled methionine, which unfortunately has a very short half life and is therefore too expensive to make and use here in the United States. A much more stable compound,
however, has recently come on the market called flu sick living, and so I just wanted to introduce you to a new image Ng trial that we’re starting here. So pursue is a phase 2B trial which is currently open for any brain metastasis patient with lesions regrowing after radiosurgery. Its purpose is to gather preliminary data to help define the image in cutoff values for classic luvene pet by correlating preoperative imaging with post craniotomy pathology. Once these image in cut offs have been defined though,
then we’ll be opening revelate, which will be a phase three study to determine the efficacy of flu sick Lavigne Pat. In different shading, tumor from radiation necrosis. For this study, both patients undergoing craniotomy and laser thermal coagulation, which will talk about a little bit later, will be eligible, and so hopefully you’ll be seeing this study coming around and will be able to move closer towards obtaining a noninvasive method of differentiating
00:43:24.090 --> 00:43:25.770 tumor from radiation process.
NOTE Confidence: 0.83972985
00:43:28.250 --> 00:43:30.634 So the next challenge is what to do
NOTE Confidence: 0.83972985
00:43:30.634 --> 00:43:33.500 once we workout, whether the lesion is
NOTE Confidence: 0.83972985
00:43:33.500 --> 00:43:35.550 regrowing tumor or radiation necrosis.
NOTE Confidence: 0.83972985
00:43:35.550 --> 00:43:39.099 What’s interesting over the years is that
NOTE Confidence: 0.83972985
00:43:39.099 --> 00:43:41.830 management options for radiation necrosis
NOTE Confidence: 0.83972985
00:43:41.830 --> 00:43:45.214 have become more available than tumor.
NOTE Confidence: 0.83972985
00:43:45.220 --> 00:43:47.607 And so these are the options available.
NOTE Confidence: 0.83972985
00:43:47.610 --> 00:43:49.058 Obviously for radiation necrosis
NOTE Confidence: 0.83972985
00:43:49.058 --> 00:43:51.230 it’s possible just to observe the
NOTE Confidence: 0.83972985
00:43:51.287 --> 00:43:53.225 lesions because some of these lesions
NOTE Confidence: 0.83972985
00:43:53.225 --> 00:43:54.800 will resolve on their own.
NOTE Confidence: 0.83972985
00:43:54.800 --> 00:43:57.187 We’ve learned though, as I said before,
NOTE Confidence: 0.83972985
00:43:57.190 --> 00:43:59.188 that radiation necrosis tends to occur
NOTE Confidence: 0.83972985
00:43:59.188 --> 00:44:01.859 in patients tends to occur more often
NOTE Confidence: 0.83972985
00:44:01.859 --> 00:44:03.567 in patients receiving immunotherapy.
And so stopping immunotherapy as an option, and certainly avoiding reradiation, is probably one of the biggest ways of avoiding making this worse.

There are many medical therapies that have been tried. The only one that has been demonstrated to be efficacious’s purpose is a map in a randomized trial. But what we’ve also learned is that surgical management has been very effective, and so back in the day we only had craniotomy available. But if you completely remove a radiation across this lesion,
then resolution is rapid.

Not everybody wants a craniotomy though, and so over the last five or six years we've developed a technique called laser thermal coagulation. Shorten does lit, which is helped us with this population. And so again, for those who are not familiar letters is a minimally invasive stereotactic procedure. So through the same smaller 5 millimeter stab incision in the skin, we can introduce a biopsy needle through the skull into the lesion, and then take out the needle and through
the same hole we can introduce the laser, which is what you can see on the left. Patient then gets introduced into the MRI machine. Um and we check to make sure that the laser is inside the middle of the lesion. We then turn the laser on and you can see the yellow lines around the lesion. Those are the lines are the heat lines that allow us to know when to stop. Turn off the laser. And so this is an example of how radiation necrosis works best, and so to the left you can see a patient who had in fact 23 lesions treated.
with radiosurgery of all of them.

Though this was the only lesion in the right basal ganglia that became a problem.

So it started to regrow, was associated with a lot of adima around it.

We went ahead and treated this lesion.

And you can see that the incision is only a couple staples.

Long patient was able to go home first day after surgery.

They were able to come off steroids in a week and you can see in two weeks how quickly.

Even though the lesion size itself is not decreased, that the edema has gotten
better by six weeks.

Obviously good resolution and so so the nice thing is we haven’t had to do craniotomies for these lesions, which are obviously significantly morbid. And have been able to offer one additional option.

Home and so how we decide which option to treat with for radiation necrosis still remains highly variable. So we went back and looked at our institutional experience to try and work out if we could start to standardize how we choose what we do.

So the first study we did looked
So what we learned was that both tools are pretty good at taking care of radiation necrosis. What it appears though, is that symptom resolution and ability to wean off steroids may be better with craniotomy. But what we realized also was that the lesion volume was larger in our craniotomy patients. And so when we took out all the lesions that were greater than 3 centimeters in diameter, what you can see all the way to the left is that is that in fact,
the two surgical tools, litton craniotomy basically become comparable in efficacy. And really what becomes a decider for how well things work is whether or not the lesion is radiation, necrosis, or tumor, and so from this we started first of all to try and detect lesions when they’re small so that we can take advantage of the minimally invasive technique of lit, rather than having to condemn the patient to craniotomy.
00:48:09.500 --> 00:48:10.142 But obviously,
NOTE Confidence: 0.858445
00:48:10.142 --> 00:48:12.068 if the lesion is larger than
NOTE Confidence: 0.858445
00:48:12.068 --> 00:48:13.556 3 centimeters then craniotomy
NOTE Confidence: 0.858445
00:48:13.556 --> 00:48:14.738 is still effective.
NOTE Confidence: 0.685159811764706
00:48:17.100 --> 00:48:21.591 Um? The what we did next was then can
NOTE Confidence: 0.685159811764706
NOTE Confidence: 0.685159811764706
00:48:26.120 --> 00:48:29.067 And what you can see here is
NOTE Confidence: 0.685159811764706
00:48:29.067 --> 00:48:32.115 that we actually have two very
NOTE Confidence: 0.685159811764706
00:48:32.115 --> 00:48:34.363 different populations being chosen
NOTE Confidence: 0.685159811764706
00:48:34.363 --> 00:48:38.109 for the two different treatments.
NOTE Confidence: 0.685159811764706
00:48:38.110 --> 00:48:41.305 So lit patients tending to be a little bit
NOTE Confidence: 0.685159811764706
00:48:41.305 --> 00:48:44.340 better functionally, and not only that,
NOTE Confidence: 0.685159811764706
00:48:44.340 --> 00:48:46.830 but the time from radiosurgery tool.
NOTE Confidence: 0.685159811764706
00:48:46.830 --> 00:48:49.326 It tends to be significantly longer
NOTE Confidence: 0.685159811764706
00:48:49.326 --> 00:48:52.219 than for those getting bear versus man.
NOTE Confidence: 0.685159811764706
00:48:52.220 --> 00:48:53.800 So for whatever reason,
00:48:53.800 --> 00:48:56.170 patients who have lesions that are
NOTE Confidence: 0.685159811764706
00:48:56.245 --> 00:48:58.657 regrowing early after radiosurgery are
NOTE Confidence: 0.685159811764706
00:48:58.657 --> 00:49:01.769 tend to be getting drug more frequently.
NOTE Confidence: 0.8684395
00:49:03.980 --> 00:49:05.064 In addition to that,
NOTE Confidence: 0.8684395
00:49:05.064 --> 00:49:07.170 when we look at local lesional control,
NOTE Confidence: 0.8684395
00:49:07.170 --> 00:49:09.282 what we also see is 2 very different
NOTE Confidence: 0.8684395
00:49:09.282 --> 00:49:11.458 patterns of response, again making the
NOTE Confidence: 0.8684395
00:49:11.458 --> 00:49:13.654 two treatments very hard to compare.
NOTE Confidence: 0.8684395
00:49:13.660 --> 00:49:16.828 If we start with the graph on the right,
NOTE Confidence: 0.8684395
00:49:16.830 --> 00:49:19.385 the graph shows 3D volume change overtime
NOTE Confidence: 0.8684395
00:49:19.385 --> 00:49:22.209 again and you can see that the black
NOTE Confidence: 0.8684395
00:49:22.209 --> 00:49:24.920 line which is the business, is a Medline.
NOTE Confidence: 0.8684395
00:49:24.920 --> 00:49:27.020 There’s a relatively rapid decrease in
NOTE Confidence: 0.8684395
00:49:27.020 --> 00:49:29.150 lesion size in response to Adbaston,
NOTE Confidence: 0.8684395
00:49:29.150 --> 00:49:30.890 but this response ultimately
NOTE Confidence: 0.8684395
00:49:30.890 --> 00:49:32.630 does not last forever.
NOTE Confidence: 0.8684395
00:49:32.630 --> 00:49:34.751 In addition, on the left you can
NOTE Confidence: 0.8684395
00:49:34.751 --> 00:49:37.149 see based on the runner criterion,
NOTE Confidence: 0.8684395
00:49:37.150 --> 00:49:39.438 that while a 15% a subset of patients
NOTE Confidence: 0.8684395
00:49:39.438 --> 00:49:42.030 had an excellent response to Avastin,
NOTE Confidence: 0.8684395
00:49:42.030 --> 00:49:45.153 showing a CR both at three and six months,
NOTE Confidence: 0.8684395
00:49:45.160 --> 00:49:47.967 the majority of patients only have disease
NOTE Confidence: 0.8684395
00:49:47.967 --> 00:49:49.980 stabilization and then progression.
NOTE Confidence: 0.8684395
00:49:49.980 --> 00:50:02.504 In comparison, after lit,
NOTE Confidence: 0.8684395
00:49:51.372 --> 00:49:53.932 there is the expected increase in lesion
NOTE Confidence: 0.8684395
00:49:53.932 --> 00:49:56.410 volume from the surgical procedure itself,
NOTE Confidence: 0.8684395
00:49:56.410 --> 00:49:59.182 but then a good long term
NOTE Confidence: 0.8684395
00:49:59.182 --> 00:50:00.106 volumetric response.
NOTE Confidence: 0.8684395
00:50:00.110 --> 00:50:02.504 You Irano this is less easy to
NOTE Confidence: 0.8684395
00:50:02.504 --> 00:50:04.259 interpret because much of the
NOTE Confidence: 0.8684395
00:50:04.259 --> 00:50:06.233 volume change were large enough to
result in a progression of disease.

Reading early on that then resolved to stable disease by six months.

And so ultimately, local control was significantly better at six months and beyond for laser compared to Avastin.

But obviously if you have a large lesion with Mass Effect relatively early on, that can’t be surgically respected than Avastin.

Now clearly plays a role.

Lastly, from a multi institutional study of lit, we learned that complete ablation of a radiation
across this lesion results in better local control than partial ablation. They can see in the first 2 lines of the table to the left, and so the smaller the lesion at the time of lit, the more likely it will resolve post operatively. And so this last point is you can see also applies to regrowing tumor which is the bottom two rows of the table to the left. And for this reason we have started advocating for lit much earlier in the course of these patients. Whether we think it’s radiation, necrosis, or tumor.
To the right, the study also underscores one more problem in brain metastasis and that is that regrowing tumor both in the local control as well as survival. Data is a much bigger problem to manage the radiation necrosis. And so this brings us to, kind of how we offer radiation dosing here. And so while we would prefer that our patients not get either complication, if we had to pick one complication, radiation necrosis would be the preferable one because we seem to have
better treatment options available.

Alright, and so for the last few minutes I wanted to move away from surgery and radiation and talk a little bit about work that we’ve been doing. Looking at recurrent tumors. So recurrent tumor being the most difficult of the problems that we manage. Unfortunately more radiation and surgery is usually morbid for the patient, and so is there a way that we look at changing systemic therapy to be more effective in the brain? And so I want to thank doctor Hertz and the support group for the opportunity to participate in the lung score.
And credit for the work that I'm about to present goes mostly to my collaborators Don Wayne and pathology and Abby Patel and radiation oncology and the labs for hosting us, but also to Stephanie Chokers. One of our star neurosurgery residents who is really the force behind getting a lot of this work done. And so as background, the two proposed mechanisms for CNS failure, particularly, we've been looking at lung cancers with targetable mutations or either that drug penetration into the CNS remains low.
and so compared with the systemic concentrations, tolerance can develop in the central nervous system over time. Or the second mechanism is that as shown by Priscilla breast, you know through the whole exome sequencing data that she’s presented before that clinically actionable gene alterations can be present in brain metastases. That would that may not be found in the primary tumor. Brain metastasis tissue, however, is often difficult to obtain and
so we propose that perhaps by looking at cell free DNA in the CSF, we may be able to better study CNS tumor mutations. So we started a CSF biorepository in 2017 and have been collecting time matched CSF blood and brain metastasis tissue where possible. Things slow down a little bit with kovid, but we have over 100 samples down. This is a breakdown of their pathologies. And this is the gene panel that we’ve been using, which we recognize it would be a little bit limited,
but we had to start it somewhere.

And so this is a little bit of a busy slide, but what you can see is that we’ve been successful at finding tumor DNA in the CSF in about 2/3 of our patients with purely intra parenchymal brain metastasis. So not left a meningeal disease, although the amount of DNA has been highly variable.

In addition, in the table on the left to the top you can see that while tumor DNA was also detectable in the blood of many of our patients, with interpretable brain metastases,
Neither patient with cytology had tumor DNA in their plasma. And so when we broke down our population into patients with no stable or progressing systemic disease, you can see that plasma DNA tends actually to be more reflective of extracranial disease than intra cranial disease. And Lastly to the right, when matching mutations found in CSF plasma and brain metastasis tissue, it appears in fact that tumor DNA matches the brain metastasis.
much better than plasma circulating DNA. And so it seems that tumor DNA found in the CSF may be a better way to study brain metastases. Mutation. We need to collect obviously more samples and so will be coming to you all to try and get these samples, but we’re hoping that if the data is in fact validated that will be able to UCSF, perhaps as a way to inform changes in their systemic therapy options for current brain metastases. Thank you very much and I’m happy to take questions. Thanks Veronica, that was wonderful. We do have time for questions.
as the questions come in.

Just wanna remind everyone that we have our ask a review on October 23rd. This year we’re doing it virtually from 821.

So tell us a little bit more about how you get the CSF from the patients. These are lumbar punctures that are done on patients identified from the clinics. So yeah, we can get CSF so the biggest one is mostly been from craniotomy so we try and identify a site where
we can get CSF that’s distant.

Then the lesion that we’re about to respect and we get the CSF before we reset the lesion.

So hopefully there’s no contamination, but yes the other places, so one is on the wards and so I think if there’s any concern in patients for leptomeningeal disease and we’re getting a diagnostic lumbar puncture, then it would be nice to get CSF at that time. And then the last mechanism is one that’s a little bit unique and has provided a little bit of a challenge also.
So patients who are actually getting re biopsy as part of kind of the lung protocols for progression of disease if they also have progression in their central nervous system. So untreated brain metastases that we’ve been asking those patients at the time of their broad to have a lumbar puncture performed to get CSF as well, and so those are kind of the three opportunities that we have. And then yes, and then obviously in the clinic, if we’re seeing patients that need number of functions for clinical reasons,
00:57:13.770 --> 00:57:14.025 right?
NOTE Confidence: 0.8060832
00:57:14.025 --> 00:57:14.280 We
NOTE Confidence: 0.80774677
00:57:14.280 --> 00:57:15.828 do have a question someone asks,
NOTE Confidence: 0.80774677
00:57:15.830 --> 00:57:17.538 they say thank you for your wonderful
NOTE Confidence: 0.80774677
00:57:17.538 --> 00:57:19.126 program and all your help with
NOTE Confidence: 0.80774677
00:57:19.126 --> 00:57:20.476 brain metastases over the years.
NOTE Confidence: 0.80774677
00:57:20.480 --> 00:57:22.802 Is there a limit to the number of metastases
NOTE Confidence: 0.80774677
00:57:22.802 --> 00:57:24.597 that you can use gamma knife for?
NOTE Confidence: 0.88614994
00:57:26.070 --> 00:57:29.086 Yeah, so I think it goes back to,
NOTE Confidence: 0.88614994
00:57:29.090 --> 00:57:31.358 you know, kind of what we
NOTE Confidence: 0.88614994
00:57:31.358 --> 00:57:32.870 think patients can tolerate.
NOTE Confidence: 0.88614994
00:57:32.870 --> 00:57:34.004 So gamma knife.
NOTE Confidence: 0.88614994
00:57:34.004 --> 00:57:35.894 Obviously there is no limit.
NOTE Confidence: 0.88614994
00:57:35.900 --> 00:57:38.539 The planning system allows us to treat,
NOTE Confidence: 0.88614994
00:57:38.540 --> 00:57:41.174 I think over. Over 100 lesions
NOTE Confidence: 0.88614994
00:57:41.174 --> 00:57:43.580 now within the planning system,
so logistically it’s it’s not impossible to do that. As I had said though, I think to treat 25 lesions is hard enough for a patient in a single day, and certainly those are 25 lesions that are easy to plan and. And relatively easy to treat. I think for those patients who have larger lesions and lesions in more complex areas. Such as up against the brain stem or the optic nerves or whatever. Then you know the the planning
and the treatment for those lesions takes even longer, so we are our radiation oncologists are trying to keep the cap at 25 because we had shown that the whole brain dose is about four Gray. But in addition to that it’s about as long as a patient can tolerate 7 or 8 hours with us. It’s not so fun with us down the basement. That’s great in the final question from someone who’s obviously been watching the entire day. They ask. Are you doing the gamma knife at sites outside of Cedar Street or is
it all being done at the main center? And are there plans to expand this around Connecticut?

So, so the Gamma Knife Machine Percy. There's only one of those here in Connecticut. The Certificate of need. It's difficult to get more than one in our little state, but brain radiosurgery, which can be done either with gamma knife or mlynek based techniques. There's actually 11 centers around the state that are capable of it. With linac based radiosurgery, though.
this software is not capable really of treating more than 10 lesions at a time, and once you’ve exceeded 10 total, whether it be all at one time or over several treatments, then it gets really difficult to take into account what’s been treated before as versus what needs to be treated going forward, and it’s the reason why the multiple metastases always end up here, and so I think, as Doctor Boffa was saying before. You know it is the reason why we are the referrals. I’m not sure that there’s enough volume
necessarily to grow around the state, and it’s very expensive and time consuming. You know, treatment so. It’s hard to cultivate elsewhere. I know, I said last question, but I can’t not ask Doctor Sklar’s question. Jeff, thank you. He has. How do you propose to UCSF DNA in patients with multiple lesions? For example, your patient who had both tumor necrosis and regrowth of tumor? So. So it’s interesting, I don’t. I think that finding so we
01:00:39.360 --> 01:00:41.965 don’t have a marker necessarily
NOTE Confidence: 0.81545657
01:00:41.965 --> 01:00:45.109 for radiation Necrosis Persay.
NOTE Confidence: 0.81545657
01:00:45.110 --> 01:00:47.670 What I think that we care about is,
NOTE Confidence: 0.81545657
01:00:47.670 --> 01:00:49.819 is there regrowing tumor and so I
NOTE Confidence: 0.81545657
01:00:49.819 --> 01:00:51.786 think that if we find mutational
NOTE Confidence: 0.81545657
01:00:51.786 --> 01:00:53.742 DNA first of all we don’t.
NOTE Confidence: 0.81545657
01:00:53.750 --> 01:00:55.688 We don’t 100% know that it
NOTE Confidence: 0.81545657
01:00:55.688 --> 01:00:57.270 correlates with active disease yet,
NOTE Confidence: 0.81545657
01:00:57.270 --> 01:00:59.314 but if we’re able to demonstrate that
NOTE Confidence: 0.81545657
01:00:59.314 --> 01:01:01.922 then we need to be concerned that we’re
NOTE Confidence: 0.81545657
01:01:01.922 --> 01:01:03.975 not just treating radiation to process
NOTE Confidence: 0.81545657
01:01:03.975 --> 01:01:06.229 and I think that’s really the issue.
NOTE Confidence: 0.8395945
01:01:06.870 --> 01:01:08.702 Great, well, I think that we are at
NOTE Confidence: 0.8395945
01:01:08.702 --> 01:01:10.667 time and actually a few minutes over,
NOTE Confidence: 0.8395945
01:01:10.670 --> 01:01:12.694 but no one needs to walk back to
NOTE Confidence: 0.8395945
01:01:12.694 --> 01:01:14.425 their office. So I figured I could
NOTE Confidence: 0.8395945
01:01:14.425 --> 01:01:16.229 get a few more minutes in there.
NOTE Confidence: 0.8395945
01:01:16.230 --> 01:01:17.748 Thank you, Veronica, that was wonderful.
NOTE Confidence: 0.8395945
01:01:17.750 --> 01:01:18.545 Thank you, Dan.
NOTE Confidence: 0.8395945
01:01:18.545 --> 01:01:20.689 Thank you to the organizers Renee and the
NOTE Confidence: 0.8395945
01:01:20.689 --> 01:01:22.553 team and we’ll see you back next week.
NOTE Confidence: 0.8395945
01:01:22.560 --> 01:01:24.580 It’s been a pleasure moderating today. Have a
NOTE Confidence: 0.8395945
01:01:24.580 --> 01:01:27.765 good day. Everyone. Thank you.